

**Evidence-based Clinical Care Guidelines for Cystic Fibrosis Related Diabetes
Recommendations from the Cystic Fibrosis Foundation, the American Diabetes Association,
and the Pediatric Endocrine Society**

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Introduction

Cystic Fibrosis Related Diabetes (CFRD) is the most common co-morbidity in people with cystic fibrosis (CF), occurring in approximately 20% of adolescents and 40-50% of adults (1). While it shares features of type 1 and type 2 diabetes, CFRD is a distinct clinical entity. It is primarily caused by insulin insufficiency, although fluctuating levels of insulin resistance related to acute and chronic illness also play a role. The additional diagnosis of CFRD has a negative impact on pulmonary function and survival in CF, and this risk disproportionately affects women (2-4). In contrast to patients with other types of diabetes, there are no documented cases of death from atherosclerotic vascular disease in patients with CFRD, despite the fact that some now live into their sixth and seventh decades.

These guidelines are the result of a joint effort between the Cystic Fibrosis Foundation (CFF), the American Diabetes Association (ADA) and the Pediatric Endocrine Society (PES). They are intended for use by CF patients, their care partners, and health care professionals, and include recommendations for screening, diagnosis, and medical management of CFRD. This report focuses on aspects of care unique to CFRD. A comprehensive summary of recommendations for all people with diabetes can be found in the ADA Standards of Medical Care, published annually in the January supplement to *Diabetes Care* (5).

Methods

In 2009 the CF Foundation, in collaboration with the ADA and the PES, convened a committee of CF and diabetes experts to update clinical care guidelines for CFRD. Investigators at Johns Hopkins University conducted evidence reviews on relevant clinical questions identified by the guidelines committee, which were provided to the committee to use in developing

recommendations. Where possible, the evidence for each recommendation was considered and graded by the committee using the ADA (5) and the US Preventive Services Task Force (USPSTF) (6) grading systems (Table 1). Recommendations from existing published guidelines were used when available and appropriate, and these are indicated as consensus statements. The committee also made consensus recommendations for topics not included in the evidence reviews. Recommendations will be updated as warranted by new evidence and the guidelines will be reviewed 3 years after release date to determine if an update is needed. A summary of the committee's recommendations is presented in Table 2.

I. SCREENING

CFRD is often clinically silent. In other populations, the primary consequences of unrecognized diabetes are macrovascular and microvascular disease. In CF, the nutritional and pulmonary consequences of diabetes are of greater concern. CFRD is associated with weight loss, protein catabolism, lung function decline, and increased mortality (2; 3; 7-17), and thus regular screening is warranted.

Screening tests for CFRD

While hemoglobin A1c (A1c) may become the standard screening test for type 2 diabetes (5), the committee concluded that it is not sufficiently sensitive for diagnosis of CFRD and thus should not be used as a screening test. Eight studies were identified that assessed A1c as a screening test in this population (7; 18-24). The authors of one prospective cohort study with 62 participants with CF and 107 healthy controls reported that A1c levels were higher in the CF group than among the controls, leading them to suggest that the use of A1c was appropriate (18).

However, six studies with 477 participants demonstrated low degrees of correlation between A1c and glucose tolerance status (7; 19-23), including two prospective cohort studies (7; 21), two cross-sectional studies (19; 20), one case-control study (23), and one case series (22).

Additionally, a cross-sectional study with 191 participants with CF demonstrated a low positive predictive value of the A1c test (24).

The use of A1c as a screening test for CFRD is not recommended. [ADA-B; USPSTF-D]

Fructosamine, urine glucose, and random glucose levels have low sensitivity in the CF population (20; 23; 25). Continuous glucose monitoring (CGM) is not recommended as a screening tool since intermittent hyperglycemia detected in this fashion is not diagnostic for diabetes and there are no outcome data to determine its clinical significance. Fasting plasma glucose identifies patients with CFRD with but not those without fasting hyperglycemia, and thus this test will miss the diagnosis of diabetes in approximately half of CF patients (1). Self monitoring of blood glucose (SMBG) with home meters is also not sufficiently accurate to screen for CFRD, since the International Organization for Standardization only requires that 95% of readings be within 20% of the actual glucose level (26).

Because of the poor performance of A1c and other tests, the oral glucose tolerance test (OGTT) is the screening test of choice for CFRD. Although it is an imperfect test due to the inherent variability of the test and the variability observed in individual CF patients over time, longitudinal studies demonstrate that a diabetes diagnosis by OGTT correlates with clinically important CF outcomes including the rate of lung function decline over the next four years (12),

the risk of microvascular complications (27), and risk of early death (1; 2). In a multicenter, multinational study, the OGTT identified patients who benefited from diabetes therapy (28).

The OGTT should be performed in the morning during a period of stable baseline health using the World Health Organization protocol (5). Patients fast for at least 8 hours (water is permitted), and should consume a minimum of 150 grams (600 kcal) of carbohydrate per day for the preceding 3 days (generally not an issue since CF patients have high calorie diets). The patient drinks a standard beverage containing 1.75 grams/kg glucose (maximum 75 grams) dissolved in water, and sits or lies quietly for 2 hours. Glucose levels are measured at baseline and 2 hours. Unless the patient is experiencing classical symptoms of polyuria and polydipsia in the presence of a glucose level >200 mg/dl (11.1 mmol/l), the test should be confirmed by repeat testing.

Screening for CFRD should be performed using the 2-hour 75 gram oral glucose tolerance test. [ADA-E; Consensus]

The Age of Screening for CFRD

Three studies with 811 participants were identified that provided information about the appropriate age at which to start screening for CFRD (1; 21; 24). These studies, a retrospective cohort study (1), a prospective cohort study (21), and a cross-sectional study (24), reported a significantly higher prevalence and incidence of CFRD beyond the first decade of life. Screening included both pancreatic sufficient and insufficient patients. The committee concluded that these findings suggest that annual screening for CFRD should start by age 10 years in all CF patients.

Since clinical deterioration in nutritional and pulmonary status begins 6-24 months prior to a diagnosis of CFRD (29; 30), early detection by annual screening is warranted.

Annual screening for CFRD should begin by age 10 years in all CF patients who do not have CFRD. [ADA B, USPSTF-B]

Screening of CF patients during acute illness

CF patients experience frequent pulmonary exacerbations, some of which require treatment either in the hospital or at home with intravenous antibiotics. Treatment at times includes systemic glucocorticoids. In clinical experience, hyperglycemia that develops during acute illness occasionally resolves after a day or two of medical therapy, but usually lasts for at least 2-6 weeks. CF patients are frequently ill and hyperglycemia returns with each subsequent bout of illness, often several times a year. Insulin deficiency and insulin resistance generally progress over time. Long term microvascular (27) and pulmonary (1; 2) outcomes correlate with duration of CFRD first diagnosed during acute illness, even with intervening periods of normal or impaired glucose tolerance.

During acute illness and/or a pulse of systemic glucocorticoid therapy, glucose levels should be monitored for at least the first 48 hours, preferably fasting and 2 hours post-prandially. If glucose levels do not meet diagnostic criteria for CFRD, testing can be discontinued after 48 hours. For patients receiving therapy at home, SMBG can be performed. However, SMBG levels are not sufficiently accurate to make a diagnosis of CFRD and hyperglycemia should be confirmed by laboratory plasma glucose measurement.

CF patients with acute illness (e.g., pulmonary exacerbation requiring intravenous antibiotics and/or systemic glucocorticoids) should be screened for CFRD by monitoring fasting and 2 hours post-prandial plasma glucose levels for the first 48 hours. If elevated blood glucose levels are found by SMBG, the results must be confirmed by a certified laboratory. [ADA-E; Consensus]

Screening of CF patients during continuous drip enteral feedings

Supplemental continuous drip feedings are commonly prescribed in malnourished CF patients. While there are few data available specific to this situation, mid-feeding hyperglycemia may compromise efforts to gain weight. In this setting, the Committee felt glucose levels in the middle and immediately after the feeding should be measured in the hospital after gastrostomy tube placement, and at these same time points once a month at home using SMBG. SMBG levels are not sufficiently accurate to make a diagnosis of CFRD and hyperglycemia detected by SMBG should be confirmed by laboratory plasma glucose measurement.

Screening for CFRD by measuring mid- and post-feeding plasma glucose levels is recommended for CF patients on continuous enteral feedings, at the time of gastrostomy tube placement and then monthly at home. Elevated glucose levels detected by SMBG must be confirmed by a certified laboratory. [ADA-E; Consensus]

Screening CF patients who are pregnant or planning a pregnancy

Pregnancy is a state of marked insulin resistance, and many women with CF cannot produce the extra insulin required to meet this demand (31-33). In addition to the usual concerns about the effect of hyperglycemia on the fetus, diabetes can exacerbate the difficulties many women with CF have in achieving a positive protein balance and sufficient weight gain during pregnancy (32).

Women with CF not known to have CFRD who are contemplating pregnancy should be evaluated prior to conception to rule-out pre-existing CFRD or be tested immediately upon confirmation of the pregnancy if they have not had an OGTT in the previous 6 months. Because women with CF are at high risk for development of hyperglycemia during pregnancy (gestational diabetes), the 2 hour, 75 gram OGTT should be performed at the end of both the first and second trimesters.

Women with CF who are planning a pregnancy or confirmed pregnant should be screened for pre-existing CFRD with a 2 hour 75gr fasting OGTT if they have not had a normal CFRD screen in the last 6 months,. [ADA-E; Consensus]

Screening for gestational diabetes is recommended at both 12-16 weeks and 24-28 weeks gestation in pregnant women with CF not known to have CFRD, using a 2 hour 75gr OGTT with blood glucose measures at 0, 1, and 2 hours. [ADA-E; Consensus]

Screening for CFRD using a 2-hour 75 gram fasting OGTT is recommended 6-12 weeks after the end of the pregnancy in women with gestational diabetes (diabetes first diagnosed during pregnancy). [ADA-E, Consensus]

Screening CF patients undergoing transplantation

There is an almost universal requirement for insulin in the immediate critical care postoperative period in CF patients undergoing transplantation procedures, and many have long-term insulin requirements after transplantation (34-36). A diagnosis of CFRD prior to transplantation may increase complications of surgery and has a negative impact on survival, at least in the early postoperative period when infection, bleeding and multi-organ failure are the most common causes of death (34; 37). Aggressive management may have a positive impact on outcomes (35).

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. [ADA-E; Consensus]

II. DIAGNOSIS

The Spectrum of Glucose Tolerance Abnormalities in CF

Diabetes is part of a continuum of glucose tolerance abnormalities defined by the ADA ([Online Appendix Table 1](#)). Few CF patients have truly “normal” glucose tolerance. Many patients with normal fasting and 2-h glucose levels have elevation in the middle of the OGTT (indeterminate glycemia (INDET)) or when assessed randomly or by continuous glucose monitoring. Impaired fasting glucose (IFG, 100-125 mg/dl, 5.6-6.9 mmol/l) may also be present

(20; 38). The clinical significance of IFG or INDET in CF is not known. In the general population they are considered pre-diabetic conditions, associated with a high risk of future development of diabetes (39). In pre-pubertal children with CF both IGT and INDET are associated with early onset CFRD (40).

Criteria for the Diagnosis of CFRD in Stable Outpatients

The ADA has established diagnostic criteria for diabetes which include specific fasting glucose levels, 2-h OGTT glucose levels (5), and A1c levels. They are based on the population risk of microvascular disease, and patients with CF are also at risk for these complications (27; 41-43). The Committee questioned whether the diagnostic thresholds should be lower for the CF population, as CFRD is known to have a negative impact on CF pulmonary status (2; 10; 11), since pulmonary disease is the chief morbidity in CFRD. Even less severe glucose tolerance abnormalities such as IGT are associated with lung function decline (12; 17). However, sufficient outcomes-based data are not available at present to determine whether more stringent diagnostic glucose thresholds more appropriately reflect risk for the CF population.

During a period of stable baseline health the diagnosis of CFRD can be made in CF patients according to standard ADA criteria. Testing should be done on 2 separate days to rule out laboratory error unless there are unequivocal symptoms of hyperglycemia (polyuria, polydipsia). [ADA-E; Consensus]

- 1. 2 hour OGTT plasma glucose \geq 200 mg/dl (11.1 mmol/l),**
- 2. Fasting plasma glucose \geq 126 mg/dl (7.0 mmol/l),**

3. **A1c $\geq 6.5\%$ (A1c < 6.5 does not rule out CFRD because this value is often spuriously low in CF),**
4. **Classical symptoms of diabetes (polyuria, polydipsia) in the presence of casual glucose levels ≥ 200 mg/dl (11.1 mmol/l)**

Diagnosing CFRD During Acute Illness or Continuous Feedings

There are special situations when a diagnosis of CFRD must be considered in patients who are not in their baseline state of health. CF patients frequently first develop hyperglycemia during stressors such as acute illness or continuous enteral nutrition. Blood glucose levels may normalize when the stress is not present. In the past, this was called “intermittent CFRD” (44). Longitudinal outcome data have shown that CF morbidity and mortality are associated with CFRD first diagnosed in the acute illness setting when hyperglycemia has persisted beyond 48 hours (1; 2; 27). Based on this experience, the Committee developed the following recommendations.

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 hours. [ADA-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 2 separate days. [ADA-E; Consensus]

Gestational Diabetes in CF

In the general population, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study showed a continuous risk of adverse perinatal and maternal outcomes with increasing glycemia at 24-28 weeks gestation (45), and a recent multicenter, randomized study has demonstrated that aggressive treatment of mild gestational diabetes improves outcomes (46).

Diagnosis of gestational diabetes should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study Group (45) where diabetes is diagnosed based on 0, 1, and 2-hour glucose levels with a 75 gram OGTT if any one of the following is present. CF patients with gestational diabetes are not considered to have CFRD, but require CFRD screening 6-12 weeks after the end of the pregnancy. [ADA-E; Consensus]

- **Fasting plasma glucose ≥ 92 mg/dl (5.1 mmol/l)**
- **1h plasma glucose ≥ 180 mg/dl (10.0 mmol/l)**
- **2h plasma glucose ≥ 155 mg/dl (8.6 mmol/l) [ADA-E; Consensus]**

Differentiating CFRD With and Without Fasting Hyperglycemia

The 1998 CF Foundation CFRD Consensus Conference recommended that CFRD patients with and without fasting hyperglycemia be categorized separately since differences in their treatment needs were unknown (44). However, in a recent retrospective cohort study, 78 patients with CFRD FH- and 77 with CFRD FH+ were treated with insulin with similar positive effects on nutritional status and lung function (1). In addition, in a randomized controlled trial, insulin therapy reversed chronic weight loss in patients with CFRD FH- (28), suggesting that

both groups of CFRD patients should receive insulin treatment and that there is no need to distinguish them diagnostically.

Distinguishing between CFRD with and without fasting hyperglycemia (FH+ and FH-, respectively) is not necessary. [ADA B, USPSTF D]

Date of Onset of CFRD

Defining the date of onset of CFRD is important because long term outcomes are related to disease duration. Glucose tolerance gradually worsens with age in CF due to steadily declining insulin production (1; 47). At any point in time, however, an individual's glucose tolerance may acutely fluctuate depending on his or her general state of health.

The Committee defined the onset of CFRD as the first time a patient meets diabetes diagnostic criteria. Longitudinal studies of patients whose date of diagnosis was considered to be either the first time they had a positive OGTT or the first time they had persistent hyperglycemia during acute illness have shown that duration of CFRD determined by these criteria correlates with clinically relevant outcomes including microvascular complications (27) and mortality (1; 2). Hyperglycemia may resolve without treatment during periods of stable health, but insulin secretion remains insufficient to control glucose under stress, and hyperglycemia will recur.

Although in the general population critically ill patients who experience stress hyperglycemia are not given a diagnosis of diabetes, our recommendation differs for CF patients who develop hyperglycemia during acute exacerbations of their chronic illness. In CF, illness-associated hyperglycemia is a reflection of insulin insufficiency as well as resistance, and is a recurrent

event. Defining the disease by this criterion encourages early intervention to improve long term outcomes.

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

III. MANAGEMENT OF CFRD

The Care Team

As per ADA guidelines, CFRD should be managed by a multidisciplinary team of health professionals with expertise in CF and diabetes (5). The diabetes team should be intimately familiar with CFRD, recognizing differences between this and type 1 and type 2 diabetes pathophysiology and treatment. Good communication between diabetes and CF care providers is essential. Poor team communication and inadequate or conflicting information from healthcare providers have been identified as significant sources of stress for patients with CFRD (48).

While there are few CF-specific data, it has been well established in the general diabetes population that patients must be given the educational tools and support they need to assume a central role in determining their treatment goals and implementing the management plan (5). Initial and on-going diabetes self-management education (DSME) is an integral component of care. In addition to medical issues, the treatment team should address psychosocial issues and recognize the risk of depression. Emotional well-being is strongly correlated to diabetes outcomes, and the additional diagnosis of diabetes can be a significant burden. There may also be financial concerns associated with this diagnosis.

Patients with CFRD should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF. [ADA-E; Consensus]

Patients with CFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards for DSME. [ADA-E; Consensus]

Medical Therapy

Patients with CFRD are insulin insufficient, and based on available data, insulin is the only recommended treatment. There is evidence that CF patients on insulin therapy that achieve glycemic control demonstrate improvement in weight, protein anabolism, pulmonary function and survival. Ten studies (with 783 participants) were identified that addressed insulin therapy in CFRD, including one randomized controlled trial (28), five before-after studies (49-53), one retrospective cohort study (1), one prospective cohort study (54) and two case-control studies (29; 30). These studies reported improved outcomes associated with the use of insulin in patients with CFRD, including those without fasting hyperglycemia. Reported outcomes included improved lung function (5 studies) (29; 30; 49; 51; 54), improved nutritional status (7 studies), (28; 29; 49-53), improved blood glucose/A1c control (2 studies) (50; 53), decreased pulmonary exacerbation rates (1 study) (49), and decreased mortality (1 study) (1).

There is little evidence regarding the superiority of specific insulin regimens in CFRD, and clinical judgment should be used to choose what works best for the patient. CFRD FH+ is usually treated with standard basal-bolus insulin regimens, including a combination of basal and rapid-acting insulin by multiple daily subcutaneous injections, or rapid-acting insulin by continuous subcutaneous infusion (insulin pump) (1; 50; 54; 55). CFRD patients still have endogenous insulin secretion and, except during acute illness, treatment is often similar to that of

patients with type 1 diabetes in the honeymoon period. Specific insulin treatment suggestions are presented in [Online Appendix, Table 2](#).

At the time of the last consensus conference (44) it was not clear whether CFRD patients without fasting hyperglycemia should receive insulin treatment. A recently completed trial demonstrated that pre-meal rapid-acting insulin was able to reverse chronic weight loss in this population, and thus, insulin therapy is indicated (28). Whether basal insulin therapy alone (54) or basal-bolus insulin therapy would be as beneficial as pre-meal insulin alone in CFRD without fasting hyperglycemia remains to be determined.

The available data suggest that oral agents are not as effective as insulin in CFRD. Four studies (with 153 participants) compared oral hypoglycemic therapy with insulin therapy in CFRD (14; 28; 56; 57). These included one randomized controlled trial (28), one randomized controlled crossover trial (57), one prospective cohort study (56), and one retrospective cohort study (14). Oral hypoglycemic agents studied included sulfonylureas (e.g. glibenclamide), metformin, meglitinides (e.g. repaglinide), and thiazolidinediones. The two observational studies (14; 56) reported no differences in lung function, nutritional status, and blood glucose/A1c control comparing those who received oral hypoglycemic agents with those who received insulin. However, two randomized studies suggested that oral hypoglycemic agents were not as effective as insulin in improving nutritional status (28), blood glucose/A1c control (28), and 2-hour and 5-hour insulin area under the curve (AUC) (57).

Potential CF-specific concerns associated with various non-insulin diabetes agents are presented in [Online Appendix Table 3](#).

CF patients with CFRD should be treated with insulin therapy. [ADA-A, USPSTF-B]

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. [ADA-A, USPSTF-D]

Management Goals

The ADA has established plasma glucose goals for people with diabetes (5). These are primarily based on the need to decrease the risk of microvascular complications and thus apply to CFRD with slight modifications ([Online Appendix Table 4](#)). Whether more stringent goals should be adopted for CF patients based on the relationship between hyperglycemia, nutrition and pulmonary disease cannot be determined at present.

To safely achieve glucose goals, the ADA recommends that all patients on insulin therapy perform SMBG at least three times daily (5). Continuous glucose monitoring has been validated in CF and may be useful for clinical management in some patients (58-60).

Patients with CFRD who are on insulin should perform self monitoring of blood glucose at least three times a day. [ADA-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. [ADA-E; Consensus]

The ADA considers A1c the primary target for glycemic control in type 1 and type 2 diabetes (5). Although A1c levels may be spuriously low in CF (7; 20; 21; 23; 27; 59; 61), they are generally higher in CF patients with CFRD compared to those with NGT or IGT, and elevated levels are associated with increased risk of microvascular complications (27). In one study of patients with >10 years duration CFRD, those with retinopathy and/or microalbuminuria had average A1c levels of 8.0% compared to 5.8% in CFRD patients with no eye or kidney changes, and 83% of those with microvascular complications had A1c levels $\geq 7.0\%$ (27), consistent with data in the general diabetes population. For a given patient, the rise and fall in A1c may be a useful indicator of trends in glycemic control. Thus, regular monitoring of A1c is advised.

Hemoglobin A1c measurement is recommended quarterly for patients with CFRD.

[ADA-E; Consensus]

For most patients with CFRD the hemoglobin A1c treatment goal is $\leq 7\%$ 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. [ADA-B; USPSTF-B]

Diet and Exercise in CFRD

CF patients have nutrition requirements which are well established (62-64) . Because adequate caloric intake to maintain BMI is critical to their health and survival, the additional diagnosis of CFRD does not alter usual CF dietary recommendations (Table 3). The goal is to achieve and maintain good nutritional status and normalize blood glucose levels.

CF patients require a very high calorie diet which is usually 120-150% of the daily recommended intake for age, because they have both increased resting energy expenditure and

increased loss of calories through malabsorption. Thus, calories should almost never be restricted. Specifically, a BMI $\geq 50^{\text{th}}$ percentile for ages 2-20 years and for adults a BMI ≥ 22 kg/m² for females and ≥ 23 kg/m² for males is the goal for all persons with CF (64). The use of carbohydrate counting in conjunction with the usual CF diet to guide insulin therapy can help to optimize glycemic control.

CF Foundation evidence-based guidelines for nutritional management are recommended for patients with CFRD. [ADA-E; Consensus]

Exercise is beneficial and is recognized to play a vital role in overall health. Most CF patients including those with severe pulmonary disease (<40% predicted FEV₁) are capable of engaging in strength and aerobic exercise activities (65).

Patients with CFRD should be advised to do moderate aerobic exercise for at least 150 minutes per week. [ADA-E; Consensus]

IV. COMPLICATIONS

Acute Complications of CFRD

Acute complications of CFRD include hypoglycemia and, rarely, diabetic ketoacidosis (DKA) or nonketotic hyperosmolar state (NKHS). Because DKA is so uncommon (66), patients are not routinely taught to measure ketones and any CF patient with DKA should be screened for diabetes autoantibodies to rule out type 1 diabetes.

Hypoglycemia which is not severe (i.e. not requiring assistance from another individual) is common even in CF patients without CFRD. It occurs both in the fasting state, where it may reflect malnutrition and/or increased energy needs due to inflammation and infection, and post-prandially, where it is related to delayed and disordered insulin secretion (67). Insulin-induced hypoglycemia can occur in CFRD as in any patient on insulin therapy, although severe hypoglycemia may be less common in CF (68). While CF patients do not have a good glucagon response to hypoglycemia (69), they have a brisk catecholamine response and normal hypoglycemia awareness. Hypoglycemia education including the use of glucagon is important for patients and their families. Regular SMBG, especially during unusual activity, diet changes, or illness is the best protection against insulin-induced hypoglycemia (5). Patients should be counseled regarding the hypoglycemic effects of alcohol and the risks of driving or operating machinery while hypoglycemic. They should be encouraged to exercise; however, they should be counseled to check their glucose level before vigorous physical activity and to potentially consume extra carbohydrate or alter their insulin dose, depending on the glucose level and the intensity and duration of the planned exercise.

Education about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon, is recommended for patients with CFRD and their care partners.

[ADA-E; Consensus]

Chronic Complications of CFRD

Microvascular disease does not typically become clinically apparent in CFRD until patients have had the disease for at least 5 years and have developed fasting hyperglycemia (27;

41; 70). Tight glycemic control and treatment of microalbuminuria with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) combined with optimal control of hypertension delay progression of diabetic renal disease in the general diabetes population (5). They are assumed to also be beneficial in CFRD although there are no specific data in this population. ACE inhibitors are associated with development of cough in about 10% of subjects and this can occur months after drug initiation, a side effect with special significance in CF as increased cough is among the symptoms of a pulmonary exacerbation (71). Cough may also occur with ARBs but is less frequent (~1%).

Early diabetic nephropathy is characterized by microalbuminuria (a spot urine albumin to creatinine ratio of 30-299 $\mu\text{g}/\text{mg}$ creatinine) (5). Macroalbuminuria (≥ 300 $\mu\text{g}/\text{mg}$ creatinine) indicates clinically significant nephropathy that is progressing toward renal failure. A patient must demonstrate 2 out of 3 abnormal tests within a 3-6 month period to receive a diagnosis. Renal failure due solely to diabetes is uncommon in CF, but microalbuminuria has been reported to occur in 4-21% of individuals with CFRD (27; 41; 70). Recent strenuous exercise, fever, hypertension, congestive heart failure, infection, menstruation and orthostatic proteinuria can result in a positive screen. It is therefore important to exclude other causes before concluding that microalbuminuria is CFRD related.

Diabetic retinopathy is seen in approximately 10-23% of patients with CFRD and is seldom severe, although isolated severe cases have been reported (27; 41; 43; 70; 72). As in all persons with diabetes, dilated retinal exams are necessary in patients with CFRD to evaluate for the presence of retinopathy and the need for treatment.

Annual neurologic assessment and foot evaluation are recommended for the general diabetes population (5). Current data suggest that the severity of this microvascular complication

may be less in CFRD (27). Gastroparesis is common in CF patients with and without CFRD, and the role that CFRD plays in aggravating this condition can be difficult to determine (27).

Gastroparesis may make good glycemic control difficult to achieve.

Hypertension is not uncommon in adult CF patients, particularly after transplantation (41). While atherosclerotic vascular disease has not been described in CF, hypertension is a known risk factor for diabetic kidney disease. As for all persons with diabetes, the recommended blood pressure goals are ≤ 130 mmHg systolic and ≤ 80 mmHg diastolic (5). Hyperlipidemia is rare in CF but may occur after transplantation or in pancreatic sufficient individuals. CFRD is not an autoimmune disease; thus, there is no increased risk of other autoimmune endocrinopathies.

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 should have repeat measurement on a separate day to confirm a diagnosis of hypertension. [ADA-E; Consensus]

Annual monitoring for microvascular complications of diabetes is recommended using ADA guidelines, beginning five 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. [ADA-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. [ADA-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 on immunosuppressive therapy following transplantation. [ADA-E; Consensus]

V. FUTURE RESEARCH CONSIDERATIONS

The CFRD Guidelines Committee identified the following as the most pressing research questions in CFRD:

1. Do non-diabetic CF patients with abnormal glucose tolerance benefit from diabetes therapy and, if so, what method of treatment has the greatest impact on nutritional and pulmonary status?
2. What are the obstacles to OGTT screening of the CF population and how can they best be overcome?
3. What are the mechanisms by which CFRD impacts pulmonary function and survival in CF?
4. Should target goals for glucose and/or A1c in CFRD differ from ADA target goals?
5. How can we assess and improve patient acceptance of the diagnosis of CFRD to improve diabetes self-management and psychosocial well-being?

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Online Appendix Table 1. Classification of oral glucose tolerance categories in CF follows ADA criteria.

Fasting Plasma Glucose	2-Hour OGTT Plasma Glucose
mg/dl (mmol/l)	mg/dl (mmol/l)
<100 (5.6) = normal	<140 (7.8) = NGT
100-125 (5.6-6.9) = IFG	140-199 (7.8-11.1) = IGT
≥126 (7.0) = diabetes	≥200 (11.1) = diabetes

IGF=impaired fasting glucose, NGT=normal glucose tolerance, IGT=impaired glucose tolerance.

When mid-OGTT glucose levels are obtained, levels ≥ 200 mg/dl (11.0 mmol/l) in a person with otherwise NGT are considered indeterminate glycemia (INDET).

Online Appendix Table 2. Best practice principles of insulin therapy for CFRD.

Patients are generally treated with standard basal-bolus insulin therapy by multiple subcutaneous injections or by insulin pump according to the following principles. They should be taught to adjust their insulin dose for special circumstances such as exercise, travel, and acute illness. Those already on insulin therapy usually require 2-4 times as much insulin during illness or steroid therapy. The dose must subsequently be reduced to baseline when the patient recovers. Sometimes a steep increase in insulin requirements is the first sign of an impending acute illness. CF patients often have minimal subcutaneous fat, and thus the shortest needles should be used.

Basal insulin

- Many CF patients require a 50:50 basal:bolus insulin ratio. Some require lower amounts of basal insulin, likely because of residual endogenous insulin secretion.
- Subcutaneous basal insulin is often given in the morning or at mid-day rather than bedtime to reduce the risk of nocturnal hypoglycemia.
- Fasting glucose levels help determine if the basal insulin dose is appropriate.
- CFRD without fasting hyperglycemia does not require basal insulin therapy to normalize fasting glucose levels. Whether basal insulin is beneficial for anabolic purposes is a research question.

Meal Coverage

- Usual doses of rapid-acting insulin for meal coverage range from 0.5 units to about 2.0 units per 15 grams of carbohydrate, with the lower doses being more common when patients are in their stable baseline state of health.
- If meal coverage doses greater than ~2.0 units per 15 grams of carbohydrate are needed, the basal insulin dose is probably not high enough.
- If the meal coverage dose is appropriate (the insulin is matched to the carbohydrate intake), glucose levels pre- and 2-3 hours post-prandially should be about the same.

Correction Dose (“Sensitivity Factor”)

- A typical starting correction dose is 1 unit of rapid-acting insulin to lower the glucose by about 50 mg/dl (2.8 mmol/L).
- During a period when the patient is not eating or exercising, the correction dose can be tested and readjusted as necessary by determining how much it lowers the glucose level over a 2-3 hour period.

Overnight Continuous Drip Gastrostomy Feedings

- These are “long” meals which require about 8-10 hours of insulin coverage.
 - A single injection of regular and NPH insulin prior to the feeding (with or without rapid-acting insulin as correction for the pre-feeding glucose level) covers the feeding. The regular insulin covers the first half and the NPH covers the last half.
 - The usual starting dose is 0.5-1.0 units per 15 grams carbohydrate in the total feeding, divided as half regular and half NPH insulin.
 - Glucose levels 3-4 hours into the feeding are used to adjust the regular insulin dose and at the end of the feeding to adjust the NPH insulin.
-

On-Line Table 3. CF-specific issues related to diabetes medications other than insulin

Insulin Sensitizers

- The biguanides (e.g. metformin) may increase the risk of lactic acidosis in patients with hypoxia. They may cause significant GI discomfort which may interfere with efforts to maintain weight in CF patients.
- The thiozolidinediones (e.g. pioglitazone, rosiglitazone) are potentially attractive for use in CF because they are associated with weight gain and because they have anti-inflammatory actions; however, bone demineralization has been described in association with these agents which is a significant concern in CF and thus would require close monitoring. Liver disease may also be a concern.

Insulin Secretagogues

- Sulfonylureas (e.g. glipizide, glyburide, glimepiride) have been anecdotally associated with hypoglycemia in CF.
- Meglitinides (e.g. repaglinide, nateglinide): In the only randomized controlled clinical trial of diabetes oral agents in CF published to date, repaglinide therapy improved weight in CFRD FH- during the first 6 months of therapy, but this benefit was not sustained and at 12 months all of the initial weight gain had been lost (28).

Alpha-Glucosidase Inhibitors (e.g. acarbose, miglitol)

- There is concern about using a drug that delays absorption and causes GI discomfort in patients with primary malabsorption and malnutrition problems.

Incretin Mimetics (e.g. exenatide, liraglutide), Dpp-4 Inhibitors (e.g. sitagliptin, saxagliptin)

- There are no data in CF.
- GI side-effects of the incretin mimetics may be unacceptable in CF, including delayed gastric emptying, nausea, and weight loss.
- The dpp-4 inhibitors are associated with pancreatitis which is a concern in pancreatic sufficient CF patients.

Amylin Analogs (e.g. pramlintide)

- There are no data in CF.
 - Drugs that reduce post-prandial glucagon levels may be irrelevant in CF given the low glucagon levels present in these patients.
-

Online Appendix Table 4. Plasma glucose goals for patients with CFRD*

	Fasting and Pre-Meal	2-3h Post Prandial	Bedtime
	mg/dl (mmol/l)	mg/dl (mmol/l)**	mg/dl (mmol/l)
Adults	70-130 (3.9-7.2)	<180 (10.0)	90-150 (5.0-8.3)
Adolescents	90-130 (5.0-7.2)	<180 (10.0)	90-150 (5.0-8.3)
School-Age Children	90-180 (5.0-10.0)	<200 (11.1)	100-180 (5.6-10.0)
Children <6 yrs	100-180 (5.6-10.0)	<200 (11.1)	110-200 (6.1-11.1)
Pregnant women	≤ 95 (5.3)	≤ 120 (6.7)	60-99 (3.3-5.5)

* Similar to ADA criteria, except that the post-prandial level is obtained 2-3 hours after the start of the meal rather than 1-2 hours because of delayed gastric emptying in CF

**criteria also apply to overnight gastrostomy drip feedings

Table 1. Evidence-grading system for clinical practice recommendations.

American Diabetes Association Classification System				
Level of evidence	Description			
A	<p>Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including:</p> <ul style="list-style-type: none"> • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis <p>Compelling non experimental evidence, i.e., “all or none” rule developed by the Centre for Evidence-Based Medicine at Oxford</p> <p>Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including</p> <ul style="list-style-type: none"> • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis 			
B	<p>Supportive evidence from well-conducted cohort studies, including:</p> <ul style="list-style-type: none"> • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies <p>Supportive evidence from a well-conducted case-control study</p>			
C	<p>Supportive evidence from poorly controlled or uncontrolled studies including:</p> <ul style="list-style-type: none"> • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high-potential for bias (such as case series with comparison with historical controls) <p>Conflicting evidence with the weight of evidence supporting the recommendation</p>			
E	Expert consensus or clinical experience			
US Preventive Service Task Force Recommendation Classification System				
	Estimate of Effect			
Quality of Evidence	Substantial	Moderate	Small	Zero/Negative*
High	A	B	C	D
Moderate	B	B	C	D
Low	Insufficient (I)			

*Note, a study with significant findings *against* something is given a grade of D.

Table 2. Summary of Recommendations for the Clinical Care of CFRD

Screening Recommendations

1. The use of A1c as a screening test for CFRD is not recommended. [ADA-B; USPSTF-D]
2. Screening for CFRD should be performed using the 2-hour 75 gram oral glucose tolerance test. [ADA-E; Consensus]
3. Annual screening for CFRD should begin by age 10 years in all CF patients who do not have CFRD. [ADA B, USPSTF-B]
4. CF patients with acute illness (e.g., pulmonary exacerbation requiring intravenous antibiotics and/or systemic glucocorticoids) should be screened for CFRD by monitoring fasting and 2 hours post-prandial plasma glucose levels for the first 48 hours. If elevated blood glucose levels are found by SMBG, the results must be confirmed by a certified laboratory. [ADA-E; Consensus]
5. Screening for CFRD by measuring mid- and post-feeding plasma glucose levels is recommended for CF patients on continuous enteral feedings, at the time of gastrostomy tube placement and then monthly by SMBG. Elevated glucose levels detected by SMBG must be confirmed by a certified laboratory. [ADA-E; Consensus]
6. Women with CF who are planning a pregnancy or confirmed pregnant should be screened for pre-existing CFRD with a 2 hour 75gr fasting OGTT if they have not had a normal CFRD screen in the last 6 months,. [ADA-E; Consensus]
7. Screening for gestational diabetes is recommended at both 12-16 weeks and 24-28 weeks gestation in pregnant women with CF not known to have CFRD, using a 2 hour 75gr OGTT with blood glucose measures at 0, 1, and 2 hours. [ADA-E; Consensus]

8. Screening for CFRD using a 2-hour 75 gram fasting OGTT is recommended 6-12 weeks after the end of the pregnancy in women with gestational diabetes (diabetes first diagnosed during pregnancy). [ADA-E, Consensus]
9. 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. [ADA-E; Consensus]

Diagnosis Recommendations

1. During a period of stable baseline health the diagnosis of CFRD can be made in CF patients according to standard ADA criteria. Testing should be done on 2 separate days to rule out laboratory error unless there are unequivocal symptoms of hyperglycemia (polyuria, polydipsia). [ADA-E; Consensus]
 - 2 hour OGTT plasma glucose ≥ 200 mg/dl (11.1 mmol/l),
 - Fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l),
 - A1c $\geq 6.5\%$ (A1c < 6.5 does not rule out CFRD because this value is often spuriously low in CF),
 - Classical symptoms of diabetes (polyuria, polydipsia) in the presence of casual glucose levels ≥ 200 mg/dl (11.1 mmol/l)
2. 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 hours. [ADA-E; Consensus]
3. 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 2 separate days. [ADA-E; Consensus]
 4. Diagnosis of gestational diabetes should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study Group (45) where diabetes is diagnosed based on 0, 1, and 2-hour glucose levels with a 75 gram OGTT if any one of the following is present. CF patients with gestational diabetes are not considered to have CFRD, but require CFRD screening 6-12 weeks after the end of the pregnancy. [ADA-E; Consensus]
 - Fasting plasma glucose ≥ 92 mg/dl (5.1 mmol/l)
 - 1h plasma glucose ≥ 180 mg/dl (10.0 mmol/l)
 - 2h plasma glucose ≥ 155 mg/dl (8.6 mmol/l) [ADA-E; Consensus]
 5. Distinguishing between CFRD with and without fasting hyperglycemia (FH+ and FH-, respectively) is not necessary. [ADA B, USPSTF D]
 6. The onset of CFRD should be defined as the date a person with CF first meets diagnostic criteria, even if hyperglycemia subsequently abates. [ADA-E; Consensus]

Management Recommendations

1. Patients with CFRD should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF. [ADA-E; Consensus]

2. Patients with CFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards for DSME. [ADA-E; Consensus]
3. Patients with CFRD should be treated with insulin therapy. [ADA-A, USPSTF-B]
4. 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 [ADA-A, USPSTF-D]
5. Patients with CFRD who are on insulin should perform self monitoring of blood glucose at least three times a day. [ADA-E; Consensus]
6. 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. [ADA-E; Consensus]
7. Hemoglobin A1c measurement is recommended quarterly for patients with CFRD. [ADA-E; Consensus]
8. For many patients with CFRD the hemoglobin A1c treatment goal is $\leq 7\%$, bearing in mind that higher or lower goals may be indicated for some patients, and that individualization is important. [ADA-B; USPSTF-B]
9. CF Foundation evidence-based guidelines for nutritional management are recommended for patients with CFRD. [ADA-E; Consensus]
10. Patients with CFRD should be advised to do moderate aerobic exercise for at least 150 minutes per week. [ADA-E; Consensus]

Diabetes Complications Recommendations

1. Education about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon, is recommended for patients with CFRD and their care partners. [ADA-E; Consensus]
 2. 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 should have repeat measurement on a separate day to confirm a diagnosis of hypertension. [ADA-E; Consensus]
 3. Annual monitoring for microvascular complications of diabetes is recommended using ADA guidelines, beginning five 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. [ADA-E; Consensus]
 4. 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. [ADA-E; Consensus]
 5. 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 on immunosuppressive therapy following transplantation. [ADA-E; Consensus]
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Table 3. Dietary recommendations for CFRD

DRI=daily recommended intake

Nutrient	Type 1 and 2 Diabetes	CFRD
Calories	As needed for growth, maintenance, or reduction diets	1.2-1.5 times DRI for age; individualized based on weight gain and growth.
Carbohydrate	Individualized. Monitor carbohydrates to achieve glycemic control. Choose from fruits, vegetables, whole grains and fiber containing foods, legumes and low fat milk. Sugar alcohols and non-nutritive sweeteners are safe within FDA established consumption guidelines.	Individualized. Carbohydrates should be monitored to achieve glycemic control. Use of artificial sweeteners should be used sparingly due to lower calorie content.
Fat	Limit saturated fat to <7% of total calories, intake of trans fat should be minimized, limit dietary cholesterol <200mg/day. Consume two or more servings per week of fish high in n-3 polyunsaturated fatty acids.	No restriction on type of fat. High fat necessary for weight maintenance. Aim for 35-40% total calories.
Protein	15-20% of total calories; reduction to 0.8-1.0 gm/kg with nephropathy	Approximately 1.5-2.0 times the DRI for age, no reduction for nephropathy
Sodium	<2300 mg/day for blood pressure control	Liberal, high salt diet, especially in warm conditions and/or when exercising
Vitamins, Minerals	No supplementation necessary unless deficiency noted	Routine supplementation of fat soluble vitamins (ADEK) and a multivitamin
Alcohol	If consumed, limit to a moderate amount; 1 drink per day for women, 2 drinks per day or less for men	Consult with physician due to the higher prevalence of liver disease in CF and possible use of hepatotoxic drugs
Special Circumstances		
-Gestational DM	-Restricted calories/carbohydrate for weight and blood glucose control	-No calorie or carbohydrate restriction. Adequate kcals for weight gain.
-IGT	-Weight loss of 5-10% recommended, low fat diet	-No weight loss, spread carbs throughout day, consume nutrient dense beverages