

REVIEW

# A Practical Approach to Glucose Abnormalities in Cystic Fibrosis

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## ABSTRACT

Cystic fibrosis is a common genetic condition and abnormal glucose handling leading to cystic fibrosis-related diabetes (CFRD) is a frequent comorbidity. CFRD is mainly thought to be the result of progressive pancreatic damage resulting in beta cell dysfunction and loss of insulin secretion. Whilst Oral Glucose Tolerance Testing is still recommended for diagnosing CFRD, the relationship between glucose abnormalities and adverse outcomes in CF is complex and occurs at stages of dysglycaemia occurring prior to diagnosis of diabetes by World Health Organisation criteria. Insulin remains the mainstay of treatment of CF-related glucose abnormalities but the timing of insulin commencement, optimum insulin regime and targets of glycaemic control are not clear. These complexities are compounded by common issues with nutritional status, need for

enteral feeding, steroid use and high disease burden on CF patients.

**Keywords:** Cystic fibrosis; Cystic fibrosis-related diabetes; Diabetes; Hypoglycaemia

## INTRODUCTION

Cystic fibrosis (CF) is a common life-limiting autosomal recessive condition with the highest prevalence in populations with Northern European ancestry. The disease is caused by gene mutation causing defective function of a chloride channel—the cystic fibrosis transmembrane conductance regulator (CFTR)—which is vital for mucociliary clearance in the airways [1]. Cystic fibrosis impacts several organ systems including the liver, skin sweat glands and pancreas, but its classical impact on morbidity and mortality is via bronchiectasis, airways obstruction and progression to respiratory failure.

Abnormalities of glucose metabolism are an important co-morbidity of CF. Classically, progressive loss of beta cell function in CF

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leads to abnormal glucose levels and progression to cystic fibrosis-related diabetes (CFRD) [2–4]. The development of glucose abnormalities is recognised to herald a clear increase in morbidity and mortality in patients with CF, leading to a focus on identifying and controlling disordered glucose metabolism in CF [5, 6].

The management of CFRD is complex and importantly it differs significantly from that of type 1 and type 2 diabetes. Management of CFRD requires a multidisciplinary approach to attempt to ensure the best possible clinical outcome, whilst minimising treatment-associated adverse events.

This article explores the pathophysiology, diagnosis and clinical impact of glucose abnormalities in CF and discusses the approach to treatment of this challenging problem.

### Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## PATHOPHYSIOLOGY

CFRD is primarily characterisable as a defect of insulin release resulting from the secretions blocking pancreatic ducts, autodigestion, oxidative stress and destructive fibrotic pancreatic disease that ultimately destroys islet cell function [2–4]. Pancreatic beta cell function and first phase insulin secretion have been shown to be reduced in CFRD when compared to normal glucose tolerance (NGT) patients with CF where no difference is observed in insulin resistance [7]. Patients with CF also have

more rapid small bowel glucose absorption further exacerbating postprandial glucose excursions [8].

Patients with CF have also been shown to have decreased GLP-1 activity compared to normal controls, which may contribute to glucose abnormalities [9]. CF is a complex multisystem disease, and multiple defects in nutritional status and metabolism also contribute to observed glucose abnormalities. Table 1 summarises these defects and their consequences for glucose metabolism.

## EPIDEMIOLOGY

CFRD is clinically and pathophysiologically distinct from either type 1 or type 2 diabetes. It occurs in children and young adults with a median age at onset of 20 years. It appears to develop earlier in female than male patients [10]. Of 158 adults (categorised by WHO OGTT criteria or physician insulin initiation) over 16 years of age attending a CF service in the UK, 51 (32.3%) had CFRD, 24 (15.2%) had impaired fasting glucose or impaired glucose tolerance, and 83 (52.5%) had normal glucose tolerance [11]. CFRD appears to be more common in patients who are homozygous for the most common CFTR gene mutation,  $\Delta F508$ .10 [3]. Ketoacidosis is rare but can occur if CFRD goes untreated or in the presence of significant intercurrent infection [12]. As the age at which CFRD and type 1 diabetes usually present overlaps, it is important to remember that patients with CF can also develop type 1 diabetes.

The recent history of CF has been one of greatly improved survival. Improvements in physiotherapy and drugs to clear mucus from the lungs and aggressive treatment of infection, combined with pancreatic exocrine

**Table 1** Factors impacting on glucose regulation in CF

System	Defect	Impact on metabolism
Endocrine pancreas	Reduced insulin secretion	Postprandial hyperglycaemia
	Reduced glucagon secretion	Progression to CFRD
Exocrine pancreas	Reduced pancreatic enzyme production	Malabsorption of fat, protein and carbohydrate
Gut	Malabsorption of fat and protein	Rapid postprandial glucose excursions
	Rapid glucose absorption	Low glucose preprandial
	Less active GLP-1	Reduced insulin and increased glucagon secretion
Liver	Liver insulin insensitivity	Hyperglycaemia
	Reduced glycogen storage	Reduced response to hypoglycaemia
	Cirrhosis	
Fat/muscle	Decreased fat stores	Increased insulin sensitivity
	Decreased muscle mass	
	Insulin sensitivity	
Adrenal	Cortisol response to intercurrent infections	Stress hyperglycaemia
	Use of exogenous steroid treatment	Steroid related hyperglycaemia

supplements and enhanced nutrition, have all contributed to significant improvements in morbidity and mortality in patients with cystic fibrosis. In Europe a significant reduction in potential years life lost (PYLL) for patients between 0 and 30 years old has been described. In males, the standardised PYLL decreased from 14.65 (11.37–17.93) lost years per million persons per year in 1994 to 7.49 (6.14–8.84) in 2010 [13]. In Canada, median survival age increased from 31.9 years (95% CI 28.3–35.2 years) in 1990 to 49.7 years (95% CI 46.1–52.2 years) in the 5-year window ending in 2012 [14]. As patients with CF live longer it is likely therefore that the prevalence of CFRD will increase.

## DIAGNOSIS

The onset of CFRD cannot reliably be detected symptomatically, with around 2/3 of patients

asymptomatic at diagnosis [15]. Given the potential impact of CFRD on morbidity and mortality, a reliable biochemical screening test for CFRD is vital. There is general agreement between national and international societies that CFRD should be diagnosed using the standard 75 g Oral Glucose Tolerance Test (OGTT) with the general recommendation that this should be carried out annually in all patients from childhood [16, 17]. Use of the OGTT in the diagnosis of CFRD does however have a number of disadvantages. First, it is a time-consuming investigation for patients and staff to perform. Furthermore, the OGTT was primarily developed as a way of predicting risk of microvascular and macrovascular complications of hyperglycaemia, and as such it does not necessarily predict the risks and complications associated with dysglycaemia in CF. The response of measured glucose to an oral glucose challenge is especially variable in

patients with CF. In one study glucose tolerance improved [from normal to impaired glucose tolerance (IGT) or from CFRD to normal or IGT] in 18% of patients over 4 years whilst 19% worsened in category over the same time period [18]. Crucially, early CFRD is classically characterised by postprandial glucose excursions secondary to loss of first phase insulin. In order to have an optimal chance of detecting this abnormality a 1 h glucose estimation would be required during OGTT, and indeed it has been shown that 1 h glucose levels are a better predictor of decline in pulmonary function than 2 h levels during GTT [19].

Whilst HbA1c is now accepted as a diagnostic tool within the field of diabetes, it is difficult to interpret as a diagnostic test for CFRD. Relatively brief periods of postprandial hypoglycaemia with low normal pre-meal glucose levels have the potential to lead to reassuringly normal HbA1c values. Studies assessing the consistency of HbA1c as a measure of mean blood glucose in CFRD and HbA1c have shown conflicting results [20, 21]. CFRD is additionally associated with a lower than normal red cell lifespan, which could reduce diagnostic utility [22]. In one prospective study an HbA1c of  $>46$  mmol/mol showed a positive predictive value of 50% when compared with OGTT [15]. In another study elevated HbA1c  $>42$  mmol/mol was seen in only 38% of patients with diabetes, confirming a poor sensitivity as a diagnostic test in CFRD [7]. If HbA1c is to have utility, lower levels will need to be considered as clinically important. An HbA1c  $\geq 40$  mmol/mol has been proposed as a diagnostic level for CFRD screening and is suggested to reduce the need for an OGTT by 50.7% [23]. A systematic review of screening tests for CFRD agreed that the sensitivity of

HbA1c is too low to recommend it as a diagnostic test [24].

Given that pulmonary consequences of CFRD are known to occur when only 1 h postprandial glucose is elevated when measured during an OGTT, there is theoretical merit in using 1 h levels measured by capillary blood glucose (CBG) monitoring or continuous glucose monitoring when performing this investigation [25–28].

Our local practice is to recommend annual OGTT for all patients from age 10 years and 1 h postprandial CBG monitoring in patients where clinically indicated by declining lung function, recurrent infection or weight loss. Table 2 shows a summary of diagnostic guidelines.

## IMPACT ON PROGNOSIS

Abnormalities of glucose metabolism have a clear association with morbidity and mortality in CF patients. It is less clear whether hyperglycaemia or insulin deficiency have a causal relationship with poor outcomes or are simply markers of more advanced or complicated disease.

Worsening lung function is clearly associated with glucose abnormalities, and a decline in pulmonary function appears to be related to the severity of glucose intolerance and insulin deficiency [18]. Patients with CFRD have more episodes of infection and have higher rates of colonisation with important pathogenic organisms such as *BurkholderiaCepacia* and *Aspergillus* suggesting impaired immunity [29]. It has been suggested that an association between poor lung function and dysglycaemia may be more important in females [30].

In a UK registry study of 5892 patients with CF the presence of diabetes was an independent

**Table 2** Suggested criteria for diagnosis of CFRD (Adapted from ADA guidelines [16])

Patient status	Suggested diagnostic glucose level (mmol/l) (all CBG results to be confirmed by laboratory measurement)
Healthy outpatients	75 G OGTT fasting $\geq 7$ or 2 h $\geq 11.1$ Random $> 11.1$ on 2 measures with osmotic symptoms, declining weight or lung function
Enteral tube feeding	$\geq 11.1$ during feed on 2 occasions
Acute illness or steroid use	Fasting $\geq 7$ Random $\geq 11.1$ on 2 occasions over 48 h

risk factor for death (hazard ratio 1.31 (95% CI 1.03–1.67)) [31]. Registry data from the US show that in patients with CF, controlling for other risk factors, diabetes is associated with a 55% increase in 5-year mortality [32].

These consistent associations between insulinopenic dysglycaemia and adverse outcome suggest correcting glucose abnormalities with insulin or insulin secretagogues may confer benefit.

Whilst the the primary focus in CFRD is on lung function and nutritional status, it is important to remember that, as with all types of diabetes mellitus, effective screening for microvascular complications is required. Compared to patients with type 1 diabetes patients with CFRD have a similar incidence of microvascular disease with a lower prevalence of retinopathy and a higher prevalence of microalbuminuria [33]. Screening for microvascular complications is likely to increase in importance with increasing longevity of patients with CFRD.

## TREATMENT OF HYPERGLYCAEMIA

Unlike other forms of diabetes where control of glucose is primarily to prevent microvascular and macrovascular complications, the main goal in CFRD is prevention and improvement

of declining respiratory function and nutritional status. Several small non-randomised studies, retrospective reviews and case series have suggested a benefit of insulin in both reducing the decline of lung function and weight loss. These studies use a variety of insulins with various levels of glycaemia and clinical triggers for patient selection [34–37]. We have reported retrospective, observational data from our unit, which suggest that introducing insulin at the stage of impaired glucose tolerance seems to ameliorate loss of lung function and increase weight [38]. One open-label randomised study attempted to assess the impact on clinical outcomes of preprandial insulin treatment compared to repaglinide and placebo in patients with CFRD but no fasting hyperglycaemia. There was no change in decline in lung function or infections in the insulin group at 12 months, but there was a significant improvement in BMI. It was felt that the short duration of the study made it unlikely that changes in lung function would have been detected [39]. A systematic review performed by the National Institute for Health Research concluded that insulin appears beneficial in CFRD and probably at the IGT stage [24].

Hypoglycaemia is an obvious potential risk when using insulin in CF patients.

Hypoglycaemia can be observed in CF patients even before they have treatment for dysglycaemia, perhaps suggesting a mismatch between the increased late insulin secretion and rapid carbohydrate absorption [40]; 6.1% of CBG measurements performed in hospitalised patients with CF who were treated with insulin were found to be in the hypoglycaemia range (<4.0 mmol/l). Hypoglycaemia was also found to be associated with a significantly higher rate of readmission or death over the 3.5-year follow-up period ( $P = 0.03$ ) [41]. This is a higher rate of hypoglycaemia than that previously reported in the general population of inpatients with diabetes [42]. Hypoglycaemia in CF patients treated with insulin has also been associated with high levels of loss of awareness of hypoglycaemia, which may reflect loss of glucagon response or high exposure to hypoglycaemic range glucose [38]. It is therefore important to balance the potential benefit of insulin use in CF with the burden and harm of hypoglycaemia.

Continuous subcutaneous insulin infusion (CSII) by pump would seem in theory to offer significant potential advantages of flexibility and avoidance of hypoglycaemia, which could be of particular benefit in CFRD. Despite this CSII is not commonly used in patients with CFRD, perhaps reflecting increased cost or a feeling that CSII may be too much of a burden to patients already requiring intensive medical intervention [43].

There have been some small studies of insulin secretagogues showing reductions in glucose levels in CFRD; however none have shown significant benefit to important outcomes of lung function or weight [39, 44]. We do not presently recommend the use of insulin secretagogues in CFRD.

It is our local practice to consider insulin initiation where hyperglycaemia

(glucose >11.1 mmol/l) is detected either by screening or clinical monitoring triggered by clinical concern such as where the patient has poor nutritional status, declining lung function or recurrent lung infection. We favour the use of the prandial insulin bolus initially in the majority of cases for reasons of flexibility and as postprandial hyperglycaemia is usually the primary abnormality. We add basal insulin when fasting glucose becomes abnormal or bolus requirements become high.

There is insufficient evidence to be dogmatic about what glycaemic target should be aimed for in patients with CFRD. The ADA recommend achieving the same target CBG levels as those with type 1 diabetes (preprandial 4.4–7.2 mmol/l and postprandial <10 mmol/l) [16, 45]. This seems a reasonable goal, and patients should be encouraged to perform CBG testing regularly including postprandially if possible. Table 3 suggests a guideline for management of glucose abnormalities in CF with insulin.

## IMPACT OF OTHER THERAPIES

Nutritional status is of great importance in CF patients who have both increased resting energy expenditure and increased loss of calories through malabsorption and in whom cachexia is known to worsen outcome [46]. Optimising nutritional status is therefore an important goal, which has been shown to improve the ability to undertake normal daily activities [47]. Patients with CF are therefore recommended to take a high calorie diet (usually 120–150% of the daily recommended intake for age) [16]. To maintain high calorific intake enteral tube feeding (ETF) is commonly utilised and is thought to improve outcome [48]. Schedules for tube feeding vary and take into account the patient's schedule and other treatments,

**Table 3** Suggested approach (based on or local practice) to insulin treatment in CFRD

	Reason to commence	Starting dose	Optimal target glucose
Prandial bolus insulin	1–2 h postprandial glucose >11.1 mmol/l  With clinical indication <sup>a</sup>	0.5 units per 10 g CHO	1–2 h postprandial glucose <10 mmol/l
Basal insulin	If fasting >7.2 mmol/l or if boluses needed greater than 1.5 units per 10 g CHO	Add 0.1 unit per kg either long acting insulin (e.g., glargine) morning or intermediate acting (e.g., insulatard) night if fasting high adding morning if bolus requirements high	Fasting <7.2 mmol/l Premeal <7.2 mmol/l
Enteral tube feeding insulin	6–8 h feed with glucose >11.1 mmol/l	Add insulatard 0.5 units per 10 g CHO	During or end of feed <10 mmol/l
	4–6 h feed with glucose >11.1 mmol	Add actrapid 0.5 units per 10 g CHO	

Existing and required dose of insulin may double during acute illness and steroid therapy

<sup>a</sup> Osmotic symptoms, weight loss, recurrent lung infection, or decline in lung function

making evidence-based guidelines used in other settings for control of glucose during ETF less applicable [49]. Our experience suggests that liaisoning between the diabetes team and specialist dieticians is crucial when planning ETF. In CF patients ETF is often performed at home and overnight, and timing of feeds can vary from 4–12 h. Variation in the timing and tolerability of ETF can make choosing the optimum insulin to maximise energy conservation from the feed challenging. Choice of insulin should be made by matching the duration of insulin action to the agreed enteral feeding regimen. Dosing and insulin type can then be altered dependent on CBG readings before, during, and after ETF starts. Overnight CBG monitoring during ETF will disturb sleep and is therefore particularly burdensome to patients.

Use of steroids (usually prednisolone or methylprednisolone) has been common in patients with CF and can cause transient

hyperglycaemia or worsen glucose control in existing CFRD. It has been reported that over 50% of CFRD patients who have been admitted to hospital will have had at least one course of steroid treatment [50]. There is little evidence to guide management of hyperglycaemia related to steroid use in the general population let alone in CFRD. National guidelines suggest enhanced CBG monitoring and the use of insulin to correct hyperglycaemia [51]. We recommend CBG monitoring of fasting and postprandial glucose in all CF patients started on steroids.

## SUMMARY

Glucose abnormalities related to CF pose unique challenges to both diabetes and respiratory teams. The close associations between worsening dysglycaemia and poor outcome suggest benefit from insulin replacement therapy, but the time to start treatment and desired CBG levels remain

controversial. Insulin therapy has significant potential to cause harm—especially by inducing hypoglycaemia. At present we recommend a pragmatic multidisciplinary approach to managing this complex area. We suggest insulin use targeting postprandial glucose excursions, initiated when risks of declining lung function and nutritional status are high. We use postprandial CBG measurements to guide insulin dosing along with pre-prandial and fasting CBG measurement to guard against hypoglycaemia. Further data would be welcomed on the optimum timing of insulin initiation and on the glycaemic targets that would best prevent decline in lung function.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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