

ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Management of cystic fibrosis-related diabetes in children and adolescents

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Cystic fibrosis-related diabetes (CFRD) is the most common co-morbidity associated with cystic fibrosis (CF).
- The pathophysiology of CFRD is complex and includes the loss of pancreatic islet cells leading to both insulin and glucagon deficiency, fluctuating insulin resistance, the requirement for high caloric intake, gut abnormalities including delayed gastric emptying, altered intestinal motility, and liver disease.
- CFRD can occur at any age, including infancy, and its prevalence increases as patients get older.
- Few individuals with CF have normal glucose tolerance and even when the fasting and 2-h oral glucose tolerance test (OGTT) glucose levels are normal, variable, intermittent post-prandial hyperglycemia can often be detected by continuous glucose monitoring (CGM).
- CF is associated with a progressive deterioration in glucose tolerance as individuals grow older, including indeterminate glycemia followed by impaired glucose tolerance (IGT) and finally diabetes.
- Early CFRD is characterized by normal fasting glucose levels, but over time fasting hyperglycemia develops. At any particular time blood glucose levels can vary, dependent upon acute changes in pulmonary and infectious status.
- The majority of patients have no obvious symptoms at diagnosis, although symptoms may develop insidiously. Presentation with CFRD is more likely during times when insulin resistance is increased (e.g. pulmonary infection, use of glucocorticoid agents).
- Presentation with Diabetic ketoacidosis (DKA) is rare.
- The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates. [E, Consensus]
- During a period of stable baseline health the diagnosis of CFRD can be made in CF patients according to standard American Diabetes Association (ADA) criteria. [E, Consensus]
- The diagnosis of CFRD can be made in CF patients with acute illness when fasting plasma glucose (FPG) levels ≥ 126 mg/dL (7.0 mmol/L) or 2-h post-prandial

- plasma glucose levels ≥ 200 mg/dL (11.1 mmol/L) persist for more than 48 h. [E, Consensus]
- CF patients with gestational diabetes are not considered to have CFRD, but require CFRD screening 6–12 wk after the end of the pregnancy. [E, Consensus]
 - Distinguishing between CFRD with and without fasting hyperglycemia is not necessary. [B]
 - The use of hemoglobin A1c (HbA1c) as a screening test for CFRD is not recommended. [B]
 - Screening for CFRD should be performed using the 2-h 75 g (1.75 g/kg) OGTT. [E, Consensus]
 - Annual screening for CFRD should begin by age 10 yr in all CF patients who do not have CFRD. [B]
 - Patients with CFRD should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF. [E, Consensus]
 - Patients with CFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards. [E, Consensus]
 - CF patients with CFRD should be treated with insulin therapy. [A]
 - Oral diabetes agents are not as effective as insulin in improving nutritional and metabolic outcomes in CFRD, and are not recommended outside the context of clinical research trials. [A]
 - Patients with CFRD who are on insulin should perform self-monitoring of blood glucose at least three times a day. [E, Consensus]
 - Patients with CFRD should strive to attain plasma glucose goals as per the ADA recommendations for all people with diabetes, bearing in mind that higher or lower goals may be indicated for some patients, and that individualization is important. [E, Consensus]
 - HbA1c measurement is recommended quarterly for patients with CFRD to guide insulin therapy decisions. [E, Consensus]
 - CF Foundation evidence-based guidelines for nutritional management of all persons with CF are recommended for patients with CFRD. [E, Consensus]
 - Education about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon, is recommended for patients with CFRD and their care partners. [E, Consensus]
 - Annual monitoring for microvascular complications of diabetes is recommended, beginning 5 yr after the diagnosis of CFRD or, if the exact time of diagnosis is not known, at the time that fasting hyperglycemia is first diagnosed. [E, Consensus]
 - Patients with CFRD diagnosed with hypertension or microvascular complications should receive usual treatment, except that there is no restriction of

sodium and, in general, no protein restriction. [E, Consensus]

- An annual lipid profile is recommended for patients with CFRD and pancreatic exocrine sufficiency [E, Consensus]

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) is the most common co-morbidity in CF. There are important pathophysiologic differences between CFRD and type 1 and type 2 diabetes (Table 1); which necessitate a unique approach to diagnosis and management. Factors specific to CF which impact glucose metabolism include the loss of total islets leading to both insulin and glucagon deficiency, chronic and acute inflammation and infection which cause fluctuating insulin resistance, a requirement for high caloric intake because of increased energy expenditure and malabsorption, risk of life-threatening malnutrition, and gut abnormalities including delayed gastric emptying, altered intestinal motility, and liver disease.

Diagnostic criteria for CFRD and abnormal glucose tolerance

The diagnostic criteria for CFRD were updated in 2010 in North America by the CFRD Guidelines Committee, in a position statement co-sponsored by the American Diabetes Association (ADA) and the Cystic Fibrosis Foundation, and endorsed by the Pediatric Endocrine Society (1). They are identical to those used to diagnose other forms of diabetes, including the relatively recent addition of hemoglobin A1c (HbA1c) as a diagnostic criterion. It should be noted, however, that low or normal HbA1c levels do not exclude the diagnosis of CFRD because HbA1c is often spuriously low in CF.

CFRD is part of a spectrum of progressive glucose tolerance abnormalities defined by a standard oral glucose tolerance test (OGTT) (Table 2). Few individuals with CF have truly normal glucose tolerance (NGT). Even when the fasting and 2-h OGTT glucose levels normal, variable, intermittent post-prandial hyperglycemia can often be detected at home by continuous glucose monitoring (CGM) (2, 3). With time, as glucose tolerance worsens, indeterminate glycemia develops (INDET, mid-OGTT glucose ≥ 11.1 mmol/L), followed by impaired glucose tolerance (IGT) and finally diabetes. The early stage of diabetes is characterized by normal fasting glucose levels, but over time fasting hyperglycemia develops. Isolated impaired fasting glucose (IFG) is sometimes present in persons with CF (4, 5).

There is a general pattern of progressive deterioration of glucose tolerance as individuals with CF grow

Table 1. Comparison of features of different forms of diabetes

	Type 1	Type 2	CFRD
Prevalence	0.2%	11%	35%
Onset	Usually acute	Insidious	Insidious
Peak age of onset	Children, Youth	Adults	18–24 yr
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*
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

CFRD, cystic fibrosis-related diabetes.

*Insulin sensitivity becomes severely decreased during acute illness.

Table 2. Abnormal glucose tolerance categories in CF

Category	FPG (mmol/L)	2-h glucose (mmol/L)	Notes
Normal (NGT)	<7.0	<7.8	All glucose levels <11.1
Indeterminate (INDET)	<7.0	<7.8	Mid-OGTT glucose ≥11.1
Impaired (IGT)	<7.0	7.8–11.1	
CFRD FH–	<7.0	≥11.1	
CFRD FH+	≥7.0		

FPG = fasting plasma glucose; FH = fasting hyperglycemia; CFRD, cystic fibrosis-related diabetes; OGTT, oral glucose tolerance test.

older. However, at any particular time glucose levels can vary, dependent upon acute changes in pulmonary and infectious status. The CFRD Guidelines Committee defined the onset of CFRD as the first time a patient meets diagnostic criteria for diabetes, even if glucose tolerance subsequently appears to improve, because long-term outcomes in microvascular disease and mortality correlate with a duration of diabetes that includes these early years when diabetes appears to wax and wane, and because once a patient has experienced significant hyperglycemia, even in the context of acute illness, it generally recurs (1). Hyperglycemia is common during pregnancy in women with CF because of their underlying insulin insufficiency (6, 7); women with CF who have gestational diabetes and who do not meet diagnostic criteria for diabetes before or after pregnancy are not considered to have CFRD.

Incidence and prevalence

The incidence and prevalence of diabetes in persons with CF is higher than in any other age-matched group. An age-dependent incidence of 4–9% per year was

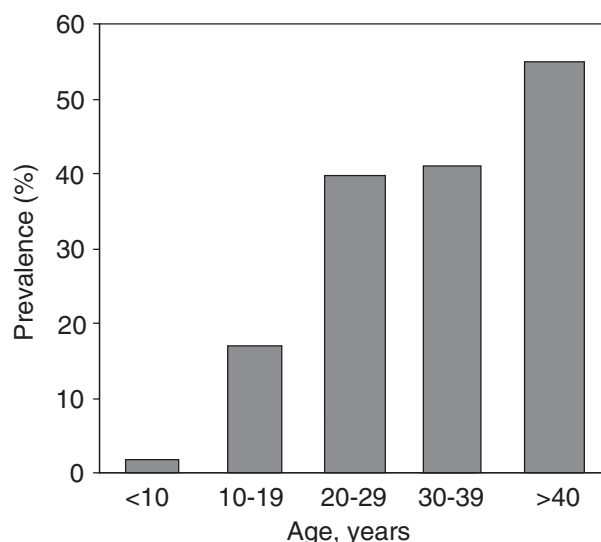


Fig. 1. Prevalence of CFRD by age group at the University of Minnesota, in a population of more than 500 patients (9).

reported in the 1990s in Denmark (8). The University of Minnesota has reported an incidence of 2.7 cases per 100 patient years (9). The reported prevalence of CFRD may be underestimated at centers which do not do universal OGTT screening.

CFRD can occur at any age including infancy. However, prevalence increases as patients get older. The European Epidemiologic Registry of Cystic Fibrosis (ERCF) reported 5 and 13% prevalence in age groups 10–14 and 15–19 yr, respectively (10). A prospective trial from Ireland reported similar prevalence figures: NGT-69%, IGT-14%, and CFRD-17% in the 10–19 yr age group (11). In Denmark, 50% of patients developed CFRD by 30 yr of age (12). At one US center, diabetes was found in <5% of children aged 10 yr and younger, 15–20% of adolescents, ~40% of those in their 20s and 30s, and >50% of those older than 40 yr (9) (Figure 1).

Pathophysiology of CFRD

The pathophysiology of CFRD is complex. The primary defect, insulin insufficiency, is present in essentially all CF patients, and is related to collateral damage to the islets as exocrine tissue is destroyed. Not all CF patients develop diabetes, however, and metabolic outcome is influenced by other factors including the severity of inflammation and infection, genetic susceptibility, malnutrition, and perhaps the CF chloride channel defect itself.

Pancreatic pathology

Abnormal chloride channel function results in thick viscous secretions and 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 (13–15). Most CF patients, with or without diabetes, have lost about half of their islet mass. Beta-cell destruction is not related to autoimmune disease in CF, since the frequency of diabetes autoantibodies and human leukocyte antigen (HLA) types associated with type 1 diabetes are similar to that of the general population (16, 17). However, individuals have occasionally been found to have both type 1 diabetes and CF.

The role of insulin insufficiency

The primary defect in CFRD is severe but not absolute insulin insufficiency. Virtually all exocrine insufficient patients with CF, with and without diabetes, show evidence of beta-cell dysfunction (8, 18). Fasting insulin and C-peptide concentrations are initially normal, but there is delay and blunting of peak insulin secretion during a standard OGTT (19). This effect is more pronounced with worsening glycemic status (20–22). 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 (23). Glucagon secretion is also impaired in CF because total islets are destroyed (19, 23).

The role of insulin resistance

In CF patients *without* diabetes, insulin sensitivity has generally been reported to be intact, although some investigators have found insulin resistance which is likely related to more severe illness (24–28). While most of these patients are sensitive to insulin when they are in their baseline state of health, insulin resistance is acutely increased during periods of active infection. CF patients *with* diabetes are modestly insulin resistant, with both decreased peripheral glucose uptake and

poor insulin suppression of hepatic glucose production (26, 27). Insulin resistance is not as important as insulin insufficiency in the pathogenesis of CFRD, but it assumes a greater role during periods of stress such as acute pulmonary disease from infectious exacerbations.

Genetics of CFRD

CF is caused by a mutation in the CF transmembrane conductance regulator (CFTR), a chloride channel. Diabetes mainly occurs in people with CFTR mutations which produce severe disease including exocrine pancreatic insufficiency. CFTR is expressed in the beta cell (29, 30), where its role is unknown. The ferret model of CF demonstrates abnormal insulin secretion from birth, suggesting that CFTR might play an intrinsic role in insulin secretion (31). This notion is supported by a small human pilot study in CF patients who demonstrated an improved insulin response to oral and intravenous glucose after receiving a new CFTR corrector agent (32).

A genetic association between CF and type 2 diabetes is suggested by the increased prevalence of type 2 diabetes in monozygotic vs. dizygotic twins with CF (33), an increased prevalence of CFRD in individuals with a family history of type 2 diabetes (34), and an association with type 2 diabetes susceptibility loci (34, 35). There is also a relation between CFRD and genes associated with inflammation such as tumor necrosis factor (36), heat shock protein (37), and calpain 10 (38). These findings have led to the hypothesis that while the primary pathologic defect in CFRD is partial loss of islets due to physical destruction, those subjects with underlying defects in insulin secretion or sensitivity may be more susceptible to diabetes because they are less able to compensate for reduced beta-cell mass.

Clinical features of CFRD

CFRD develops insidiously. Symptoms of CFRD are listed in Table 3. It is important to note, however, that the majority of patients have no obvious symptoms. Diabetic ketoacidosis (DKA) is rare, most likely because of the persistence of endogenous insulin

Table 3. Symptoms of CFRD

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- 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
 - There may be no symptoms
-

CFRD, cystic fibrosis-related diabetes.

secretion or because glucagon secretion is also impaired. CFRD may first present during situations where insulin resistance is increased, such as acute pulmonary infection or glucocorticoid therapy, or during high-carbohydrate food supplementation such as continuous nighttime drip feedings. Diabetes is common in the setting of lung transplantation, where pre-transplant patients are critically ill and thus quite insulin resistant, and where post-transplant patients receive diabetogenic medications such as steroids and calcineurin inhibitors (39–42). The prevalence of CFRD is higher in patients with liver disease (43).

Survival and prognosis

Increased mortality in CFRD

Beginning in the 1980s, several investigators in the USA and Europe documented that the additional diagnosis of diabetes was associated with increased mortality in CF, and that women with CFRD were at particularly high risk for early death (44–48). Those with CFRD, like all CF patients, almost always die from pulmonary failure rather than from the macrovascular and microvascular disease associated with death in persons with type 1 and type 2 diabetes. Diabetes has been directly implicated in the pathophysiology of CF lung function decline because of both the catabolic effect of insulin insufficiency on nutritional status and muscle mass (49–52) and the negative impact of chronic hyperglycemia on lung function (53–56), the latter of which may be mediated at least in part by permitting a pro-inflammatory, bacteria-permissive environment.

A 2009 report examined temporal trends in CFRD mortality in a large well-defined CF population that had been followed longitudinally at one institution since the early 1990s (9). Between 1992 and 2008, there was a significant and steady decline in the risk of death associated with CFRD. In the early 1990s, mortality was 13.4-fold greater in individuals with CFRD compared to those without diabetes; by 2008 this had dropped to a 3.5-fold difference which was only significant in patients older than 30 years, and the gender difference in mortality had disappeared. This substantial improvement in the mortality associated with CFRD was attributed to annual diabetes screening and early institution of insulin therapy.

Microvascular and macrovascular complications

Diabetes microvascular complications occur in CFRD, but they tend to be relatively mild in nature (although there are case reports of patients with more severe disease). In Denmark, 36% of patients with more than 10 yr duration of diabetes had retinopathy (57). In a US series of 285 CFRD patients, diabetes complications

were rare before 10 yr duration of diabetes, after which time, in subjects with fasting hyperglycemia, microalbuminuria was found in 14%, retinopathy 16%, neuropathy 55%, and gastropathy 50% of subjects (58). No microvascular complications were found in CFRD patients who had never experienced fasting hyperglycemia (1).

Death from macrovascular complications has not been reported in CF. This is important because the risk of macrovascular disease has shaped treatment and therapy recommendations for persons with type 1 and type 2 diabetes; many of these recommendations are not relevant in CF and may even be harmful. Cholesterol levels are generally low in CF, but isolated triglyceride elevation is not uncommon (59–63). Lipid elevation may be more common after lung transplantation and in older patients with less severe CF mutations. The clinical significance of abnormal lipid levels is unknown but may assume more relevance as the CF population ages.

Hypoglycemia

Hypoglycemia is relatively common in persons with CF with or without diabetes. Fasting hypoglycemia was found in 14% of 129 children and adults with CF at an Italian center and was related to poor clinical status (worse lung function, increased hospitalizations) (28). In this same cohort, reactive hypoglycemia was found during 15% of OGTTs, whereas in a German study 6.3% of patients had reactive hypoglycemia following their OGTT (64). This is presumed to be related to delayed insulin secretion. Although CF patients have diminished glucagon secretion, they have normal recovery from insulin-induced hypoglycemia, likely because of an intact catecholamine response (23). As with all patients on insulin therapy, hypoglycemia is a risk that patients and their families must know how to anticipate, prevent, and treat.

Increased morbidity in the pre-diabetes state

Several studies have shown an insidious decline in clinical status in the years before the diagnosis of CFRD, in the insulin insufficient, pre-diabetic state (44, 65–68). In a prospective study, the decline in pulmonary function over 4 yr was least in patients with NGT, greater in patients with IGT, and greatest in CF patients with untreated early (without fasting hyperglycemia) diabetes (66). In this study and others (28), pulmonary deterioration correlated with the severity of insulin insufficiency. Because of the association between protein catabolism, malnutrition and death in CF and the potent anabolic effect of insulin, the nutritional impact of insulin insufficiency appears to be of greater consequence in CF than the

metabolic impact of hyperglycemia. This may result in clinical compromise long before glucose levels are high enough to qualify for a diagnosis of diabetes. The catabolic effect of insulin insufficiency may be most important in growing children (69–71).

Screening for CFRD

Because CFRD is often clinically silent, routine screening is important. The standard OGTT (patient fasted for 8 h, 1.75 g/kg body weight oral glucose up to a maximum of 75 g, 2-h test) is at present the only accepted screening test.

Oral glucose tolerance testing (OGTT)

The North American CFRD Guidelines Committee determined that the OGTT is the screening test of choice for CFRD (1), based on the poor performance of other tests in CF, the availability of long-term prognostic data linking OGTT results to relevant clinical outcomes, and the importance of diagnosing diabetes early in its course when fasting glucose levels are still normal. Nearly two thirds of patients with CFRD do not have fasting hyperglycemia (9), and this condition can only be detected by OGTT. It is important to identify these individuals because they are at high risk for significant lung function decline and for progression to fasting hyperglycemia (8), and because insulin therapy has been shown to improve nutritional status in this population (72). The OGTT also identifies individuals with abnormal glucose tolerance. In a large study of more than 1000 German and Austrian CF patients, IFG, IGT, and indeterminate glycemia were all predictors of future CFRD (73).

During pregnancy, diabetes poses a risk for both the mother and fetus. Gestational diabetes develops early in pregnancy in CF (6, 7, 74). OGTT screening for pre-existing diabetes should be done before or immediately after the onset of pregnancy, and screening for gestational diabetes is recommended at the end of both the first and second trimesters (1).

There is emerging evidence that mid-OGTT glucose levels may be even more predictive of clinical decline than the 2-h level, and thus consideration should be given to measuring glucose levels every half an hour during the 2-h test (55, 73, 75, 76). It is recommended that OGTT screening begin by at least 10 yr of age. While diabetes *per se* is rare before age 10, 42–78% of children aged 9 and below are reported to have abnormal glucose tolerance (7, 77, 78). A prospective longitudinal study at one North American CF center found that in children aged 6–9, IGT or indeterminate glycemia each predicted a high risk of progression to diabetes in the early adolescent years (78). For this

reason, some centers chose to begin screening at the age of 6.

HbA1c as a diagnostic tool

HbA1c has been shown by several investigators to be unreliable in the diagnosis of CFRD because it is spuriously low (8, 44, 79). This has been postulated to be due to increased red blood cell turnover related to inflammation. In one study, only 16% of patients with CFRD had an elevated HbA1c at the time of diagnosis (8). An elevated HbA1c is evidence of hyperglycemia, but a normal HbA1c does not exclude it.

Random and fasting glucose levels, SMBG for CFRD diagnosis

Normal fasting or random glucose levels do not exclude a diagnosis of diabetes in CF. In some high-risk situations such as home intravenous antibiotic or glucocorticoid therapy or nighttime gastrostomy feedings, it is practical to have the patient perform initial pre-screening at home by self-monitoring of blood glucose (SMBG). SMBG is not sufficiently accurate to make a diagnosis of diabetes, and subsequent laboratory screening by the methods listed below under ‘Recommendations’ must occur in patients identified as high risk by SMBG.

Continuous glucose monitoring (CGM)

CGM has been validated and proven to be useful in children and adolescents with CFRD, where it can help guide safe and effective insulin therapy (2). Its role in CF patients who do not have diabetes is less clear. CGM is not accurate enough to be used to make a diagnosis of diabetes. Furthermore, while it is well known that post-prandial glycemic abnormalities that can be detected by CGM exist in patients with CF long before OGTT results move from NGT to IGT or diabetes, to date the clinical significance of these brief elevations in glucose excursion remains unknown (75, 80).

Treatment of CFRD

Medical nutritional therapy

The dietary recommendations for persons with CFRD are very different from those for persons with type 1 and type 2 diabetes (Table 4), both because their needs are very different, and because they are at low risk for cardiovascular disease. All CF patients, including those with diabetes, require a high calorie, high salt, high fat diet. Caloric restriction is almost never appropriate (although it may be considered in older patients

Table 4. Dietary recommendations for CFRD

	Types 1 and 2 diabetes	CFRD
Calories	≤100% of normal 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	<35% of total energy	40% of total energy
Total carbohydrate	45–60% total energy	45–50% of total energy
Fiber	~3.3 g of fiber per megajoule	Encouraged in the well-nourished, but in poorly nourished patients may compromise energy intake
Protein	15–20% of total energy; ~1–2 g/kg/d	200% of reference nutrient intake
Salt	Range 1000–1500 mg/d	Increased requirement: unrestricted intake

CFRD, cystic fibrosis-related diabetes.

with milder CF mutations who are overweight). For patients on insulin therapy, carbohydrate counting is useful for determining the pre-meal insulin dose. Large quantities of sugary beverages such as soda pop may be difficult to adequately cover with insulin and are generally discouraged.

Insulin therapy

Insulin insufficiency is the primary pathologic feature of CFRD, and insulin replacement is the only recommended medical treatment (1). Insulin therapy stabilizes lung function and improves nutritional status in patients with CFRD (9, 72, 81). The general principles of insulin therapy are presented in Table 5. When patients are in their baseline state of health, insulin requirements tend to be modest because of the persistence of endogenous insulin secretion and perhaps because of decreased levels of glucagon (average insulin dose <0.5–0.8 units/kg/d in both adolescents and adults) (82, 83). Patients with fasting hyperglycemia are generally treated with basal-bolus therapy, with an insulin pump or with a combination of long-acting basal insulin and rapid-acting insulin to cover carbohydrates and correct hyperglycemia. In patients with CFRD without fasting hyperglycemia, pre-meal rapid-acting insulin reversed chronic weight loss and is now considered standard care (72). Because of the relation between nutritional status and survival in CF, the anabolic effects of insulin may be the most critical aspect of therapy. Thus, the goal is to provide as high an insulin dose as the patient can safely tolerate.

Oral diabetes agents

Oral diabetes agents are currently not recommended in CFRD. A Cochrane review did not identify any randomized-controlled trials other than the CFRDT Trial (84), where the insulin secretagogue repaglinide was not able to produce sustained weight gain in individuals with CFRD without fasting hyperglycemia

(72). Agents that reduce insulin resistance are unlikely to be effective in CFRD, because insulin resistance is not the major etiological factor. Furthermore, there are problems with currently available insulin sensitizers that might be particularly unacceptable in the CF population, including gastrointestinal side effects (metformin) and osteoporosis (thiazolidinediones). There are no data on the clinical use of incretin mimetic agents such as the glucagon-like peptide-1 (GLP-1) agonists or the dipeptidyl peptidase-4 (dpp-4) inhibitors in CF, but they would not be expected to be good candidates for use in this population given that their mechanism of action includes reducing gastric emptying and decreasing glucagon levels.

Inpatient management of CFRD

During acute illness, CF patients are at increased risk for developing hyperglycemia (85, 86). While data from other populations suggest that intensive insulin therapy may be beneficial in the hospital setting, no studies have examined the benefits of maintaining tight euglycemia in hospitalized CF patients. In those with pre-existing diabetes, insulin requirements are usually much larger during illness: up to four times the usual insulin may be needed. The insulin dose must be quickly reduced as clinical status improves to avoid hypoglycemia, although this may take a couple of months (85). In CF patients who had normal glucose levels prior to becoming ill, blood glucose levels may return to normal after the illness resolves although it is likely that hyperglycemia will occur again with the next acute exacerbation.

Treatment of CF patients with abnormal glucose tolerance

Small, uncontrolled studies suggest that patients with IGT might benefit from insulin therapy (81, 87–89). However, there are no definitive data on the benefits of insulin therapy for CF patients without an actual

Table 5. Principles of insulin therapy in CFRD

General principles	<ul style="list-style-type: none"> • CFRD patients typically require 0.5–0.8 units insulin per kg body weight per day when they are in their usual state of health. Much more may be required during stress. • Because of the catabolic effects of insulin insufficiency, the goal is to give the patient as much insulin as can be safely tolerated. • Choose the insulin regimen that best fits the patient’s lifestyle and meets the needs of their CF management.
Basal insulin	<ul style="list-style-type: none"> • Generally the goal is about 0.25 IU/kg body weight per 24 h; start at half this and adjust upward based on fasting glucose levels.
Meal coverage	<ul style="list-style-type: none"> • 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 post-prandial blood glucose goals. • For very young patients or those who are unsure of what they will eat due to nausea or gastroparesis, the dose may need to be given right after the meal (although before is always better if possible). • Patients with CFRD without fasting hyperglycemia may be managed with pre-meal insulin alone, or with basal alone (depending on patient factors, including eating habits)
Correction dose (Sensitivity)	<ul style="list-style-type: none"> • Pre-meal correction is usually started at 0.5–1 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.
Coverage of overnight drip feeding	<ul style="list-style-type: none"> • Frequently a single dose of regular/soluble plus NPH (e.g., Humulin N, Protaphane, Novolin N, Insulatard, Isophane, etc) insulin will cover an overnight drip feeding. The regular insulin covers the first half and the NPH the second half of the feeding. • Starting dose: calculate the total grams carbohydrate in the feeding, determine a total insulin dose based on the insulin to carbohydrate ratio (typically 0.5–1 units per 15 g), and deliver half of this as regular and half as NPH insulin. • Glucose levels 4 h into the feeding are used to adjust the regular insulin dose and those at the end of the feeding to adjust the NPH insulin dose. Occasionally a little rapid-acting insulin is also needed at the beginning. • Think of this as a ‘long meal’. It does not replace basal insulin, and patients should only take this insulin when they have the feeding.
Limited care in a resource poor setting	<ul style="list-style-type: none"> • When analog insulin is not available, NPH insulin (e.g., Humulin N, Protaphane, Novolin N, Insulatard, Isophane, etc) and regular/soluble insulin can be used to treat CFRD, but care needs to be taken to avoid late post-prandial hypoglycemia. One possible regimen is NPH insulin at bedtime, and regular insulin with breakfast, lunch, and supper, in a patient who is eating three meals and three snacks a day.

CFRD, cystic fibrosis-related diabetes

diagnosis of diabetes. This has been identified as a high-priority research question (1).

Recommended care

ISPAD endorses the 2010 recommendations sponsored by the American Diabetes Association and the Cystic Fibrosis Foundation and endorsed by the Pediatric Endocrine Society, published as an American Diabetes Association Position Statement (1).

Diagnosis

- The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates. [E, Consensus]

- During a period of stable baseline health the diagnosis of CFRD can be made in CF patients according to standard ADA criteria. [E, Consensus]

- FPG ≥ 126 mg/dL (7.0 mmol/L), or
- 2-h OGTT plasma glucose ≥ 200 mg/dL (11.1 mmol/L), or
- HbA1c ≥ 48 mmol/mol (6.5%) (HbA1c below this does not exclude CFRD), or
- Random glucose ≥ 200 mg/dL (11.1 mmol/L) with symptoms

- The diagnosis of CFRD can be made in CF patients with acute illness (intravenous antibiotics in the hospital or at home, systemic glucocorticoid therapy) when fasting plasma glucose (FPG) levels ≥126 mg/dL (7.0 mmol/L) or 2-h post-prandial

plasma glucose levels ≥ 200 mg/dL (11.1 mmol/L) persist for more than 48 h. [E, Consensus]

- The diagnosis of CFRD can be made in CF patients on enteral continuous drip feedings when mid- or post-feeding plasma glucose levels exceed 200 mg/dL (11.1 mmol/L) on two separate days. [E, Consensus]
- Diagnosis of gestational diabetes should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study Group (90) where diabetes is diagnosed based on 0, 1, and 2-h glucose levels with a 75-g OGTT if any one of the following is present:
 - FPG ≥ 92 mg/dL (5.1 mmol/L)
 - 1 h plasma glucose ≥ 180 mg/dL (10.0 mmol/L)
 - 2 h plasma glucose ≥ 153 mg/dL (8.5 mmol/L)
- CF patients with gestational diabetes are not considered to have CFRD, but require CFRD screening 6–12 wk after the end of the pregnancy. [E, Consensus]
- Distinguishing between CFRD with and without fasting hyperglycemia is not necessary. [B]

Screening

- The use of HbA1c as a screening test for CFRD is not recommended. [B]
- Screening for CFRD should be performed using the 2-h 75 g (1.75 g/kg) OGTT. [E, Consensus]
- Annual screening for CFRD should begin by age 10 in all CF patients who do not have CFRD. [B]
- CF patients with acute pulmonary exacerbation requiring intravenous antibiotics and/or systemic glucocorticoids should be screened for CFRD by monitoring fasting and 2-h post-prandial plasma glucose levels for the first 48 h. [E, Consensus]
- Screening for CFRD by measuring mid- and immediate post-feeding plasma glucose levels is recommended for CF patients on continuous enteral feedings, at the time of gastrostomy tube feeding initiation and then monthly at home. Elevated glucose levels detected by SMBG must be confirmed by a certified laboratory. [E, Consensus]
- Women with CF who are planning a pregnancy or confirmed pregnant should be screened for pre-existing CFRD with a 2 h 75-g fasting OGTT if they have not had a normal CFRD screen in the last 6 months. [E, Consensus]
- Screening for gestational diabetes is recommended at both 12–16 wk and 24–28 wk gestation in pregnant women with CF not known to have CFRD, using a 2 h 75-g OGTT with blood glucose measures at 0, 1, and 2 h. [E, Consensus]
- Post-pregnancy screening for CFRD using a 2-h 75 g fasting OGTT is recommended 6–12 wk after the

end of the pregnancy in women with gestational diabetes (diabetes first diagnosed during pregnancy). [E, Consensus]

- CF patients not known to have diabetes who are undergoing any transplantation procedure should be screened pre-operatively by OGTT if they have not had CFRD screening in the last 6 months. Plasma glucose levels should be monitored closely in the peri-operative critical care period and until hospital discharge. Screening guidelines for patients who do not meet diagnostic criteria for CFRD at the time of hospital discharge are the same as for other CF patients. [E, Consensus]

Management of CFRD

- Patients with CFRD should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF. [E, Consensus]
- Patients with CFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards. [E, Consensus]
- CF patients with CFRD should be treated with insulin therapy. [A]
- Oral diabetes agents are not as effective as insulin in improving nutritional and metabolic outcomes in CFRD, and are not recommended outside the context of clinical research trials. [A]
- Patients with CFRD who are on insulin should perform self-monitoring of blood glucose at least three times a day. For many patients, four to eight or more times a day is appropriate, depending on meal pattern, exercise, intestinal concerns such as gastroparesis, and acute state of health. [E, Consensus]
- Patients with CFRD should strive to attain plasma glucose goals as per the ADA recommendations for all people with diabetes, bearing in mind that higher or lower goals may be indicated for some patients, and that individualization is important. [E, Consensus]
- HbA1c measurement is recommended quarterly for patients with CFRD to guide insulin therapy decisions. [E, Consensus]
 - For most patients with CFRD the HbA1c treatment goal is $<7\%$ (53 mmol/mol) to reduce the risk of microvascular complications, bearing in mind that higher or lower goals may be indicated for some patients, and that individualization is important. [B]
- CF Foundation evidence-based guidelines for nutritional management of all persons with CF

are recommended for patients with CFRD. [E, Consensus]

- Patients with CFRD should be advised to do moderate aerobic exercise for at least 150 min/wk. [E, Consensus]

Complications

- Education about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon, is recommended for patients with CFRD and their care partners. [E, Consensus]
- Patients with CFRD should have their blood pressure measured at every routine diabetes visit as per ADA guidelines. Patients found to have systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg or >90 th percentile for age and gender for pediatric patients should have repeat measurement on a separate day to confirm a diagnosis of hypertension. [E, Consensus]
- Annual monitoring for microvascular complications of diabetes is recommended using ADA guidelines, beginning 5 yr after the diagnosis of CFRD or, if the exact time of diagnosis is not known, at the time that fasting hyperglycemia is first diagnosed. [E, Consensus]
- Patients with CFRD diagnosed with hypertension or microvascular complications should receive treatment as recommended by the ADA for all people with diabetes, except that there is no restriction of sodium and, in general, no protein restriction. [E, Consensus]
- An annual lipid profile is recommended for patients with CFRD and pancreatic exocrine sufficiency, or if any of the following risk factors are present: obesity, family history of coronary artery disease, or immunosuppressive therapy following transplantation. [E, Consensus]

Conflict of interest

The authors have declared no relevant conflicts of interest.

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