



CME article

Cystic fibrosis related diabetes

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EDUCATIONAL AIMS

- The reader will identify the diagnostic criteria for cystic fibrosis related diabetes [CFRD].
- To enable the reader to discuss the clinical course of CFRD.
- The reader will understand the prognostic consequences of CFRD.
- The reader will appreciate the current management recommendations for CFRD.

ARTICLE INFO

Keywords:

Cystic fibrosis related diabetes mellitus [CFRD]
pancreatic insufficiency
diagnosis
management and prognosis

SUMMARY

Diabetes is a frequent complication seen in cystic fibrosis patients as they reach adulthood. Cystic fibrosis related diabetes (CFRD) is distinguished as a separate entity with features that include progressive loss of islet beta cell mass and insulin deficiency, as well as insulin resistance. Abnormalities in glucose tolerance may be detectable for many years prior to the development of overt diabetes. Therefore oral glucose tolerance testing is the preferred screening method for the identification of those patients at the highest risk for progression to diabetes. Progression to diabetes has been linked to poor outcomes in CF including loss of pulmonary function and increased mortality among females. Given the role that insulin deficiency plays in CFRD, insulin replacement therapy remains the only recommended intervention. In the absence of definitive supportive data, the use of oral antidiabetic agents is not considered standard therapy and needs further study. As with other forms of diabetes, CFRD patients also experience microvascular complications and should be periodically evaluated for manifestations.

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INTRODUCTION

Cystic fibrosis (CF) is an inherited disorder occurring in almost every ethnic group, but with a higher incidence among Caucasians^{1,2}. Children with cystic fibrosis [CF] are increasingly being diagnosed by newborn screening programmes but may present with a variable spectrum of disorders that includes chronic respiratory symptoms, pancreatic insufficiency and malnutrition, high content of chloride in the sweat, and male infertility^{3–5}. Most of the morbidity and mortality of this progressive disease is related to its pulmonary manifestations, which are primarily due to chronic inflammation and infection of the airways, with episodic exacerbations and tissue destruction as a result of the inflammatory response⁶. The median life expectancy is by most recent estimates approaching 40 years^{7–9}. Thus, CF is not a disease of childhood anymore and there has become an expectation for patients to reach

adulthood. The increasing numbers of adults with CF has led to the increased recognition of the development of complications associated with aging with CF. Diabetes is one of these complications, with an estimated 13% of CF patients in the US being insulin dependent diabetics⁷.

Diabetes in cystic fibrosis patients has features of both type I and type II diabetes and to distinguish it as a separate entity it has been named Cystic Fibrosis Related Diabetes (CFRD)¹⁰. The primary determinant for the development of CFRD is insulin deficiency, a consequence of progressive loss of islet beta cell mass. However, glucose metabolism is strongly influenced by factors unique to CF, including poor nutrition, chronic and acute infection, elevated energy expenditure, glucagon deficiency, malabsorption, abnormal gastrointestinal transit time and liver dysfunction. These factors are not static, and glucose tolerance (GT) may fluctuate over time¹¹.

DIAGNOSIS

In the majority of patients with CF, the occurrence of GT abnormalities may not be recognized for a number of years prior to overt presentation of diabetes symptoms. Several studies have

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Table 1

Recommended categories of glucose tolerance for CF patients based on response to oral glucose tolerance testing

Condition	Fasting Plasma Glucose (mmol/L)	2 Hour Plasma Glucose (mmol/L)
Normal (NGT)	<7.0	<7.8
Impaired (IGT)	<7.0	7.8 – 11.1
CFRD without fasting hyperglycaemia (FH)	<7.0	>11.1
CFRD with FH	>7.0	OGTT not indicated

found a gradual deterioration in health outcomes prior to the presentation of diabetes^{12–14}. This would suggest the presence of a subclinical prediabetic state with detrimental consequences. Thus, it is of great importance to screen for abnormalities in glucose metabolism before the development of overt diabetes¹⁵.

Oral glucose tolerance testing (OGTT) is the recommended screening method for the detection of CFRD^{10,16}. Given that acute illness or stress may affect glucose metabolism, OGTT should be performed during periods of clinical stability¹⁰. Patients should be instructed to fast overnight and on the day of testing they should be given 1.75 g of anhydrous glucose per kilogram of body weight (to a maximum of 75 g) dissolved in 250–300 ml of water and consumed orally over 5 minutes. Blood samples are collected before and 2 hours after glucose ingestion. Patients are categorized based on their glucose values as shown in Table 1. Glycosylated haemoglobin (HbA_{1c}) is not considered an adequate screening test due to its poor sensitivity to the early stages of CFRD and is reserved as a monitoring tool for those patients already requiring therapy¹⁷. On the other hand, continuous glucose monitoring (CGM) seems to be more sensitive to the occurrence of glucose tolerance abnormalities^{18,19}. It has the advantage of offering a broader view of glycaemic status under a real life scenario as opposed to the artificial conditions implied by the OGTT. However, its use is limited at this point to clinical research given its cost and limited equipment availability, in addition to the lack of demonstrated interventions for the earliest stages of CFRD.

PATHOPHYSIOLOGY

Significant pancreatic involvement occurs early in life in approximately 85–90% of the individuals diagnosed with CF. The deficiency of CFTR function in the pancreatic ducts produces obstruction to pancreatic secretion flow. The resulting inspissation of pancreatic secretions produces acinar destruction. This induces

fibrosis and progressive adipose replacement of the pancreatic tissue. This destructive process eventually compromises the endocrine tissue with progressive loss of islets. Pancreatic tissue examined at autopsy demonstrates in addition to fibrosis and fatty infiltration, disruption of the islet architecture^{20,21}. The absolute number of pancreatic islets is diminished and their cellular composition is altered, with a significantly decreased percentage of beta cells²². Eventually with aging and disease progression, a diabetic state will insidiously develop. The primary defect noted in patients with CFRD is diminished, but not immeasurable, insulin secretion. First-phase insulin secretion in response to intravenous stimulation is markedly impaired in patients with cystic fibrosis with both impaired glucose tolerance and CFRD^{23–27}. Insulin response to oral glucose is delayed, and the peak insulin response is diminished in patients with CFRD²⁵. In addition, glucagon and pancreatic polypeptide secretion are also decreased in cystic fibrosis, a consequence of the destruction of entire islets rather than a beta cell-specific defect²⁷. Possibly, genetic factors associated with islet amyloid deposition²⁸ are also involved in the loss of functional islets.

Insulin resistance also plays an important role in the pathophysiology of glucose intolerance in CF. In addition to islet mass loss, the spectrum of glucose tolerance abnormalities seen in CF patients is also determined by the insulin sensitivity of the individual patient at a given point in time^{23,24,29–32}. During periods of health stability, insulin resistance in CF patients has been reported to be decreased^{29,30}, normal^{23,24,31}, or increased^{23,32}. This reported spectrum of insulin resistance in CF patients is likely related to differences in factors such as the age of the individuals, their nutritional status, the severity of their underlying pulmonary disease and the presence of varying degrees of chronic infection and inflammation. Consequently, glucose tolerance at the individual level is a dynamic and variable process where patients fall over time on a continuum ranging from normal tolerance, to increasingly severe intolerance, to diabetes without fasting hyperglycaemia (FH), and ending in diabetes with fasting hyperglycaemia³³. Where patients fall on this spectrum at any given point in time is determined by their insulin secretory capacity as well as by the degree of insulin resistance determined by their overall health status. However, most patients experience fluctuations in their course over time, coming in and out of more severe degrees of glucose intolerance depending on their overall health, medications (particularly systemic corticosteroids) and nutritional status. Thus, it is not unusual to encounter patients presenting with significant hyperglycaemia requiring insulin

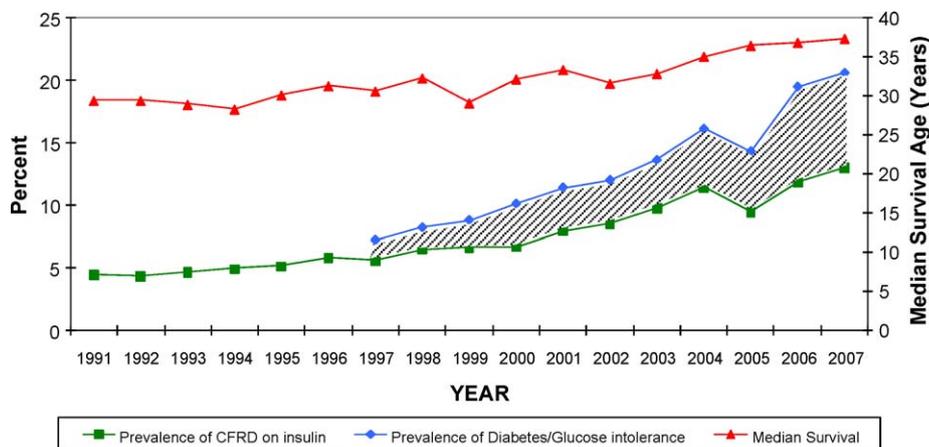


Figure 1. Secular trends in the prevalence of CFRD and median survival in the US CF patient population. From 1997 the prevalence of glucose intolerance in addition to diabetes have been tracked. The shaded area represents a growing number of individuals with abnormalities in glucose tolerance but are not receiving insulin therapy. (adapted from the US CF Foundation Patient Registry reports 1991 to 2007).

therapy transiently during pulmonary exacerbations. However, this need for insulin may not be apparent again for many years.

EPIDEMIOLOGY

It is clearly recognized that the risk for developing CFRD increases with age, primarily among those patients who are pancreatic insufficient³⁴. Data from registries and large centres indicate that as the life expectancy of CF patients continues to increase so does the prevalence of CFRD. This is likely due to a combination of larger numbers of adults and an increased recognition of CFRD in treatment centres. Fig. 1 demonstrates the secular trends noted in the US CF registry from 1991 to 2007. Prior to 1997 only the occurrence of diabetes with insulin dependence as a complication was reported. After 1997 a separate more inclusive category was added to include patients with glucose tolerance abnormalities. The data suggests a growing patient population sitting in a virtual 'gray zone' of abnormal glucose tolerance but not yet being considered ready to start therapy. In great part this is due to a lack of evidence as to the most effective and beneficial treatments for the patients without FH. Most recent estimates report the prevalence of CFRD on insulin therapy as 13% in the US⁷. Furthermore, life table analysis of the Copenhagen cohort suggests 70–90% of adults surviving to age 40 will develop diabetes.³⁵

SURVIVAL

Survival for patients with cystic fibrosis has substantially improved over the past decade. However, individuals with CFRD have a dramatically poorer prognosis particularly in the female population. In a large single centre study, the reported median survival age for patients with CFRD was 35.6 years which was significantly lower than the observed median survival age of 47.0 years in the non-CFRD patient population³⁶. Most of the difference in survival was explained by poorer survival in females with CFRD since males with CFRD had survival rates comparable to those seen in males and females without CFRD (Fig. 2). In addition, lung

function was demonstrated to be worse in females compared to their male cohorts at the time of diabetes diagnosis and this conferred them a higher risk of death³⁶.

Previous studies have clearly associated the presence of CFRD with shortened survival and increased morbidity. Finkelstein *et al.*¹² in a retrospective study of 448 patients reported a significantly shortened survival in CF patients with diabetes¹², with less than 25% surviving to age 30. In contrast, 60% of a control group of CF patients without diabetes survived to age 30. Clinical deterioration, as assessed by NIH score, was apparent 2 years before the diagnosis of diabetes was made¹². In addition, CF patients with diabetes are more likely to be malnourished and have significant pulmonary dysfunction than CF patients without diabetes^{14,37}. The reasons for these associations are not well understood but these studies raise the question as to whether a pre-diabetic state develops insidiously and per se contributes to clinical decline, or alternatively that the sickest patients are simply the most likely to develop diabetes. In Denmark, where annual glucose tolerance testing is performed, CF patients were found to have a significant decline in pulmonary function and weight up to 6 years before the diagnosis of diabetes¹³. Interestingly, these parameters not only improved but returned to levels seen 4 to 6 years earlier once therapy with insulin was instituted, suggesting a cause and effect relationship between insulin deficiency and clinical health decline³⁸.

Longitudinal studies have also demonstrated a direct relationship between abnormal glucose tolerance and deterioration in pulmonary function. In a prospective 4 year cohort of 152 CF patients categorized by their response to an OGTT the rate of decline in pulmonary function was found to be directly correlated with the degree of glucose intolerance at baseline³⁹. At the beginning of the study, the groups did not differ significantly in age, weight, pulmonary function or bacterial colonization. Subjects with normal GT experienced no decline in the percent predicted forced expiratory volume in 1 second (FEV₁), while those with impaired GT experienced a significant decline and those with CFRD without FH experienced the greatest rate of decline. Importantly, the rate of pulmonary decline was inversely related to the

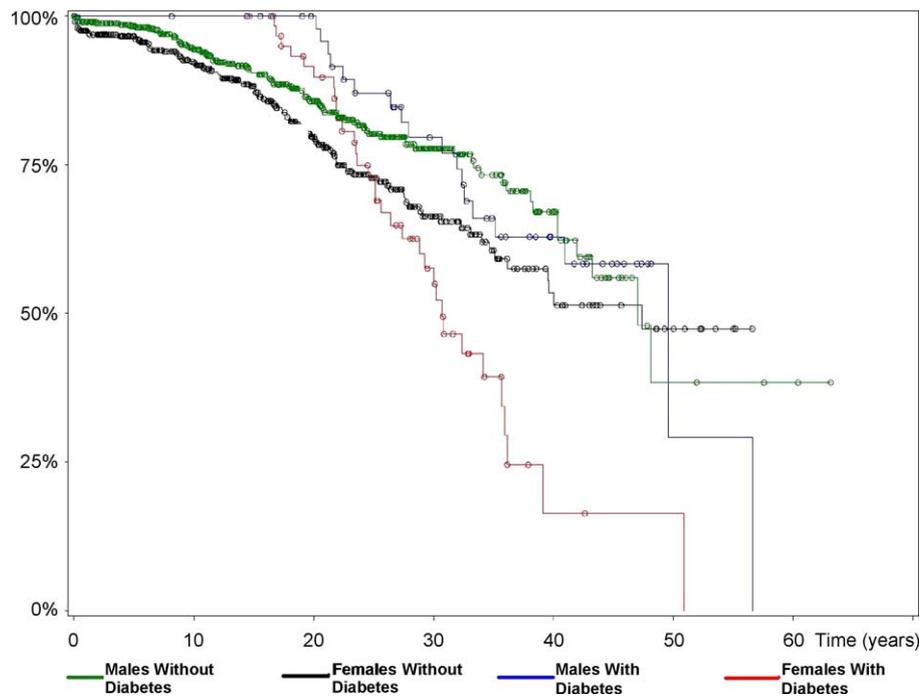


Figure 2. Survival distribution by gender and diabetes status in a large cohort of CF patients from a single centre. A marked decrease in survival was only apparent for females with diabetes. (adapted from Milla *et al.*³⁶).

magnitude of insulin secretion at baseline, suggesting a relationship between insulin deficiency and clinical deterioration. In addition, the degree of insulin deficiency as assessed by the 2 hour Insulin AUC during the baseline OGTT was strongly correlated with the higher rates of decline. Since subjects at baseline were no different in terms of pulmonary function and nutritional status, these data strongly support the concept that the insulin deficient state by itself leads to health decline and detrimental pulmonary outcomes.

The mechanism behind the deleterious effects of impaired glucose tolerance is not entirely clear from the published studies. One mechanism by which insulin deficiency might impact pulmonary function in CF patients is by adversely affecting nutrition as it may promote a catabolic state. Insulin is a potent anabolic hormone and its absence is clearly associated with protein catabolism. CF patients have been shown to have chronically elevated rates of protein catabolism as demonstrated by 13-C leucine kinetics, 3-methylhistidine excretion, and urinary nitrogen balance studies^{40–45}. Poor insulin-induced suppression of protein catabolism has been found in CF, and the severity of protein catabolism is related to the severity of illness^{45,46}. Negative protein balance may contribute to morbidity and mortality in CF since FEV₁ correlates with lean body mass⁴⁷, and reversal of protein catabolism stabilizes pulmonary function and decreases the number of hospitalizations for acute pulmonary exacerbations⁴⁸. Damaging endobronchial proteolytic enzyme activity and oxidant species burden, well known to be present in CF patients^{49–51} even at the very early stages of the disease^{52,53}, have been clearly shown to correlate with lung dysfunction⁵⁴. The inability to counter-balance this process accelerates the progression of the lung damage⁶. Nutrition is probably involved in the maintenance of adequate anti-proteolytic and anti-oxidant protection mechanisms, with the presence of an anabolic state playing a key role in the ability to maintain a positive balance. Thus, the insulin deficient state in CF patients may impair the ability to maintain an adequate balance and determine significant lung destruction from endobronchial enzymatic activity and unopposed oxidant injury. In addition, it has already been demonstrated that glucose is maintained at low concentrations in the airway surface and in the presence of hyperglycaemia the glucose concentration becomes abnormally high⁵⁵. This has been correlated with the presence of infection in intubated patients⁵⁶. Potentially this could also contribute to lung disease in CFRD patients, were high glucose levels have been reported in nasal secretions, as a surrogate of the airway surface⁵⁷.

MANAGEMENT

The general principles of management for patients with CFRD are similar to those for patients with types I or II diabetes: maintain adequate glucose control, avoiding the occurrence of hypoglycaemia^{10,16,58}. Additionally for patients with CFRD achieving adequate nutritional status, as well as growth in children, is of great importance given the effects of nutrition on long term pulmonary health. Thus, dietary restrictions are not recommended and the glucose control regimen has to be titrated to allow for an unrestricted caloric intake. Since insulin deficiency is one of the key pathophysiologic features of CFRD, insulin is the currently recommended standard treatment for the glucose control of the CFRD patient with FH¹⁰. Although there is a lack of randomized trials supporting this recommendation, previous small observational studies suggest that aggressive insulin therapy for CFRD might have a beneficial effect on CF pulmonary disease. Lannig *et al.*³¹ reported that two years of insulin therapy restored weight and pulmonary function to levels seen years before the onset of overt diabetes in 18 CF patients³⁸. In addition, it has also been

demonstrated that protein catabolism in CF is normalized if high enough insulin levels are achieved (100 μ U/ml)⁴⁵. Thus, insulin treatment may be effective in breaking the cycle of protein catabolism present in these patients because of the potent anabolic effects of insulin on muscle mass. Insulin deficiency caused by diabetes mellitus is associated with protein catabolism and reduced muscle mass^{59–61}, and acute and chronic administration of insulin in diabetic humans and animals reduces protein breakdown^{60,62}. Previous small observational studies suggest that aggressive insulin therapy for CFRD might have a beneficial effect on CF pulmonary disease. In Denmark, two years of insulin therapy restored weight and pulmonary function to levels seen years before the onset of overt diabetes in 18 CF patients. The most commonly accepted strategy for the insulin management of CFRD patients is with the use of a flexible scheme with pre-meal short-acting insulin and dosing based on the carbohydrate content of the meal¹⁰. Thus, patients with CFRD should be managed in an interdisciplinary team setting at an accredited CF Centre. Patients and families are taught carbohydrate counting and their insulin dose is determined by a fixed ratio to the carbohydrate intake. This ratio is adjusted based on response and frequently needs to be titrated during periods of disease exacerbation, even more if patients require treatment with corticosteroids⁵⁸.

Registries data indicates that some CFRD patients are being managed with oral hypoglycaemic agents^{7,37,63}. However, the use of oral agents is at this point not recommended due to lack of sufficient evidence supporting their use. Sulfonylureas have been tried in CFRD patients but minimal improvement, if any, was found^{64–66}. In addition, most of the oral diabetes agents available have features that will make them potentially problematic in CF patients due to their side effect profile. Of all of the currently available oral agents, the meglitinide analogs such as repaglinide and nateglinide appear to hold some promise in CF. These are non-sulfonylurea insulinotropic agents that lower blood glucose levels by interacting with the ATP-sensitive potassium channel on pancreatic beta cells inducing insulin secretion⁶⁷. This effect diminishes at low glucose concentrations. This, combined with a short half-life promotes improvement of meal-stimulated insulin secretion and minimizes the chances of hypoglycaemic episodes. One previous small study on the acute effects of repaglinide suggested that these class of drugs may have therapeutic potential in CFRD⁶⁸. Nonetheless its effects on glucose and insulin excursion were significantly lower than those seen with the short acting insulin lispro. Certainly more research is needed in this area, but the use of oral agents at this point should be considered only within the clinical research context⁵⁸.

The management of CFRD patients without FH is more controversial. These patients certainly need frequent monitoring including the use of blood glucose monitoring at home. Case series reports and small studies point towards a benefit of starting early insulin therapy with small doses^{69,70}. However, in some of these patients the diabetic condition is temporary and often related to their overall health status with great fluctuations over time. Then, a recommendation for long term insulin therapy is difficult to justify. Certainly more studies are needed in this area given the potential implications for long term preservation of pulmonary health. A large, long term, multi-centre study to more formally evaluate the benefits of chronic insulin therapy in the management of CFRD has recently been completed in the US and Canada⁷¹. The results of this study are much anticipated and hopefully they will shed some light into this controversial topic.

COMPLICATIONS

In addition to the deleterious effects of CFRD on pulmonary outcomes and survival there is now emerging evidence for the

occurrence of microvascular complications in association with CFRD. Three recent large studies^{72–74} describe a prevalence of microalbuminuria ranging from 10% to 21%, retinopathy from 10% to 36% and neuropathy from 2.9% to 17%. However, the patient populations in these studies were not directly comparable given that one study excluded post transplant patients and there were variable degrees of CFRD duration. Still, the data in these studies suggests that patients with CFRD are at risk for microvascular complications at rates comparable to those seen in patients with type 1 diabetes and that these risk seems to be associated also with the duration of CFRD. Gastrointestinal manifestations of autonomic neuropathy such as delayed gastric emptying, diarrhoea and constipation have also been described in CFRD⁷³. As opposed to type 2 diabetes, macrovascular complications have not been reported in association with CFRD.

RESEARCH DIRECTIONS

- More studies are needed in CFRD with fasting hyperglycaemia and the implications for pulmonary health.
- The role of oral agents in the management of CFRD needs to be better defined through randomized clinical trials.
- Risk factors and genetics for developing CFRD need further study.

PRACTICE POINTS

- Diagnosis of CFRD is made by oral glucose tolerance testing (OGTT).
- The risk of developing CFRD increases with age and pancreatic insufficiency.
- The presence of CFRD is associated with shortened survival and worse lung function.
- Insulin deficiency is a key feature in CFRD.

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Educational questions

Answer true or false to the following questions:

1. The primary defect in patients with CFRD is
 - a. Genetic factors associated with islet amyloid deposition
 - b. Increased glucagon secretion.
 - c. Decreased insulin secretion.
 - d. Irregularities in beta cell function.
 - e. Liver dysfunction.
2. Key features in the management for CFRD include
 - a. weight reduction
 - b. dietary restrictions
 - c. oral hypoglycaemic agents
 - d. insulin therapy
 - e. all of the above
3. Recommended screening methods for CFRD include
 - a. continuous glucose monitoring
 - b. oral glucose tolerance testing (OGTT)
 - c. random blood glucose monitoring
 - d. glycosylated haemoglobin (HbA_{1c})
 - e. fasting blood glucose
4. Complications of CFRD include
 - a. coronary artery disease
 - b. retinopathy
 - c. constipation
 - d. foot ulcers
 - e. ketoacidosis
5. Epidemiologic aspects of CFRD include
 - a. associated with decreased survival
 - b. variable prevalence with age
 - c. increased pancreatic complications
 - d. no gender differential in outcomes
 - e. all of the above