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Management of cystic fibrosis-related diabetes

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Cystic fibrosis (CF) is the most common lethal genetic autosomal recessive disease in Caucasians, with a worldwide prevalence of 1 in 2500 live births. Cystic fibrosis-related diabetes (CFRD) has emerged as the most common co-morbidity in CF (1, 2). There are important differences between CFRD and both type 1 diabetes (T1D) and type 2 diabetes (T2D), which necessitate a unique approach to diagnosis and management (Table 1).

Definitions

Modified oral glucose tolerance test (OGTT) categories have been developed by the 1998 North American CFRD Consensus Committee in reporting CFRD *with* and *without* fasting hyperglycemia [fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) or < 7 mmol/L; and 2-h plasma glucose ≥ 11.1 mmol/L (200 mg/dL)] based on the suggestion that the prognosis may differ between these two groups in CF (2) (E). CFRD falls at one end of a spectrum of progressive glucose tolerance abnormalities. Few CF patients have completely normal blood glucose levels at all times. The earliest change is variable, intermittent postprandial hyperglycemia, followed by impaired glucose tolerance (IGT), then diabetes without fasting hyperglycemia, and diabetes with fasting hyperglycemia. A diagnosis of ‘normal’ glucose tolerance on oral glucose tolerance testing does not exclude abnormal postprandial glucose levels at

home (when far more than 75 g of carbohydrate may be consumed) (2) (B).

Assigning a specific diagnostic category to CF patients is complicated by the fact that glucose tolerance and insulin resistance are often variable in an individual subject. Factors specific to CF that cause fluctuations in glucose metabolism include: respiratory infection and inflammation, increased energy expenditure, malnutrition, glucagon deficiency, and gastrointestinal abnormalities (malabsorption, altered gastric emptying and intestinal motility and liver disease).

Prevalence

The reported prevalence of CFRD varies depending on the screening and diagnostic criteria utilized. The prevalence may be underestimated at centers where universal screening is not undertaken. While it can occur at any age, CFRD prevalence increases with age: 9% of 5–9 yr olds, 26% of 10–20 yr olds [Minnesota (3)] (Fig. 1) and 50% by 30 yr [Denmark (4)]. Repeated OGTTs have shown that glucose tolerance status can vary from year to year in CF patients (5) (B).

Pathophysiology of CFRD

Genetics of CFRD and relation to the CF mutation

CFRD mainly occurs in people with the most severe CF mutations, all of which are associated with

Table 1. A comparison of T1D, T2D, and CFRD

	T1D	T2D	CFRD
Onset	Acute	Insidious	Insidious
Peak age of onset	Children and adolescents	Adults	18–24 yr
Antibody (+)	Yes	No	Probably no
Insulin secretion	Eventually absent	Decreased	Severely decreased but not absent
Insulin sensitivity	Somewhat decreased	Severely decreased	Somewhat decreased*
Treatment	Insulin	Diet, oral medications, and insulin	Insulin
Microvascular complications	Yes	Yes	Yes but less
Macrovascular complications	Yes	Yes	No
Cause of death	Cardiovascular disease, nephropathy	Cardiovascular disease	Pulmonary disease

CFRD, cystic fibrosis-related diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes.

*Insulin sensitivity becomes severely decreased during acute illness.

exocrine pancreatic insufficiency (6–8) (C). There is no correlation with known T1D susceptibility genes, such as human leukocyte antigen class II (4) (B) or insulin variable number of tandem repeats (VNTR) (6) (C), but a possible link has been described between CFRD and T1D susceptibility genes associated with inflammation, such as tumor necrosis factor (4) (B) and heat shock protein (4, 9) (B, C), and T2D susceptibility genes, such as calpain10 (10) (C).

Pancreatic pathology

Abnormal chloride channel function in CF results in thick viscous secretions causing obstructive damage to the exocrine pancreas with progressive fibrosis and fatty

infiltration. This results in disruption and destruction of islet architecture leading to loss of endocrine beta, alpha, and pancreatic polypeptide cells (11–13) (B). Beta-cell dysfunction is not related to autoimmune disease in CF, outside of isolated case reports of autoantibody positive individuals with CFRD (14).

The role of insulin deficiency

The primary defect in CFRD is severe but not absolute insulin deficiency. Virtually, all exocrine insufficient patients with CF, with and without diabetes, show evidence of beta-cell dysfunction (5, 15–17) (A)). Fasting insulin and C-peptide concentrations are normal, but there is delay and blunting of peak insulin secretion during a standard OGTT (18) (B). This effect is more pronounced with worsening glycemic status (18–21) (B, C). Delayed insulin secretion during the OGTT is related to loss of first-phase insulin secretion, which is found even in CF patients with normal glucose tolerance(22) (B). Secretion of other islet hormones is also impaired in CF, in particular loss of glucagon responses (18, 22) (B).

The role of insulin resistance

In CF patients without diabetes, insulin sensitivity is variable (21, 23–26) (B) (17, 27) (B). While most of these patients are sensitive to insulin in their baseline state of

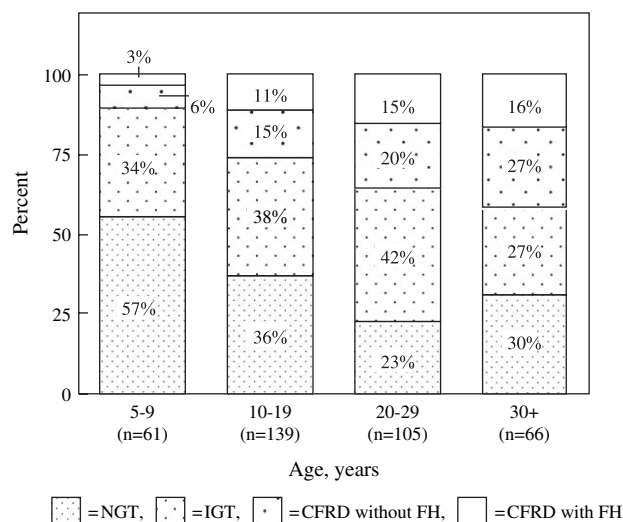


Fig. 1. Glucose tolerance categories in cystic fibrosis patients at the University of Minnesota, expressed as percent prevalence within age groups. n = total number of patients studied within that age group [from reference (3)]. CFRD, cystic fibrosis-related diabetes; FH, fasting hyperglycemia; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Table 2. Clinical symptoms that may indicate the presence of cystic fibrosis-related diabetes (2) (E)

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

health, infection and inflammation increase insulin resistance (28) (B). CF patients with diabetes are insulin resistant because of both decreased peripheral glucose uptake and poor insulin suppression of hepatic glucose production (26, 27) (B). Insulin resistance can become acutely severe during infectious exacerbations (E).

Clinical features of CFRD

CFRD develops insidiously and patients may be asymptomatic for years. Symptoms of CFRD are listed in Table 2. Diabetic ketoacidosis is rare, most likely because of the persistence of endogenous insulin secretion or because glucagon secretion is also impaired (22, 29, 30) (B). CFRD often first presents during situations where insulin resistance is increased, such as acute pulmonary infection, chronic severe lung disease, glucocorticoid therapy, high-carbohydrate food supplementation (oral, intravenous, nasogastric, or percutaneous gastrostomy tubes), and in association with immunosuppressive regimens following transplantation. The incidence of CFRD is higher in those with CF liver disease (31) (C). Hypoglycemia is more common and more concerning in CF patients with liver disease. In the absence of liver disease, fasting hypoglycemia is generally only seen in malnourished patients and the very young. Reactive hypoglycemia may occur in CF patients with IGT and may be helped by spreading carbohydrate intake more evenly during the day (E).

Survival and prognosis

Increased mortality in CFRD

The presence of CFRD is associated with worse lung function, poorer nutritional status, and decreased survival compared with non-diabetic CF patients (31–38) (A–C). One retrospective analysis of 448 CF patients, followed for 10 yr, demonstrated 25% survival with CFRD at 30 yr compared with 60% of those without CFRD (32) (C). Recently, a marked gender difference in survival in CFRD has been documented with median survival of 47–49 yr for male subjects in comparison with only 31 yr for female subjects (39) (B). This survival gender difference was not seen, however, in a recent 17-yr prospective cohort of 237 French children with CF (29) (B).

Increased morbidity in the prediabetes state

An insidious decline in clinical status can occur 2–6 yr before the diagnosis of CFRD (32, 34–37) (B). Pulmonary deterioration correlated with the degree of insulin deficiency at baseline (40). There is a known association between protein catabolism, malnutrition, and death in CF. The potent anabolic role of insulin (i.e., the nutritional impact and metabolic effects rela-

ting to insulin deficiency) may be of greater consequence in CF than the metabolic impact of hyperglycemia (E).

Microvascular complications

Microvascular complications have been described in CFRD patients, sometimes with significant morbidity (40–42) (C). A Danish study has reported a 36% incidence of retinopathy in patients with CFRD for more than 10-yr duration (43) (B). Another larger series of CFRD patients with fasting hyperglycemia found, microalbuminuria in 14%, retinopathy in 16%, neuropathy in 55%, and gastropathy in 50% after 10-yr duration. Microvascular complications were rare before 10-yr duration of CFRD with fasting hyperglycemia. No microvascular complications were found in CFRD patients without fasting hyperglycemia for up to 14-yr duration (44). Macrovascular complications have not been reported in CFRD to date.

Testing for CFRD

It is important to identify patients before the onset of symptoms as CFRD often has an insidious onset. The following methods of testing for CFRD have been considered: hemoglobin A1c (HbA1c), OGTT, random or fasting glucose levels, and continuous glucose monitoring (CGM).

HbA1c as a diagnostic tool

HbA1c has been shown to be unreliable in the diagnosis of CFRD (5, 19, 32, 45) (B). HbA1c is often normal, regardless of the degree of hyperglycemia, with only 16% of CF patients having elevated HbA1c values at the time of diabetes diagnosis (5) (B).

Oral glucose tolerance testing

The OGTT is the standard test for CFRD in many centers (5) (A) (46) (E). Diabetes without fasting hyperglycemia can only be detected by OGTT. Measuring insulin concentrations every half hour during the OGTT may be clinically useful to assess the degree of insulin deficiency (E).

Random and fasting glucose levels for CFRD diagnosis

While hyperglycemia is diagnostic for diabetes, normal fasting or random glucose levels do not exclude a diagnosis of diabetes in CF (A).

Continuous glucose monitoring

In the research setting, CGM can detect abnormal glucose tolerance earlier than the OGTT, but the clinical significance is still under investigation. CGM

has been validated for use in children and adolescents with CF (47–50). CGM may aid the diagnosis of CFRD when considered in conjunction with the OGTT result and the clinical scenario (16, 48, 49) (C).

Clinical suspicion of CFRD

If the OGTT result is normal or borderline abnormal and diabetes is suspected based on clinical symptoms, a period of home glucose monitoring (preprandial and 2-h postprandial and in the middle of an overnight tube feeding) or CGM may provide additional useful information (E).

Treatment of CFRD

Medical nutritional therapy

A high-calorie, high-fat diet is important in CF (51) (A). Caloric restriction is thus contraindicated. Table 3 compares the CFRD with the standard diabetes diets.

Insulin therapy

Insulin is the only recommended medical therapy for CFRD (2) (E). Insulin therapy may help stabilize lung function and improves nutritional status in patients with CFRD (34, 36, 37, 52) (C). There are no definitive data to date on the benefits of insulin therapy for CF children and adolescents with milder forms of abnormal glucose tolerance, although a small case series has demonstrated similar benefit (16, 53) (C).

Choice of the insulin regimen depends on individual needs and characteristics of the patient. The standard basal bolus regimen provides background insulin and a continuous anabolic effect. The short-acting insulin controls postprandial hyperglycemic episodes and provides flexibility for variable eating patterns (54) (B). Alternatively, effective basal–bolus therapy can be accomplished with insulin pump therapy (55, 56) (E).

Twice daily isophane with or without short-acting insulin can be used but may not be optimum therapy to

allow for meal flexibility because of nausea or anorexia or other treatment requirements especially in the morning. The current medical treatment program of the patient, and compliance history, should be evaluated when deciding on an insulin regimen.

For patients on enteral nighttime feeds, more insulin will be required at night. Monitoring of blood glucose during the feed is recommended, so the dosage can be appropriately adjusted (Table 4).

Oral diabetes agents

Oral diabetes agents are currently not recommended in CFRD (2) (E). A recent Cochrane review has highlighted the lack of randomized controlled trials (57) (A). The insulin secretagogue repaglinide increased endogenous insulin levels but was less effective than rapid-acting insulin in regulating postprandial hyperglycemia in an experimental setting (58) (B). There are concerns about hypoglycemia with sulfonylureas in patients with CF (59) (B, E). Agents that reduce insulin resistance are unlikely to be effective as a single therapy in CFRD because insulin resistance is not the major etiological factor. The gastrointestinal side effects of metformin such as nausea, diarrhea, and abdominal discomfort are unacceptable to most people with CF (60) (C). Thiazolidinediones have recently been associated with osteoporosis. The decreased gastric emptying because of incretins limits their utility in CF.

CFRD without fasting hyperglycemia and CF with IGT

While treatment of CFRD with fasting hyperglycemia is accepted practice, the treatment of CFRD without fasting hyperglycemia and CF with IGT and/or intermittent hyperglycemia is more controversial because of the limited data available. A current multicenter randomized study is investigating the role of different agents in these situations and may clarify management in the future (E).

Table 3. Differences in the dietary management of T1D and T2D versus CFRD

	T1D and T2D	CFRD
Calories	≤100% of normal caloric intake for age and gender – often have to watch or restrict calories to prevent overweight	Usually require 120–150% (or more) of normal caloric intake for age and gender to prevent underweight
Fat	30–35% of total energy	40% of total energy
Refined sugars	Up to 10% of total energy	No restriction
Carbohydrate	50–55% total energy	45–50% of total energy
Dietary fiber	Encouraged because of beneficial effects (age in years + 5 g/d)	Encouraged in the well nourished, but in poorly nourished patients, it may compromise energy intake
Protein	10–15% of total energy; not >1 g/kg body weight	200% of reference nutrient intake
Salt	Low intake ≤6 g/d	Increased requirement – unrestricted intake

CFRD, cystic fibrosis-related diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes.

Table 4. General principles of insulin therapy in cystic fibrosis-related diabetes

Meal coverage	A common starting dose is 0.5–1 IU rapid-acting insulin for every 15 g of carbohydrate consumed. Insulin pens or syringes that deliver half units may be needed The dose is adjusted by increments of 0.5 IU per 15 g carbohydrate to achieve 2-h postprandial blood glucose goals For very young patients or those who are unsure of what they will eat because of nausea or gastroparesis, the dose can be given right after the meal
Correction dose	Premeal correction can be started at 1 IU rapid-acting insulin for every 2.8 mmol/L (50 mg/dL) above 8.3 mmol/L (150 mg/dL) and adjusted as needed
Basal insulin	Basal insulin can be started at 0.25 IU/kg body weight per 24 h, and adjusted based on the fasting glucose level
Coverage of overnight drip feeding	Frequently a single dose of isophane plus regular insulin will cover an overnight drip feeding. The regular insulin covers the first 4 h and the isophane the second 4 h. Glucose levels 4 h into the feeding and at the end of the feeding are used to adjust the insulin dose

Inpatient management of CFRD

During an acute illness, CF children and adolescents are at increased risk of developing hyperglycemia (2) (E). While data from other populations suggest that intensive insulin therapy may be beneficial in this setting, no studies have examined the benefits of maintaining euglycemia in hospitalized CF patients. Insulin requirements may be large during acute illness: up to four times the usual baseline insulin dosage needed in some CFRD patients (E). The insulin dose must be aggressively reduced as the patient improves to avoid hypoglycemia, and in many CF patients, blood glucose levels return to normal after the illness resolves (2) (E).

Recommendations

Diagnostic criteria for CFRD

- CF with and without hyperglycemia have different prognoses (A).
- It is important to recognize that glucose tolerance diagnostic categories are relative rather than absolute markers of risk in CF. Glucose tolerance fluctuates with overall health status in CF.

Testing for CFRD

- Routine annual testing for diabetes should be performed in CF patients aged 10 yr and older during a time when they are clinically well (in their baseline state of health) (E).
- The 2-h OGTT is the preferred test for routine screening (E).
- Circumstances when extra glucose monitoring is recommended include:
 - Development of diabetes symptoms as listed in Table 2.
 - During infective exacerbations.
 - During systemic corticosteroid treatment.
 - After commencing supplemental enteral tube feeding.

- Before and after major surgery.
- Symptoms of hypoglycemia.
- Pregnancy requires special consideration (61) (C).

Treatment of CFRD

The decision to treat should be based on consideration of blood glucose levels and the impact of treatment on the individual’s overall condition.

CFRD with fasting hyperglycemia

- Insulin is the recommended therapy (B). The insulin regimen should be tailored to the patient’s individual needs, but in general, must be flexible enough to accommodate wide daily variation in carbohydrate timing and quantity and must take into account changing insulin requirements such as during acute illness, glucocorticoid therapy, pregnancy, or intensive enteral or parenteral nutrition (A).
- Oral agents are not recommended because of lack of efficacy data as well as concerns about potential side effects.
- The high-calorie, high-fat diet used to maintain nutritional status should continue (A). The insulin dose needs to be adjusted to match carbohydrate intake (E).
- Treatment aims are to eradicate symptoms of hyperglycemia/hypoglycemia and maintain adequate nutrition, growth, and respiratory function (A).
- Good communication between the CF pulmonary and endocrinology teams is essential. Clear roles, responsibilities and treatment aims are important, particularly at times of intercurrent illness and during admissions to the hospital (E).
- Management requires significant input from the patient or caregiver. The health-care team plays a critical role in educating, supporting, advising, and motivating the patient and family (A).
- CGM has been validated and provides additional useful information in children in CF (C).

- Patients should be screened annually for microvascular complications (B).

CFRD without fasting hyperglycemia and CF with IGT

- Currently, insulin therapy is not universally recommended unless the individual patient demonstrates persisting signs of poor growth, inability to maintain weight, unexpected decline in pulmonary function, despite optimization of other medical management, or develops overt signs of diabetes (E). Some patients may require insulin during times of increased insulin resistance (B).
- Patients with IGT and patients with CFRD without fasting hyperglycemia are at significant risk of progression to CFRD with fasting hyperglycemia and should be monitored with annual OGTTs (B).
- More intensive monitoring of blood glucose (preprandially and 2-h postprandially or CGM) should be performed during periods of increased stress, such as acute pulmonary exacerbations (E).

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