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ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents

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1 | WHAT'S NEW?

Since the original guidelines were published, there has been additional work done to characterize the pathophysiology of cystic fibrosis-related diabetes (CFRD), including the role of genes related to type 2 diabetes, the role of inflammation, and the potential role of the basic CF transmembrane conductance regulator (CFTR) chloride channel defect. Continuous glucose monitoring (CGM) data have better defined the daily glucose excursions that occur in CF and their relation to HbA1c and mean glucose level. There are currently no major changes in the clinical guidelines. On the horizon, the results of two ongoing studies examining the role of insulin therapy in non-diabetic CF patients with abnormal glucose tolerance may eventually change recommendations for this population. Likewise, new CF corrector/modulator drugs may have a profound impact on the course of CFRD and its treatment.

2 | EXECUTIVE SUMMARY

- Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity associated with cystic fibrosis (CF). [A]
- 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. [A]
- Few individuals with CF have normal glucose tolerance and even when the fasting and 2-hour oral glucose tolerance test (OGTT) glucose levels are normal, variable, intermittent postprandial hyperglycemia can often be detected by continuous glucose monitoring (CGM). [A]
- CF is associated with a progressive deterioration in glucose tolerance. It can occur at any age, including infancy, and its prevalence increases as patients get older. The earliest abnormality is often intermittent postprandial glucose excursions that can be detected by CGM, followed by indeterminate glycemia by OGTT, then impaired glucose tolerance (IGT) and finally diabetes. Individuals may move back and forth between categories, but over time there is gradual deterioration in glucose tolerance status. [A]
- Early CFRD is characterized by normal fasting glucose levels, but over time fasting hyperglycemia develops. At any particular time, blood glucose level can vary, dependent upon acute changes in pulmonary and infectious status. [A]
- The majority of patients have no obvious symptoms at diagnosis of CFRD, although symptoms may develop insidiously. Presentation with CFRD is more likely during times when insulin resistance

is greater (eg, pulmonary infection, use of glucocorticoid agents). [A]
- Presentation with diabetic ketoacidosis (DKA) is rare. [A]
- The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates. [E]
- 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]
- 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-hour postprandial plasma glucose levels ≥200 mg/dL (11.1 mmol/L) persist for more than 48 hours. [E]
- CF patients with gestational diabetes are not considered to have CFRD, but should be required to undergo CFRD screening 6 to 12 weeks after the end of the pregnancy. [E]
- Distinguishing between CFRD with and without fasting hyperglycemia (found in earlier classification schemes) is not necessary. [B]
- The use of HbA1c as a screening test for CFRD is not recommended. [B]
- Screening for CFRD should be performed using the 2-hour 75 g (1.75 g/kg) OGTT. [E]
- Annual screening for CFRD should begin at least by age 10 years 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]
- Patients with CFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards. [E]
- 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]
- 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]
- HbA1c measurement is recommended quarterly for patients with CFRD to guide insulin therapy decisions. [E]
- CF foundation evidence-based guidelines for nutritional management of all persons with CF are recommended for patients with CFRD. [E]
- Education about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon, is recommended for patients with CFRD who are on insulin therapy and their care partners. [E]
- Annual monitoring for microvascular complications of diabetes is recommended, beginning 5 years 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]
- Patients with CFRD diagnosed with hypertension or microvascular complications should receive standard treatment, except that there is no restriction of sodium and, in general, no protein restriction. [E]
- An annual lipid profile is recommended for patients with CFRD and pancreatic exocrine sufficiency [E]

3 | INTRODUCTION

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 comorbidity 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

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 y
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[a]
Ketones	Yes	Rare	Rare
Usual treatment	Insulin	Diet, oral meds, insulin	Insulin
Microvasular complications	Yes	Yes	Yes
Macrovascular complications	Yes	Yes	No
Metabolic syndrome	No	Yes	No
Cause of death	Cardiovascular	Cardiovascular	Pulmonary

Abbreviation: CFRD, cystic fibrosis-related diabetes.
[a] Insulin sensitivity becomes severely decreased during acute illness.

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.

3.1 | 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 addition of 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.[2]

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-hour OGTT glucose levels are normal, variable, intermittent postprandial hyperglycemia can often be detected at home by continuous glucose monitoring (CGM).[3–5] 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. Early 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 but the significance is unclear.[6,7]

There is a general pattern of progressive deterioration of glucose tolerance as individuals with CF grow 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[8]; 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.

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		
IFG	6.1-6.9	<7.8	All glucose levels <11.1

Abbreviations: CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; FPG, fasting plasma glucose; FH, fasting hyperglycemia; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

4 | 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% to 9% per year was reported in the 1990s in Denmark.[2] 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 to 14 and 15 to 19 years, respectively.[10] A prospective trial from Ireland reported similar prevalence figures: NGT-69%, IGT-14%, and CFRD-17% in the 10 to 19 years age group.[11] In Denmark, 50% of patients developed CFRD by 30 years of age.[12] At one US center, diabetes was found in <5% of children age 10 years and younger, 15% to 20% of adolescents, ~40% of those in their 20s and 30s, and >50% of all those older than 40 years[9] (Figure 1). Notably, in those with severe genotypes, >80% of patients had CFRD after age 40.

5 | PATHOPHYSIOLOGY OF CFRD

The pathophysiology of CFRD is complex. The primary defect, insulin insufficiency, is present in essentially all CF patients, and is related at least in part 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.

5.1 | 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.

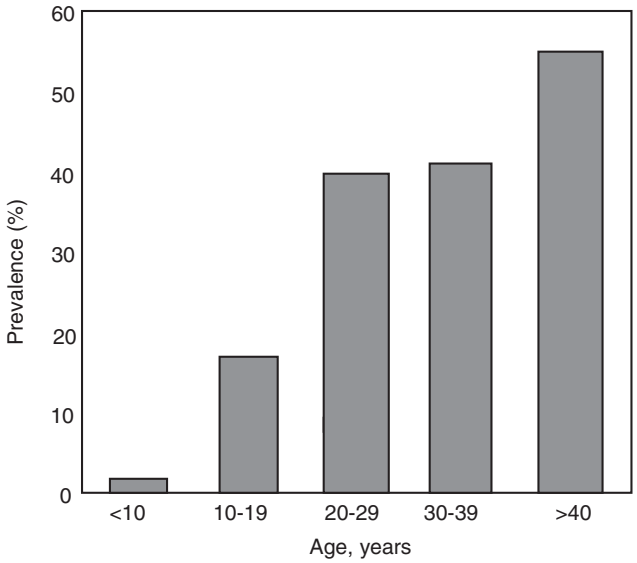

FIGURE 1 Prevalence of cystic fibrosis-related diabetes (CFRD) by age group at the University of Minnesota, in a population of more than 500 patients. Note that while >50% of the total population age 40 years and older has CFRD, more than 80% of those with severe mutations have CFRD by this age[9]

5.2 | 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.[2,18] 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.[20–23] Delayed insulin secretion during the OGTT is primarily related to loss of first phase insulin secretion, which is found even in CF patients with NGT.[24] Glucagon secretion is also impaired in CF because total islets are destroyed.[19,24]

5.3 | 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.[25–28] 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-mediated suppression of hepatic glucose production.[27,28] Insulin resistance can occur as a result of chronic hyperglycaemia due to downregulation of GLUT-4 transporters.[29] Thus, hyperglycaemia can lead to worsening glycemic abnormalities in a vicious cycle. 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 and the use of glucocorticoids.

TABLE 3 Symptoms of CFRD

- 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

Abbreviation: CFRD, cystic fibrosis-related diabetes.

5.4 | 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 appears to be expressed in the beta cell,[30,31] 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.[32] 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 CFTR modulator agent.[33]

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,[34] an increased prevalence of CFRD in individuals with a family history of type 2 diabetes,[35] and an association with type 2 diabetes susceptibility loci.[35,36] There is also a relation between CFRD and genes associated with inflammation such as tumor necrosis factor,[37] heat shock protein,[38] and Calpain-10.[39] 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.

6 | 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 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 pretransplant patients are critically ill and thus quite insulin resistant, and where posttransplant patients receive diabetogenic medications such as steroids and calcineurin inhibitors.[40–43] The prevalence of CFRD is higher in patients with liver disease.[44]

7 | SURVIVAL AND PROGNOSIS

7.1 | Increased mortality in CFRD

Beginning in the 1980s, several investigators in the United States 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.[45–49] 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[50–53] and the negative impact of chronic hyperglycemia on lung function,[54–57] the latter of which may be mediated at least in part by permitting a pro-inflammatory, bacteria-permissive pulmonary 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 and was significantly worse in women; by 2008 this had dropped to a 3.5-fold difference which was only significant in patients older than 30 years of age, 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.

7.2 | 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 years duration of diabetes had retinopathy.[58] In a US series of 285 CFRD patients, diabetes complications were rare before 10 years 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.[59] No microvascular complications were found in CFRD patients who had never experienced fasting hyperglycemia.

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.[60–64] 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.

7.3 | 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).[23] In this same cohort, reactive hypoglycemia was found during 15% of OGTTs, while in a German study 6.3% of patients had reactive hypoglycemia following their OGTT.[65] 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.[24] As with all patients on insulin therapy, hypoglycemia is a risk that patients and their families must know how to anticipate, prevent, and treat.

7.4 | Increased morbidity in the prediabetes state

Several studies have shown an insidious decline in clinical status in the years before the diagnosis of CFRD, in the insulin insufficient, prediabetic state.[45,66–69] In a prospective study, the decline in pulmonary function over 4 years was least in patients with NGT, greater in patients with IGT, and greatest in CF patients with untreated early (without fasting hyperglycemia) diabetes.[67] In this study and others,[23] 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 may 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.[70–72] Current studies in the United States and Australia (Cystic Fibrosis, Insulin Deficiency—Early Action [CF-IDEA], Trial clinicaltrials.gov: CT01100892) are exploring these associations.

8 | SCREENING FOR CFRD

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

8.1 | Oral glucose tolerance testing

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,[2] and because insulin therapy has been shown to improve nutritional status in this population.[73] 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 (all of which can only be determined by OGTT) were all predictors of future CFRD.[74]

During pregnancy, diabetes poses a risk for both the mother and fetus. Gestational diabetes develops early in pregnancy in CF.[8,75] OGTT screening for preexisting 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 hour level, and thus consideration should be given to measuring glucose levels every half hour during the 2-hour test.[56,74,76,77] It is recommended that OGTT screening begin by at least 10 years of age. While diabetes per se is rare before age 10, 42% to 78% of children aged 9 years and under are reported to have abnormal glucose tolerance.[78–80] A prospective longitudinal study at one North American CF center found that in children aged 6 to 9 years, IGT or indeterminate glycemia each predicted a high risk of progression to diabetes in the early adolescent years.[80] For this reason, some centers chose to begin screening at age 6 years.

8.2 | HbA1c as a diagnostic tool

HbA1c has been shown by several investigators to be unreliable in the diagnosis of CFRD, because it is lower than expected relative to observed glucose levels.[2,5,45] This has been postulated to be due to increased red blood cell turnover related to inflammation, but may also be related to the fact that these patients still make significant amounts of C-peptide (similar to a patient with type 1 diabetes in the honeymoon phase). In one study, only 16% of patients with CFRD had an elevated HbA1c at the time of diagnosis.[9] An elevated HbA1c is evidence of hyperglycemia, but a normal HbA1c does not exclude it.

8.3 | 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 prescreening 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.

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% to 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% to 60% total energy	45% to 50% of total energy
Fiber	No quantitative recommendation, but encouraged due to beneficial effects	Encouraged in the well-nourished, but in poorly nourished patients may compromise energy intake
Protein	10% to 20% of total energy; not >1 g/kg body weight	200% of reference nutrient intake in a non-CF patient
Salt	Low intake, ≤6 g/d	Increased requirement: unrestricted intake

Abbreviation: CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes.

8.4 | One hour plasma glucose during OGTT

The North American CFRD Consensus Conference in 2009 defined glucose tolerance in individuals with a 1 hour plasma glucose (PG1) >200 mg/dL as indeterminate glycemia (INDET), the significance of which is not completely understood. In CF, isolated elevations of the PG1 during OGTT are common, and cross-sectional data suggest that higher glucose may be associated with poor clinical outcome in CF patients.[77] A study in the United States found subjects with a 1 hour OGTT PG ≥200 mg/dL (11.1 mmol/L) were 10 times more likely to develop CFRD over the study period compared to those with PG levels ≤200 mg/dL (11.1 mmol/L).[81] Data are still lacking on the benefits of interventions targeting the PG1.

8.5 | Continuous glucose monitoring

CGM has been validated and proven to be useful in children and adolescents with insulin-treated CFRD, where it can help guide safe and effective insulin therapy.[3] Its role in CF patients who do not have diabetes is less clear. CGM is not licensed for diagnosing diabetes. Furthermore, while it is well known that postprandial 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.[76,82] For now, CGM should be considered a useful tool for insulin dosage adjustment and to alert the patient to hypoglycemia, but it cannot be used to diagnosis diabetes.

9 | TREATMENT OF CFRD

9.1 | Medical nutritional therapy

The dietary recommendations for persons with CFRD are very different from those for persons with type 1 or 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 with milder CF mutations who are overweight, and in the small but emerging population of CF patients who are obese). For patients on insulin therapy, carbohydrate counting is useful for determining the premeal insulin dose. Large quantities of sugary beverages such as soda pop may be difficult to adequately cover with insulin and are generally discouraged.

9.2 | Insulin therapy

Insulin insufficiency is the primary pathologic feature of CFRD, and insulin replacement is the only recommended medical treatment.[1]

TABLE 5 Principles of insulin therapy in CFRD

General principles	• CFRD patients typically require 0.5 to 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	• Generally the goal is about 0.25 U per kg body weight per 24 hours; start at half this and adjust upward based on fasting glucose levels.
Meal coverage	• A common starting dose is 0.5 to 1 U 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 U per 15 g carbohydrate to achieve 2-hour postprandial 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 premeal insulin alone, or with basal alone (depending on patient factors, including eating habits)
Correction dose (sensitivity)	• Premeal correction is usually started at 0.5 to 1 U 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	• Frequently a single dose of regular/soluble plus NPH (eg, 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 hours 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 for correction. • Think of this as a "long meal." It does not replace basal insulin, and patients should only take this insulin when they have the overnight feeding.
Limited care in a resource poor setting	• When analog insulin is not available, NPH insulin (eg, 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 postprandial 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. • There is often limited availability of blood glucose monitoring test strips in resource-poor settings. The goal is to test as often as possible, varying the time from fasting to 2 hour postprandial readings, to try to get a representative sample of how well the insulin dose is working.

Abbreviations: CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; NPH, Neutral protamine Hagedorn insulin.

Insulin therapy stabilizes lung function and improves nutritional status in patients with CFRD.[9,73,83] 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 of <0.5-0.8 units/kg/d in both adolescents and adults).[84,85] 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, premeal rapid-acting insulin reversed chronic weight loss and is now considered standard care.[73] Some of these patients (especially those that consume modest amounts of carbohydrates multiple times during the day) may be treated with basal insulin therapy alone. 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.

9.3 | Oral diabetes agents

Oral diabetes agents are currently not recommended in CFRD. A Cochrane review[86] did not identify any randomized controlled trials other than the CFRDT Trial, where the insulin secretagogue repaglinide was not able to produce sustained weight gain in individuals with CFRD without fasting hyperglycemia.[73] Results of a recently published multicenter European study comparing insulin and repaglinide showed no differences in HbA1c, body mass index (BMI), lung function, or adverse events between the two treatments after 2 years of therapy; they suggest that repaglinide could be considered for treatment of early CFRD.[87] These results should be interpreted with caution.[88] Problems included high dropout rates, considerable variability in insulin dose across 30 centers, and very few patients per center with recruitment stretching over almost a decade. Most concerning was the lack of improvement in either group, in contrast to previous findings of weight gain with insulin therapy in CFRD, suggesting that the inconsistent approach to insulin therapy may have influenced the results—that is, repaglinide wasn't worse than insulin, but insulin treatment in this study did not achieve previously reported benefits. 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 might 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. There are, however, ongoing studies in this area.

9.4 | Inpatient management of CFRD

During acute illness, CF patients are at increased risk for developing hyperglycemia.[89,90] 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 euglycemia in hospitalized CF patients. In those with preexisting 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 months.[89] 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.[91]

9.5 | Treatment of CF patients with abnormal glucose tolerance

Small, uncontrolled studies suggest that patients with IGT might benefit from insulin therapy.[83,92–94] However, there are no definitive data on the benefits of insulin therapy for CF patients without an actual diagnosis of diabetes. This has been identified as a high-priority research question,[1] and two large studies in the United States and Australia ("CF-IDEA Trial" clinicaltrials.gov: CT01100892 and "The Impact of Insulin Therapy on Protein Turnover in Pre-Diabetic Cystic Fibrosis Patients" clinicaltrials.gov: NCT02496780) are in progress to address this issue.

10 | 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]

10.1 | 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]
- During a period of stable baseline health the diagnosis of CFRD can be made in CF patients according to standard ADA criteria. [E]
  - FPG ≥ 126 mg/dL (7.0 mmol/L)
  - 2-hours OGTT PG ≥200 mg/dL (11.1 mmol/L)
  - HbA1c ≥ 48 mmol/mol (6.5%)—HbA1c below this does not exclude CFRD
  - 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 FPG levels ≥126 mg/dL (7.0 mmol/L) or 2-hour postprandial PG levels ≥200 mg/dL (11.1 mmol/L) persist for more than 48 hours. [E]
- The diagnosis of CFRD can be made in CF patients on enteral continuous drip feedings when mid- or postfeeding PG levels exceed 200 mg/dL (11.1 mmol/L) on two separate days. [E]
- Diagnosis of gestational diabetes should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study Group[95] where diabetes is diagnosed based on 0, 1, and 2-hour glucose levels with a 75 g OGTT if any one of the following is present:
  - Fasting PG ≥92 mg/dL (5.1 mmol/L)
  - PG1 ≥180 mg/dL (10.0 mmol/L)
  - 2 hours PG ≥153 mg/dL (8.5 mmol/L)
- CF patients with gestational diabetes are not considered to have CFRD, but should be required to have CFRD screening 6 to 12 weeks after the end of the pregnancy. [E]
- Distinguishing between CFRD with and without fasting hyperglycemia is not necessary. [B]

10.2 | Screening

- The use of HbA1c as a screening test for CFRD is not recommended. [B]
- Screening for CFRD should be performed using the 2-hour 75 g (1.75 g/kg) OGTT. [E]
- Annual screening for CFRD should begin at least by age 10 years 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 hours postprandial PG levels for the first 48 hours. [E]
- Screening for CFRD by measuring mid- and immediate postfeeding PG 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]
- Women with CF who are planning a pregnancy or confirmed pregnant should be screened for preexisting CFRD with a 2-hour 75 g fasting OGTT if they have not had a normal CFRD screen in the last 6 months. [E]
- Screening for gestational diabetes is recommended at both 12 to 16 weeks and 24 to 28 weeks gestation in pregnant women with CF not known to have CFRD, using a 2-hour 75 g OGTT with blood glucose measures at 0, 1, and 2 hours. [E]
- Postpregnancy screening for CFRD using a 2-hour 75 g fasting OGTT is recommended 6 to 12 weeks after the end of the pregnancy in women with gestational diabetes (diabetes first diagnosed during pregnancy). [E]
- CF patients not known to have diabetes who are undergoing any transplantation procedure should be screened preoperatively by OGTT if they have not had CFRD screening in the last 6 months. Plasma glucose levels should be monitored closely in the perioperative 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]

10.3 | Management of CFRD

- Patients with CFRD should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF. [E]
- Patients with CFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards. [E]
- 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]
- Patients with CFRD should strive to attain PG goals as per the ADA recommendations for all people with diabetes. Less stringent goals may be indicated for patients who experience significant or repeated hypoglycemia, and individualization is important. [E]
- HbA1c measurement is recommended quarterly for patients with CFRD to guide insulin therapy decisions. [E]
  - 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 less stringent goals may be indicated for patients who experience significant or repeated hypoglycemia, and thus individualization is important. [B]
- CF Foundation evidence-based guidelines for nutritional management of all persons with CF are recommended for patients with CFRD. [E]
- Patients with CFRD should be advised to do moderate aerobic exercise for at least 150 minutes per week. [E]

10.4 | Complications

- Education about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon, is recommended for patients with CFRD on insulin therapy and their care partners. [E]
- 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 mm Hg or diastolic blood pressure ≥80 mm Hg or >90th percentile for age and gender for pediatric patients should have repeat measurement on a separate day to confirm a diagnosis of hypertension. [E]
- Annual monitoring for microvascular complications of diabetes is recommended using ADA guidelines, beginning 5 years 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]
- Patients with CFRD diagnosed with hypertension or microvascular complications should receive standard 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]
- 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]

Conflict of interest

The authors have declared no relevant conflicts of interest.

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