

Paediatric cystic fibrosis related diabetes

Judith Campbell, Mark Bone

ARTICLE POINTS

1 Screening for diabetes in children with cystic fibrosis (CF) reveals a hidden population of CF related diabetes (CFRD).

2 Early detection of CFRD can impact positively on health outcomes.

3 Treatment needs to be individually tailored and frequently revised to match intermittent abnormal glucose handling in these patients.

4 CFRD patients can develop microvascular diabetes complications, so annual screening is important.

5 Close collaboration between CF and diabetes teams is paramount, to manage the logistical problems of clinic appointments and frequent reviews.

KEY WORDS

- CFRD
- Screening
- Oral glucose tolerance test
- Treatment
- Diabetes complications

Judith Campbell is a Paediatric Diabetes Nurse Specialist, and Dr Mark Bone is Consultant Paediatrician, at Booth Hall Children's Hospital, Central Manchester NHS Trust

Introduction

Cystic fibrosis related diabetes (CFRD) develops in 10–15% of people with cystic fibrosis. Prevalence increases with age, and is an expected complication of CF as survival rates increase. Early identification of CFRD has been shown to impact positively on health status. Treatment is aimed at achieving optimal nutritional and clinical status, avoiding metabolic derangement through maintenance of normoglycaemia. This article presents guidelines for the management of children and adolescents with CFRD, and discusses problems that may arise.

Cystic fibrosis related diabetes (CFRD) develops in individuals with cystic fibrosis (CF) as a consequence of pancreatic pathology. The prevalence of CFRD increases with age; the average age of onset is between 18 and 21 years (Finklestein et al, 1988). CFRD rarely develops in children less than 10 years of age (Langg et al, 1991).

There is clear evidence that early identification of CFRD has a positive impact on health status (Langg et al, 1992; Nousia-Arvanitakis et al, 2001; Rolan et al, 2001). Delaying the diagnosis can result in unnecessary deterioration in both lung function and clinical status. Several studies have shown that long-standing deterioration in glucose tolerance and an insidious decline in clinical status frequently occur in CF several years before a diagnosis of diabetes is made (Langg et al, 1992; Milla et al, 2000; Koch et al, 2001).

Correct screening, early diagnosis and appropriate treatment are therefore crucial to the health outcomes of children and adolescents with CF. The diabetes and CF teams at Booth Hall Children's Hospital, Manchester, began a screening and treatment programme in 2003, in order to address these concerns.

Screening for CFRD

The classic symptoms of diabetes are not sufficiently sensitive alone to be used as a screening test. Only a third of patients with CFRD have symptoms of polyuria

and polydipsia at the time of diagnosis. Patients who develop overt symptoms of hyperglycaemia on presentation have been found to have a relatively greater decline in pulmonary function and weight loss than those identified on screening. It is therefore important that glucose intolerance is diagnosed early to identify those individuals at high risk of developing a decline in lung function, a fall in nutritional status or a new diagnosis of CFRD.

A fasting venous plasma glucose of >7 mmol/l indicates diabetes in the non-CF population, but fasting plasma glucose levels may not be reliable in identifying early CFRD. According to the World Health Organization (WHO, 1999), only 16% of patients with CFRD would be identified using this criterion. Children and adolescents with CF can have transient elevation of random and fasting glucose levels with a normal oral glucose tolerance test (OGTT). Thus fasting glucose and random glucose measurements, which are routinely used for the diagnosis of type 1 and type 2 diabetes, in conjunction with patient history, have reduced sensitivity and specificity in CF. Glucose tolerance and insulin resistance often vary in CF, being influenced by factors such as nutritional status and infection.

The published consensus is that the routine use of OGTT and serial glucose home blood glucose monitoring (HBGM) appears to be the most specific and sensitive tool currently available for the

diagnosis of CFRD (Lanng et al, 1995); Cucinotta et al, 1999; Yung et al, 1999).

The North American CF Consensus Committee recognises four glucose tolerance categories in CF, based on the OGTT results (1.5 g/kg; max 75 g) (Table 1). These represent a spectrum of deteriorating glucose intolerance progressing from impaired glucose tolerance (IGT) through to CFRD with fasting hyperglycaemia.

The OGTT may be used for the diagnosis of diabetes mellitus and is also the accepted screening test for CFRD. However, in a person with CF, a 'diabetic' OGTT does not mean that the individual has diabetes, but has, at that time, abnormal glucose tolerance. In a proportion of patients, a 'diabetic' OGTT will revert to normal with time and will require ongoing assessment, especially during periods of physical stress. It is therefore recommended that the OGTT should be performed annually in children and adolescents with CF over the age of 10 years.

Symptoms of CFRD

- Unexplained polyuria or polydipsia
- Failure to maintain or gain weight despite nutritional intervention
- Poor growth velocity
- Delayed progression of puberty
- Unexplained chronic decline in pulmonary function.

CFRD may be chronic or intermittent. Patients with intermittent CFRD repeatedly require insulin therapy to control hyperglycaemia when they are physically stressed, with infection, intensive nutritional intervention or treatment with steroids for pulmonary disease. Blood glucose levels can normalise between periods of stress and thus require suspension of insulin therapy.

Guidelines for management

- All CF patients over 10 years of age should have an OGTT performed at their annual assessment (Figure 1)
- All CF patients over the age of 10 who are admitted for inpatient treatment of acute illness should have both pre-meal and 2-hour postprandial blood glucose monitoring at least twice daily for a minimum of 48 hours (Figure 2)

Table 1. North American Cystic Fibrosis Consensus

	Fasting plasma glucose	2-hour plasma glucose
Normal glucose tolerance	<7 mmol/l	<7.8 mmol/l
Impaired glucose tolerance	<7 mmol/l	7.8–11.1 mmol/l
Cystic fibrosis related diabetes (without fasting hyperglycaemia)	<7 mmol/l	>11.1 mmol/l
Cystic fibrosis related diabetes (with fasting hyperglycaemia)	>7 mmol/l	>11.1 mmol/l

- All CF patients of any age with any of the following concerns should be referred to the diabetes team for assessment of glycaemic status by OGTT and blood glucose monitoring:
 - i) symptoms of hyperglycaemia (polyuria, polydipsia, glycosuria and weight loss
 - ii) unexplained deterioration of lung function
 - iii) patient unable to gain or maintain appropriate weight
 - iv) before commencing supplemental enteral feeding
 - v) delayed progression of puberty
 - vi) during infective exacerbations or systemic corticosteroids use
 - vii) before major surgery.

How common is CFRD?

Ten to fifteen per cent of all people with CF will develop CFRD. CFRD appears to present earlier in girls, which probably reflects their earlier onset of puberty and the associated increase in insulin resistance at this time (Lanng et al, 1995) (Figure 3).

Although the prevalence of diabetes in children with CF under 10 years of age is thought to be low, this US study found that, by screening 5–9 year olds with OGTT, 9% had diabetes and a further 34% had abnormal glucose tolerance, giving a total of 43% of 5–9 year olds with abnormal glucose handling (Austin et al, 1994).

CFRD audit

Using these guidelines and recommendations as a base, the diabetes and CF teams at Booth Hall Children's Hospital commenced a structured programme of screening for all CF children and young people over the age

PAGE POINTS

1 The OGTT may be used for the diagnosis of diabetes mellitus and is also the accepted screening test for CFRD.

2 It is recommended that the OGTT should be performed annually in children and adolescents with CF over the age of 10 years.

3 Ten to fifteen per cent of all people with CF will develop CFRD. The condition appears to present earlier in girls.

of 10 years by performing an annual OGTT.

We have currently performed 71 OGTTs on 96 children and adolescents over 10 years of age. The results were:

- 42 normal glucose tolerance
- 17 IGT
- 9 CFRD (plus 6 existing CFRD) = 15
- 3 inconclusive.

For the IGT and CFRD groups (26 patients), a period of 2 weeks' HGBM was commenced. Twelve patients from this group were started on insulin therapy.

Treatment

The goal of treatment in CFRD is to achieve optimal nutritional and clinical status, avoiding metabolic derangement, through maintenance of normoglycaemia.

Insulin is the treatment of choice when CFRD is diagnosed. The decision to treat with insulin is based on both clinical grounds and the glucose level detected by home or ward glucose monitoring. There is a range of different insulin regimens available, and the choice of regimen depends on the stage of the disease and specific treatment goals for the patient.

Definite indications for initiating treatment:

Frank CFRD or hyperglycaemia with:

- Polyuria and/or polydipsia
- Diabetic ketoacidosis (rare)
- Deteriorating clinical condition
- Weight loss or poor weight gain and growth failure in a child
- Symptomatic hyperglycaemia.

Treatment should be considered when:

- IGT on OGTT is associated with weight loss or deteriorating clinical condition
- Blood glucose levels are high.

Insulin glargine (Lantus) 0.1–0.3units/kg per day would appear to be suitable for children with IGT and some clinical concerns of weight loss and/or deteriorating lung function, as it appears to prevent postprandial hyperglycaemia without causing problematic hypoglycaemia.

In those with CFRD, insulin glargine with a short-acting insulin analogue is given before meals. Dosage is obviously tailored to the individual, with considerations given to overnight gastrostomy feeding and/or bolus pump feeds. Target blood glucose levels are 4–7 mmol/l before and 2 hours post meal, and 6–10 mmol/l before bedtime.

Children and young people with CFRD and/or IGT who are on insulin are asked to test their blood glucose levels 2–4 times a day. The IGT group not on insulin are requested to test only during periods of illness.

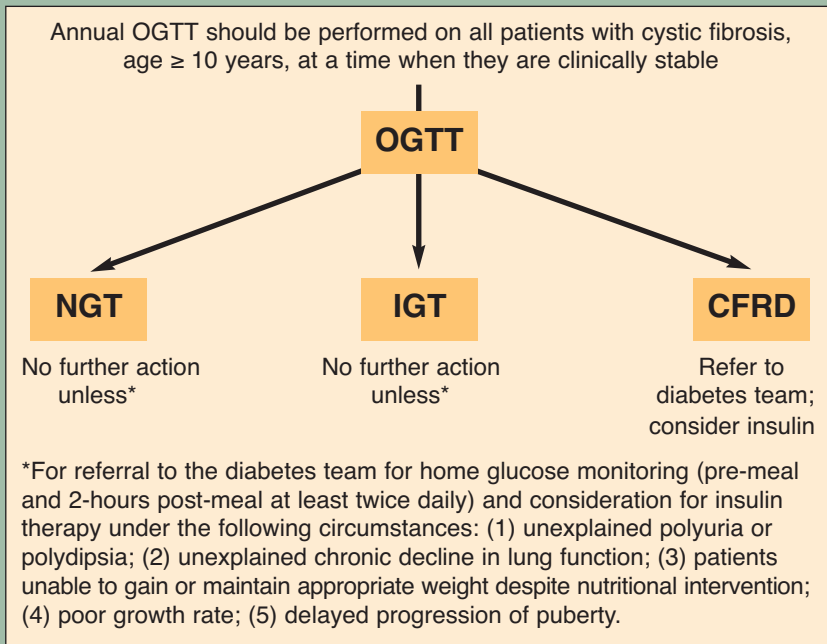


Figure 1. Procedure for annual OGTT screening for CFRD in cystic fibrosis. CFRD = cystic fibrosis related diabetes; IGT = impaired glucose tolerance; NGT = normal glucose tolerance; OGTT = oral glucose tolerance test.

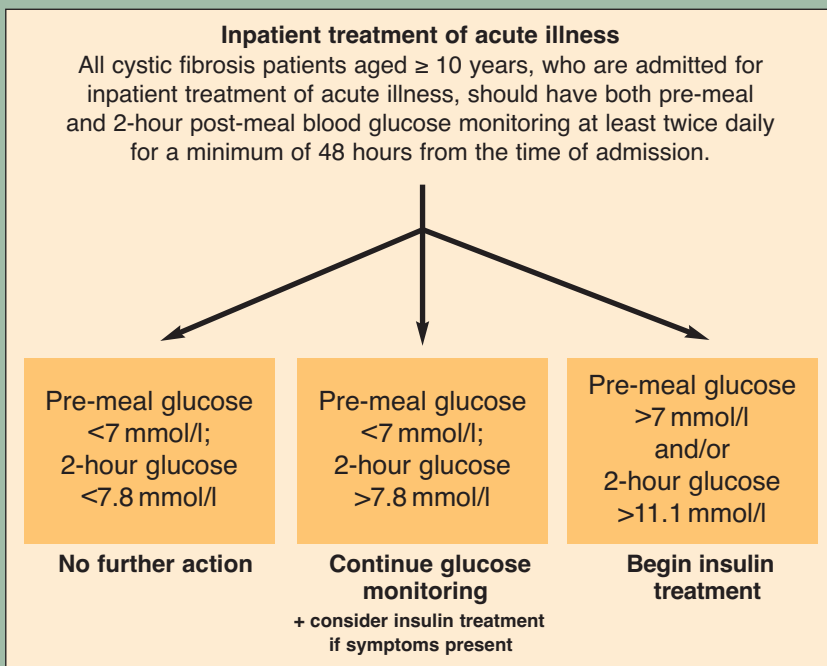


Figure 2. Procedure for routine screening for CFRD in the cystic fibrosis patient hospitalised for acute illness. CFRD = cystic fibrosis related diabetes; IGT = impaired glucose tolerance; NGT = normal glucose tolerance; OGTT = oral glucose tolerance test.

At present there are no data on the impact of specific insulin regimens on clinical status or HbA_{1c}.

Management of a CF patient with IGT

Decline in pulmonary function is well documented in CF patients with IGT. Studies comparing treatment strategies in individuals with IGT are under way. In many individuals who are asymptomatic, with stable weight, stable pulmonary function and a normal HbA_{1c}, treatment may not be indicated at this stage. In others, where weight loss is a problem or there is a persistent decline in pulmonary function, further treatment may be indicated.

There are no long-term studies examining the outcome of individuals with CFRD treated with insulin for IGT. If there are no other clinical concerns, no further action is required. Patients will require 6-monthly OGTTs.

Management of a CFRD patient with normal fasting glucose

CFRD patients with a normal fasting glucose will require referral to a diabetes team. They will be offered treatment if they are symptomatic, have a raised HbA_{1c} or decline in pulmonary function or weight less than target weight.

Management of a CFRD patient with a raised fasting glucose

Patients with predictable mealtimes and reliable food intake can sometimes be managed on twice-daily mixed insulin. Many people with CF have variable food intake due to loss of appetite, nausea, and the need to fit in other treatments especially in the mornings. Patients with variable food intake usually require a ‘basal bolus regimen’, in which a rapid-acting insulin is given with meals, and an intermediate or long-acting insulin at bedtime.

Table 2 summarises the guidelines for home glucose monitoring and insulin in individuals with cystic fibrosis.

Complications

All CFRD patients treated with insulin will require regular CF and diabetes clinic reviews, 3-monthly HbA_{1c} and an annual

diabetes assessment, including renal function, fasting cholesterol and triglyceride, early morning urine albumin: creatinine ratio, ophthalmology review, podiatry review and clinical examination (blood pressure, injection sites and pubertal staging).

Microvascular complications do occur in CFRD and are being reported with increasing frequency. Prevalence rates of 5–16% for retinopathy, 3–16% for nephropathy and 5–21% for neuropathy have been found (Rodman et al, 1986; Sullivan and Denning, 1989; Lanng et al, 1994; Moran et al, 1999).

Risk of macrovascular complications does not appear to be significant in CFRD. This may be explained by malabsorption of fat in CF. However, it is possible that CF patients have not survived long enough to develop these complications.

Implications for practice

The screening programme and subsequent identification and treatment of the 12 young people with CFRD has highlighted a number of profound and diverse issues.

Resources of time and money are finite, and the diabetes and CF teams are currently working to capacity. Yet if the present audit is to be used as a tool for future projection, we can assume that one in six CF patients will develop CFRD. This equates to a further three new patients this year, and an average annual CFRD population of three to four, newly diagnosed CFRD children and adolescents each year.

The logistics of appointing these patients into diabetes clinics is far from easy. The infective bacteria status of lung pathogens in CFRD patients means that these patients cannot mix with each other, precluding the setting up of a ‘CFRD clinic’ even if clinic time and manpower were available.

The present system of manually appointing these patients to general diabetes clinics and individually checking their pathogen status is time consuming and prone to difficulties.

Any hospital or trust considering their treatment and screening options for this group of patients would do well to negotiate and secure funding before commencing the new screening programme.

- 10–15% of all people with cystic fibrosis develop CFRD.
- In a Danish study of 278 patients aged over 2 years, 13.7% had impaired glucose tolerance test and 14.7% had CFRD. Prevalence of CFRD was 1.5%, 13%, and 50% in those aged 10, 20 and 30 years respectively (Lanng, 2001).
- In a US study of 371 patients the prevalence of CFRD was: 9% (5–9 years); 26% (10–19 years); 35% (20–30 years); 43% (30+ years) (Austin et al, 1994).

Figure 3. Prevalence of cystic fibrosis related diabetes (CFRD).

PAGE POINTS

1 There are no long-term studies examining the outcome of individuals with CFRD treated with insulin for IGT.

2 All CFRD patients treated with insulin will require regular CF and diabetes clinic reviews, 3-monthly HbA_{1c} and an annual diabetes assessment.

3 Any hospital or trust considering their treatment and screening options for CFRD patients would do well to negotiate and secure funding before commencing the new screening programme.

PAGE POINTS

1 There is clear evidence that early identification of CFRD impacts positively on health status.

2 The prevalence of CFRD increases with age and is an expected complication of CF as survival rates continue to increase.

3 CFRD patients should be screened for late diabetes complications annually as they are at risk of microvascular complications, and this risk increases with increasing survival.

Table 2. Glucose monitoring and insulin guidelines

Category	Home glucose monitoring	Insulin treatment
NGT	No (unless symptomatic)	No. Consider if symptomatic + high glucose values on home monitoring
IGT	No (unless symptomatic)	No. Consider if symptomatic + high glucose values on home monitoring Insulin regimen: once-daily insulin glargine
CFRD (without FH)	Yes 2–4 times daily	Yes if symptomatic + high glucose values on home monitoring Insulin regimen: once-daily insulin glargine, OR twice-daily premixed, OR basal bolus regimen
CFRD (with FH)	Yes 2–4 times daily	Yes. Insulin regimen: once-daily insulin glargine OR twice-daily premixed OR basal bolus regimen

FH = fasting hyperglycaemia; IGT = impaired glucose tolerance; NGT = normal glucose tolerance

Conclusion

- There is clear evidence that early identification of CFRD impacts positively on health status.
- The prevalence of CFRD increases with age and is an expected complication of CF as survival rates continue to increase.
- CFRD develops insidiously with few symptoms, and an unexplained decline in respiratory status may be the first sign. Patients with CFRD have excess mortality rate.
- The overall clinical status deteriorates 2–4 years before the development of CFRD. If patients are symptomatic, they should be offered early insulin therapy.
- The OGTT is an accepted screening test for CFRD, and all children with CF over 10 years of age should be screened annually.
- CFRD patients should be screened for late diabetes complications annually as they are at risk of microvascular complications, and this risk increases with increasing survival. ■

to poor lung function in patients with cystic fibrosis: data from the European Epidemiological Registry of Cystic Fibrosis. *Pediatric Pulmonology* **32**(5): 343–50

Lannig S, Thorsteinsson B, Erichsen G et al (1991) Glucose tolerance in cystic fibrosis. *Archives of Disease in Childhood* **66**: 612–16

Lannig S, Thorsteinsson B, Nerup J, Koch C (1992) Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. *European Journal of Pediatrics* **151**: 684–7

Lannig S, Thorsteinsson B, Lund-Andersen C et al (1994) Diabetes mellitus in Danish cystic fibrosis patients: prevalence and late diabetic complications. *Acta Paediatrica* **83**(1): 72–7

Lannig S, Hansen A, Thorsteinsson B et al (1995) Glucose tolerance in cystic fibrosis: a five-year prospective study. *British Medical Journal* **311**: 655–9

Milla CE, Warwick WJ, Moran A (2000) Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. *American Journal of Respiratory and Critical Care Medicine* **162**(3): 891–5

Moran A, Hardin D, Rodman D et al (1999) Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. *Diabetes Research and Clinical Practice* **45**(1):61–7

Nousia-Arvanitakis S, Galli-Tsinopoulou A, Karamouzis M (2001) Insulin improves clinical status of patients with cystic-fibrosis-related diabetes mellitus. *Acta Paediatrica*. **90**(5): 515–9

Rodman HM, Doershuk CF, Roland JM (1986) The interaction of two diseases: diabetes mellitus and cystic fibrosis. *Medicine (Baltimore)* **65**(6): 389–97

Rolan MA, Benali K, Munck A et al (2001) CFRD: clinical impact of pre-diabetes and effects of insulin therapy. *Acta Paediatrica* **90**(8): 860–7

Sullivan MM, Denning CR (1989) Diabetic micro-angiopathy in patients with cystic fibrosis. *Pediatrics* **84**(4): 642–7

Yung B, Kemp M, Hooper J, Hodson ME (1999) Diagnosis of cystic fibrosis related diabetes: a selective approach in performing the oral glucose tolerance test based on a combination of clinical and biochemical criteria. *Thorax*. **54**(1):40-3

World Health Organization (1999) *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus.* Report of a WHO Consultation. WHO, Geneva

Austin A, Kalhan SC, Orenstein D et al (1994) Roles of insulin resistance and beta-cell dysfunction in the pathogenesis of glucose intolerance in cystic fibrosis. *Clin Endocrinol Metab.* **79**(1):80–5

Cucinotta D, De Luca F, Scoglio R et al (1999) Factors affecting diabetes mellitus onset in CF. Evidence from a 10-year follow-up study. *Acta Paediatrica* **88**(4): 389–93

Finkelstein SM, Weilinski CL, Elliot GR et al (1988) Diabetes mellitus associated with cystic fibrosis. *Journal of Pediatrics* **112**: 373–7

Koch C, Rainisio M, Madessani U et al (2001) Presence of cystic fibrosis related diabetes mellitus is tightly linked