Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes

A position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society

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Cystic fibrosis–related diabetes (CFRD) is the most common co-morbidity in people with cystic fibrosis (CF), occurring in ~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, CFF in collaboration with ADA and 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. The reviews 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 U.S. 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 or for which limited evidence was available in the literature. 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.

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

Although 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 of 62 participants with CF and 107 healthy control subjects reported that A1C levels were higher in the CF group than among the control subjects, leading them to suggest that the use of A1C was appropriate (18). However, six studies (including two prospective cohort studies [7,21], two cross-sectional studies [19,20], one case-control study [23], and one case series [22]) with a total of 477 participants demonstrated low degrees of correlation between A1C and glucose tolerance status (7,19–23). Additionally, a cross-sectional study of 191 participants...
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Table 1—Evidence-grading system for clinical practice recommendations

| Level of evidence | Description |
|-------------------|-------------|
| A                 | Clear evidence from well-conducted, generalizable, randomized, controlled trials that are adequately powered, including • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., “all-or-none” rule developed by the Centre for Evidence-Based Medicine at Oxford |
| B                 | Supportive evidence from well-conducted, randomized, controlled trials that are adequately powered, including • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis |
| C                 | Supportive evidence from poorly controlled or uncontrolled studies, including • 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) Conflicting evidence with the weight of evidence supporting the recommendation |
| E                 | Expert consensus or clinical experience |

USPSTF recommendation classification system

| Quality of evidence | Estimate of effect |
|---------------------|--------------------|
| High                | Substantial A      |
| Moderate            | Moderate B         |
| Low                 | Small C           |
|                     | Zero/negative* D   |

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

with CF demonstrated a low positive predictive value of the A1C test (24).

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 is not recommended as a screening tool because 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 (FPG) identifies patients with CFRD with but not those without fasting hyperglycemia (FH), 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 given that 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 4 years (12), the risk of microvascular complications (27), and the risk of early death (1,2).

In a multicenter, multinational study, the OGTT identified patients who benefited from insulin therapy (28).

The OGTT should be performed in the morning during a period of stable baseline health (at least 6 weeks since an acute exacerbation) using the World Health Organization protocol (5). Patients fast for at least 8 h (water is permitted) and should consume a minimum of 150 g (600 kcal) of carbohydrate per day for the preceding 3 days (generally not an issue because CF patients have high-calorie diets). The patient drinks a standard beverage containing 1.75 g/kg glucose (maximum 75 g) dissolved in water and sits or lies quietly for 2 h. Glucose levels are measured at baseline and 2 h. 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) or has two more diagnostic criteria for diabetes (such as both fasting and 2-h glucose elevation or a diabetes pattern on OGTT in the presence of an A1C level >6.5%), the test should be confirmed by repeat testing.

Screening for CFRD should be performed using the 2-h 75-g OGTT. (ADA-E; Consensus)

The age of screening for CFRD

Three studies with a total of 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 suf-
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 a 2-h 75-g OGTT. (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 pulmonary exacerbation requiring intravenous antibiotics and/or systemic glucocorticoids should be screened for CFRD by monitoring fasting and 2-h postprandial plasma glucose levels for the first 48 h. 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 immediate postfeeding plasma glucose levels is recommended for CF patients on continuous enteral feedings, at the time of gastrostomy feeding initiation 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 preexisting CFRD with a 2-h 75-g fasting OGTT if they have not had a normal CFRD screen in the last 6 months. (ADA-E; Consensus)
7. Screening for gestational diabetes mellitus 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-h 75-g OGTT with blood glucose measures at 0, 1, and 2 h. (ADA-E; Consensus)
8. Screening for CFRD using a 2-h 75-g fasting OGTT is recommended 6–12 weeks after the end of the pregnancy in women with gestational diabetes mellitus (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 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. (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 and polydipsia); a positive FPG or A1C can be used as a confirmatory test, but if it is normal the OGTT should be performed or repeated. If the diagnosis of diabetes is not confirmed, the patient resumes routine annual testing. (ADA-E; Consensus)
   - 2-h OGTT plasma glucose ≥200 mg/dl (11.1 mmol/l)
   - FPG ≥126 mg/dl (7.0 mmol/l)
   - A1C ≥6.5% (A1C <6.5% does not rule out CFRD because this value is often spuriously low in CF.)
   - Classical symptoms of diabetes (polyuria and polydipsia) in the presence of a casual glucose level ≥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 FPG levels ≥126 mg/dl (7.0 mmol/l) or 2-h postprandial plasma glucose levels ≥200 mg/dl (11.1 mmol/l) persist for more than 48 h. (ADA-E; Consensus)
3. The diagnosis of CFRD can be made in CF patients on enteral continuous drip feedings when mid- or postfeeding plasma glucose levels exceed 200 mg/dl (11.1 mmol/l) on 2 separate days. (ADA-E; Consensus)
4. Diagnosis of gestational diabetes mellitus should be made based on the recommendations of the IADPSG (45) where diabetes is diagnosed based on 0-, 1-, and 2-h glucose levels with a 75-g OGTT if any one of the following is present:
   - FPG ≥92 mg/dl (5.1 mmol/l)
   - 1-h plasma glucose ≥180 mg/dl (10.0 mmol/l)
   - 2-h plasma glucose ≥153 mg/dl (8.5 mmol/l) (ADA-E; Consensus)
CF patients with gestational diabetes mellitus are not considered to have CFRD, but require CFRD screening 6–12 weeks after the end of the pregnancy. (ADA-E; Consensus)
5. Distinguishing between CFRD with and without FH 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 SMBG 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. A1C measurement is recommended quarterly for patients with CFRD. (ADA-E; Consensus)
8. For many patients with CFRD, A1C treatment goal is <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. CFF 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 min per week. (ADA-E; Consensus)

(continued on following page)
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Table 2—Continued

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 or >90th percentile for age and sex for pediatric patients 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 5 years after the diagnosis of CFRD or, if the exact time of diagnosis is not known, at the time that FH is first diagnosed. (ADA-E; Consensus)

4. Patients with CFRD diagnosed with hypertension or microvascular complications should receive treatment as recommended by 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 immunosuppressive therapy following transplantation. (ADA-E; Consensus)

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 (IGT).

During acute illness and/or a pulse of systemic glucocorticoid therapy, glucose levels should be monitored for at least the first 48 h, preferably fasting and 2 h postprandially. If glucose levels do not meet diagnostic criteria for CFRD, testing can be discontinued after 48 h. 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 pulmonary exacerbation requiring intravenous antibiotics and/or systemic glucocorticoids should be screened for CFRD by monitoring fasting and 2-h postprandial plasma glucose levels for the first 48 h. If elevated blood glucose levels are found by SMBG, the results must be confirmed by a certified laboratory. (ADA-E; Consensus)

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

Screening for CFRD using a 2-h 75-g fasting OGTT with blood glucose levels detected by SMBG must be discontinued after 48 h. 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.

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Screening for CFRD using a 2-h 75-g fasting OGTT with blood glucose levels detected by SMBG must be discontinued after 48 h. 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.
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 multiorgan 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 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. (ADA-E; Consensus)

**DIAGNOSIS** (Fig. 1)

The spectrum of glucose tolerance abnormalities in CF

Diabetes is part of a continuum of glucose tolerance abnormalities defined by ADA (supplementary Table 1, available at http://care.diabetesjournals.org/cgi/content/full/dc10-1768/DC1). 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 prepubertal children with CF both IGT and INDET are associated with early-onset CFRD (40).

Criteria for the diagnosis of CFRD in stable outpatients

ADA has established diagnostic criteria for diabetes that 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), given that 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 outcome-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 two separate days to rule out laboratory error unless there are unequivocal symptoms of hyperglycemia (polyuria and polydipsia); a positive FPG or A1C can be used as a confirmatory test, but if it is normal the OGTT should be performed or repeated. If the diagnosis of diabetes is not confirmed, the patient resumes routine annual testing. (ADA-E; Consensus)

- 2-h OGTT plasma glucose ≥200 mg/dl (11.1 mmol/l)
- FPG ≥126 mg/dl (7.0 mmol/l)
- A1C ≥6.5% (A1C <6.5% does not rule out CFRD because this value is often spuriously low in CF.)
- Classical symptoms of diabetes (polyuria and polydipsia) in the presence of a casual glucose level ≥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 h (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 FPG levels ≥126 mg/dl (7.0 mmol/l) or 2-h postprandial plasma glucose levels ≥200 mg/dl (11.1 mmol/l) persist for more than 48 h. (ADA-E; Consensus)**

The diagnosis of CFRD can be made in CF patients on enteral continuous drip feedings when mid- or postfeeding plasma glucose levels exceed 200 mg/dl (11.1 mmol/l) on two separate days. (ADA-E; Consensus)

**Gestational diabetes mellitus in CF**

In the general population, the Hyperglycemia and Adverse Pregnancy Outcome (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 mellitus improves outcomes (46).

**Diagnosis of gestational diabetes mellitus should be made based on the recommendations of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (45) where diabetes is diagnosed based on 0-, 1-, and 2-h glucose levels with a 75-g OGTT if any one of the following is present:**

- FPG ≥92 mg/dl (5.1 mmol/l)
- 1-h plasma glucose ≥180 mg/dl (10.0 mmol/l)
- 2-h plasma glucose ≥153 mg/dl (8.5 mmol/l)

**CF patients with gestational diabetes mellitus are not considered to have CFRD but require CFRD screening 6–12 weeks after the end of the pregnancy. (ADA-E; Consensus)**

**Differentiating CFRD with and without FH**

The 1998 CFF CFRD Consensus Conference recommended that CFRD patients with and without FH (FH+ and FH-, respectively) be categorized separately because 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 FH 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 as a result of 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)**

**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 pathophysiol-
ogy and treatment. Good communication between diabetes and CF care providers is essential. Poor team communication and inadequate or conflicting information from health care providers have been identified as significant sources of stress for patients with CFRD (48).

Although 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 ongoing diabetes self-management education (DSME) is an integral component of care. In addition to medical issues, the role of the patient-centered medical team is to encourage and support the patient and family. The treatment team should address psychosocial issues and recognize the risk of depression. Emotional well-being is strongly correlated with 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 DSME 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 who achieve glycemic control demonstrate improvement in weight, protein anabolism, pulmonary function, and survival. Ten studies (with a total of 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 FH. Reported outcomes included improved lung function (five studies) (29,30,49,51,54), improved nutritional status (seven studies), (28,29,49–53), improved blood glucose/A1C control (two studies) (50,53), decreased pulmonary exacerbation rates (one study) (49), and decreased mortality (one study) (1).

There is little evidence regarding the superiority of specific insulin regimens in CFRD, and clinical judgment should be used to choose the best regimen for each 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. During acute illness or systemic glucocorticoid treatment, insulin requirements steeply rise, two- to fourfold. Once the illness resolves, it generally takes about 4–6 weeks for insulin requirements to gradually return to baseline. Careful monitoring for hypoglycemia is required during this period. Specific insulin treatment suggestions are presented in supplementary Table 2.

At the time of the last consensus conference (44), it was not clear whether CFRD patients without FH should receive insulin treatment. A recently completed trial demonstrated that treatment with premeal 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 premeal insulin alone in CFRD FH- remains to be determined.

The available data suggest that oral agents are not as effective as insulin in CFRD. Four studies (with a total of 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., glyburide), metformin, meglitinides (e.g., repaglinide), and thiazolidinediones. The two observational studies (14,56) reported no differences in lung function, nutritional status, or 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-h and 5-h insulin area under the curve (57). Potential CF-specific concerns associated with various noninsulin diabetes agents are presented in supplementary 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**

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 (supplementary 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, 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 SMBG 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)

ADA considers A1C the primary target for glycemic control in type 1 and type 2 diabetes (5). Although A1C levels
A1C measurement is recommended quarterly for patients with CFRD. (ADA-E; Consensus)

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 that 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.

For most patients with CFRD, the A1C treatment goal is ≤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)

CFF evidence–based guidelines for nutritional management are recommended for patients with CFRD. (ADA-E; Consensus)

Exercise is beneficial and is known 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 min per week. (ADA-E; Consensus)

COMPLICATIONS

Acute complications of CFRD
Acute complications of CFRD include hypoglycemia and, rarely, diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state. 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 that 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 postprandially, 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 FH (27,41,70). Tight glycemic control and treatment of microalbuminuria with ACE inhibitors or angiotensin receptor blockers 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 ~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 angiotensin receptor blockers but is less frequent (~1%).

Early diabetic nephropathy is characterized by microalbuminuria (a spot urine ACR of 30–299 µg/mg creatinine) (5). Macroalbuminuria (≥300 µg/mg creatinine) indicates clinically significant nephropathy that is progressing toward renal failure. A patient must demonstrate two out of three abnormal tests within a 3- to 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 ~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 ~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). Although 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 systolic and diastolic blood pressure goals are ≤130 mmHg and ≤80 mmHg, respectively, or <90th percentile for age and sex for pediatric patients (5). Hyperlipidemia is rare in CF but may occur, especially after transplantation or in pancreatic-sufficient individuals. While cholesterol levels are typically quite low, isolated triglyceride elevation has been noted. Because CF patients are at low risk for atherosclerotic cardiovascular disease, it is not clear that lipid elevation requires treatment in this population, and there are no data regarding the efficacy or safety of medical therapy for CF dyslipidemia. 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 or >90th percentile for age and sex for pediatric patients 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 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. (ADA-E; Consensus)

Patients with CFRD diagnosed with hypertension or microvascular complications should receive treatment as recommended by 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 immunosuppressive therapy following transplantation. (ADA-E; Consensus)
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FUTURE RESEARCH CONSIDERATIONS — The CFRD Guidelines Committee identified the following as the most pressing research questions in CFRD: 1) Do nondiabetic 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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References
1. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis–related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 2009;32:1626–1631.
2. Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. Diabetes Care 2005;28:2141–2144.
3. Miller RJ, Tildesley HD, Wilcox PG, Zhang H, Kreissman SH. Sex disparities in effects of cystic fibrosis–related diabetes on clinical outcomes: a matched study. Can Respir J 2008;15:291–294.
4. Sims EJ, Green MW, Mehta A. Decreased lung function in female but not male subjects with established cystic fibrosis–related diabetes. Diabetes Care 2005;28:1581–1587.
5. American Diabetes Association. Clinical Practice Recommendations—2010. Diabetes Care 2010;33(Suppl. 1):S1–S100.
6. Sawaya GF, Guirguis-Blake J, LeFevre M, Harris R, Petitti D. Update on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit. Ann Intern Med 2007;147:871–875.
7. Bismuth E, Laborde K, Taupin P, Velho G, Ribaud V, Jennane F, Grasset E, Sermet I, de Blic J, Lenoir G, Robert J. Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis. J Pediatr 2008;152:540–545.
8. Cawood T, McKenna M, Gallagher CG, Smith D, Chung WY, Gibney J, O’Shea D. Cystic fibrosis related diabetes in adults.

Irish Med J 2006;99:83–86.
9. Finkelstein SM, Wielinski CL, Elliott GR, Warwick WJ, Barbosa J, Wu SC, Klein DJ. Diabetes mellitus associated with cystic fibrosis. J Pediatr 1988;112:373–377.
10. Koch C, Rainsius M, Madassani U, Harms HK, Hodson ME, Castella G, McKenzie SG, Navarro J, Strandvik B, Investigators of the European Pediatric Cystic Fibrosis. Presence of cystic fibrosis–related diabetes mellitus is tightly linked to poor lung function in patients with cystic fibrosis: data from the European Pediatric Registry of Cystic Fibrosis. Pediatr Pulmonol 2001;32:343–350.
11. Marshall BC, Butler SM, Stoddard M, Moran AM, Liou TG, Morgan WJ. Epidemiology of cystic fibrosis–related diabetes. J Pediatr 2005;146:681–687.
12. Milla CE, Warwick WJ, Moran A. Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. Am J Respir Crit Care Med 2000;162:891–895.
13. Peraldo M, Fasulo A, Chiappini E, Milò C, Marianelli L. Evaluation of glucose tolerance and insulin secretion in cystic fibrosis patients. Horm Res 1998;49:65–71.
14. Rosenhecker J, Höller R, Steinkamp G, Eichler I, Smaczny C, Ballmann M, Posselt HG, Bargon J, von der Hardt H. Diabetes mellitus in patients with cystic fibrosis: the impact of diabetes mellitus on pulmonary function and clinical outcome. Eur J Med Res 2001;6:345–350.
15. Schaedel C, de Monestrol I, Hjetle L, Johannesson M, Kornfalt R, Lindblad A, Strandvik B, Wahlgren I, Holmberg L. Predictors of deterioration of lung function in cystic fibrosis. Pediatr Pulmonol 2002;33:483–491.
16. White H, Pollard K, Etherington C, Clifton I, Morton AM, Owen D, Conway SP, Peckham DG. Nutritional decline in cystic fibrosis–related diabetes: the effect of intensive nutritional intervention. J Cyst Fibros 2009;8:179–185.
17. Tolfé S, Moreno JC, Mäiz L, Alonso M, Escobar H, Barrio R. Insulin secretion abnormalities and clinical deterioration related to impaired glucose tolerance in cystic fibrosis. Eur J Endocrinol 2005;152:247–254.
18. Hunkert F, Lietz T, Stach B, Kiess W. Potential impact of HbA1c determination on clinical decision making in patients with cystic fibrosis–related diabetes (Letter). Diabetes Care 1999;22:1008–1010.
19. Franzese D, Valerio G, Buono P, Spagnuolo MI, Sepe A, Mozzillo E, De Simone I, Raia V. Continuous glucose monitoring system in the screening of early glucose derangements in children and adolescents with cystic fibrosis. J Pediatr Endocrinol Metab 2008;21:109–116.
20. Elder DA, Wooldridge JL, Dolan LM, D’Alessio DA. Glucose tolerance, insulin...
secretion, and insulin sensitivity in children and adolescents with cystic fibrosis and no prior history of diabetes. J Pediatr 2007;151:653–658
21. Solomon MP, Wilson DC, Corey M, Kalnins D, Zieleinski J, Tsui LC, Pencharz P, Durie P, Sweezy NB. Glucose intolerance in children with cystic fibrosis. J Pediatr 2003;142:128–132
22. Holl RW, Buck C, Babka C, Wolff A, Thon A. HbA1c is not recommended as a screening test for diabetes in cystic fibrosis. Diabetes Care 2000;23:126
23. Godbout A, Hammama I, Potvin S, Mainville D, Rakel A, Berthiaume Y, Chassion JL, Codere L, Rabasa-Lhoret R. No relationship between mean plasma glucose and glycaated haemoglobin in patients with cystic fibrosis-related diabetes. Diabetes Metab 2008;34:568–573
24. Lanng S, Hansen A, Thorsteinsson B, Nerup J, Koch C. Glucose tolerance in patients with cystic fibrosis: a five year prospective study. BMJ 1995;311:655–659
25. Yung B, Kemp M, Hooper J, Hodson ME. Diagnosis of cystic fibrosis-related diabetes: a selective approach in performing the oral glucose tolerance test based on a combination of clinical and biochemical criteria. Thorax 1999;54:40–43
26. International Organization for Standardization. Requirements for in vitro blood glucose monitoring systems for self-testing in managing diabetes mellitus. ISO/TC 212/WG 3. Draft International Standard ISO/DIS 15197; Geneva, ISO, 2001
27. Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla C, Morran A. Microvascular complications in cystic fibrosis-related diabetes. Diabetes Care 2007;30:1056–1061
28. Moran A, Pekow P, Grover P, Zorn M, Slovis B, Plewski J, Tullis E, Liou TG, Allen H. Cystic Fibrosis Related Diabetes Therapy Study Group. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the Cystic Fibrosis Related Diabetes Therapy trial. Diabetes Care 2009;32:1783–1788
29. Rolon MA, Benali K, Munck A, Navarro J, Chemin A, Tana-Rufi N, Czernichow P, Polak M. Cystic fibrosis-related diabetes mellitus: clinical impact of prediabetes and effects of insulin therapy. Acta Paediatr 2001;90:860–867
30. Lanng S, Thorsteinsson B, Nerup J, Koch C. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. Acta Paediatrica 1994;83:849–853
31. Goss CH, Rubenfeld GD, Otto K, Aitken ML. The effect of pregnancy on survival in women with cystic fibrosis. Chest 2003;124:1460–1468
32. Hardin DS, Rice J, Cohen RC, Ellis KJ, Nick JA. The metabolic effects of pregnancy in cystic fibrosis. Obstet Gynecol 2005;106:367–375
33. McMullen AH, Pasto DJ, Frederick PD, Konstan MW, Morgan WJ, Schechter MS, Wagener JS. Impact of pregnancy on women with cystic fibrosis. Chest 2006;129:706–711
34. Bradbury RA, Shirkhedkar D, Glanville AR, Campbell LV. Prior diabetes mellitus is associated with increased morbidity in cystic fibrosis patients undergoing bilateral lung transplantation: an ‘orphan’ area? A retrospective case-control study. Intern Med J 2009;39:384–388
35. Hadjiliadis D, Madill J, Chaparro C, Tsang A, Waddell TF, Singer LG, Hutcheon MA, Keshavjee S, Elizabeth Tullis D. Incidence and prevalence of diabetes mellitus in patients with cystic fibrosis undergoing lung transplantation before and after lung transplantation. Clin Transplant 2005;19:773–778
36. Melck KL, Langham MR Jr, Gonzalez-Peresu CM, Hooper J, Hemming AW. Combined en bloc liver pancreas transplantation for children with CF. Liver Transpl 2007;13:406–409
37. Madden BP, Hodson ME, Tsang V, Radley-Smith R, Khaghani A, Yacoub MY. Intermediate-term results of heart-lung transplantation for cystic fibrosis. Lancet 1992;339:1583–1587
38. Mueller-Brandes C, Holl RW, Nastoll M, Ballmann M. New criteria for impaired fasting glucose and screening for diabetes in cystic fibrosis. Eur Respir J 2005;25:715–717
39. Sosenko JM, Palmer MP, Raikin-Mervlis L, Kristicher JP, Cuthbertson D, Mahon J, Greenbaum CJ, Cowie CC, Skyler JS. Diabetes Prevention Trial-Type 1 Study Group. Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1. Diabetes Care 2009;32:1603–1607
40. Ode KI, Frohnhert B, Laguna T, Phillips J, Holmes B, Regelsmann W, Thomas W, Morran AM. Oral glucose tolerance testing in children with cystic fibrosis. Pediatr Diabetes 25 February 2010 [Epub ahead of print]
41. Arsenen HU, Lanng S, Pressler T, Laugesen CS, Mathiesen ER. Cystic fibrosis-related diabetes: the presence of microvascular diabetes complications. Diabetes Care 2006;29:2660–2663
42. Lanng S, Thorsteinsson B, Lund-Andersen C, Nerup J, Schiotz PO, Koch C. Diabetes mellitus in Danish cystic fibrosis patients: prevalence and late diabetic complications. Acta Paediatr 1994;83:72–77
43. Yang B, Landers A, Mathalone B, Gygi KM, Hodson ME. Diabetic retinopathy in adult patients with cystic fibrosis-related diabetes. Respir Med 1998;92:871–872
44. Moran A, Hardin D, Rodman D, Allen HF, Beall RJ, Borowitz D, Brunzell C, Campbell PW, Chresrown SE, Duchow C, Fink RJ, FitzSimmons SC, Hamilton N, Hirsch I, Howenstine MS, Klein DJ, Madhun Z, Pencharz PB, Quittner AL, Robbins MK, Schindler T, Schissel K, Schwarzenberg SJ, Stallings VA, Tullis DE, Zipf WB. Diagnosis, screening, and management of cystic fibrosis related diabetes mellitus: a consensus conference report. Diabetes Res Clin Pract 1999;45:61–73
45. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaowarund U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002
46. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, Wapner R, Varner MW, Rouse DJ, Thorp JM Jr, Sciscione A, Catalano P, Harper M, Saade G, Lain KY, Sorokin Y, Peaceman AM, Tolosa JE, Anderson GB, Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339–1348
47. Lombardo F, De Luca F, Rosano M, Sferruzza C, Luciano C, Arigo T, Messina MF, Crisafulli G, Wolever IMS, Valenzise M, Cucinotta D. Natural history of glucose tolerance, beta-cell function and peripheral insulin sensitivity in cystic fibrosis patients with fasting euglycemia. Eur J Endocrinol 2003;149:53–59
48. Collins S, Reynolds F. How do adults with cystic fibrosis cope following a diagnosis of diabetes? J Adv Nurs 2008;64:478–487
49. Mozillo E, Franzese A, Valerio G, Sepe A, De Simone I, Mazzarella G, Ferri P, Raia V. One-year glibenclamide treatment can improve the course of lung disease in children and adolescents with cystic fibrosis and early glucose derangements. Pediatric Diabetes 2009;10:162–167
50. Hardin DS, Rice J, Rice M, Rosenblatt R. Use of the insulin pump to treat cystic fibrosis-related diabetes. J Cyst Fibros 2009;8:174–178
51. Mohan K, Israel KL, Miller H, Grainger R, Ledson MJ, Walsh MJ. Long-term effect of insulin treatment in cystic fibrosis-related diabetes. Respirilation 2008;76:181–186
52. Rafi M, Chapman K, Stewart C, Kelly E, Hanna A, Wilson DC, Tullis E, Pencharz PB. Changes in response to insulin and the effects of varying glucose tolerance on whole-body protein metabolism in patients with cystic fibrosis. Am J Clin Nutr 2005;81:421–426
53. Hayes DR, Sheehan JP, Ulchaker MM, Rebar JM. Mangement dilemmas in the indi-
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vidual with cystic fibrosis and diabetes. J Am Diet Assoc 1994;94:78–80

54. Franzese A, Spagnuolo MI, Sepe A, Valerio G, Mozzillo E, Raia V. Can glargine reduce the number of lung infections in patients with cystic fibrosis-related diabetes? Diabetes Care 2003;26:2333

55. Grover P, Thomas W, Moran A. Glargine versus NPH insulin in cystic fibrosis related diabetes. J Cyst Fibros 2008;7:134–136

56. Onady GM, Langdon LJ. Insulin versus oral agents in the management of cystic fibrosis related diabetes: a case based study. BMC Endocr Disord 2006;6:4

57. Moran A, Phillips J, Milla C. Insulin and glucose excursion following premeal insulin lispro or repaglinide in cystic fibrosis-related diabetes. Diabetes Care 2001;24:1706–1710

58. Dobson L, Sheldon CD, Hattersley AT. Validation of interstitial fluid in continuous glucose monitoring in cystic fibrosis (Letter). Diabetes Care 2003;26:1940–1941

59. Moreau F, Weiller MA, Rosner V, Weiss L, Hasselmann M, Pinget M, Kessler R, Kessler L. Continuous glucose monitoring in cystic fibrosis patients according to the glucose tolerance. Horm Metab Res 2008;40:502–506

60. Jefferies C, Solomon M, Perlman K, Sweezey N, Daneman D. Continuous glucose monitoring in adolescents with cystic fibrosis. J Pediatr 2005;147:396–398

61. Mansour KM. Investigation of screening methods for impaired glucose control in children with cystic fibrosis. TSMJ 2000;1:7–11

62. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002;35:246–259

63. Brunzell C, Schwarzenberg SJ. CFRD and abnormal glucose tolerance: overview and medical nutrition therapy. Diabetes Spectr 2002;15:124–127

64. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Clinical Practice Guidelines on Growth and Nutrition Subcommittee, Ad Hoc Working Group, for the Clinical Practice Guidelines on Growth and Nutrition Subcommittee. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc 2008;108:832–839

65. Flume PA, Robinson KA, O’Sullivan BP, Finder JD, Vender RL, Willey-Courand DB, White TB, Marshall BC. Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: airway clearance therapies. Respir Care 2009;54:522–537

66. Swartz LM, Lafler LM. A teenage girl with cystic fibrosis-related diabetes, diabetic ketoacidosis, and cerebral edema. Pediatr Diabetes 2008;9:426–430

67. Battezzati A, Battezzati PM, Costantini D, Setia M, Zazzaroni L, Russo MC, Dacò V, Bertoli S, Crosignani A, Colombo C. Spontaneous hypoglycemia in patients with cystic fibrosis. Eur J Endocrinol 2007;156:369–376

68. Tierney S, Webb K, Jones A, Dodd M, McKenna D, Rowe R, Whitehouse J, Deaton C. Living with cystic fibrosis-related diabetes or type 1 diabetes mellitus: a comparative study exploring health-related quality of life and patients’ reported experiences of hypoglycaemia. Chronic Illn 2008;4:278–288

69. Moran A, Diem P, Klein DJ, Levitt MD, Robertson RP. Pancreatic endocrine function in cystic fibrosis. J Pediatr 1991;118:715–723

70. van den Berg JM, Morton AM, Kok SW, Pijl H, Conway SP, Heijerman HG. Microvascular complications in patients with cystic fibrosis-related diabetes (CFRD). J Cyst Fibros 2008;7:515–519

71. Dykewicz MS. Cough and angioedema from angiotensin-converting enzyme inhibitors: new insights into mechanisms and management. Curr Opin Allergy Clin Immunol 2004;4:267–270

72. Sullivan MM, Denning CR. Diabetic microangiopathy in patients with cystic fibrosis. Pediatrics 1989;84:642–646