

Conference report

Diagnosis, screening and management of cystic fibrosis related diabetes mellitus

A consensus conference report

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1. Introduction

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease of Caucasians in the USA, affecting 1/3000 live births

Abbreviations: ADA, American Diabetes Association; CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes mellitus; CFTR, cystic fibrosis transmembrane regulator; DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; 2-h PG, 2-h plasma glucose during oral glucose tolerance test; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; SMBG, self-monitoring of blood glucose.

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[1]. Gene defects on the long arm of chromosome 7 lead to defective production of a protein called the cystic fibrosis transmembrane regulator (CFTR). CFTR is a cAMP-dependent chloride channel which influences the water and electrolyte composition of secretions from sweat glands, airways, pancreatic ducts, hepatobiliary ducts and intestinal glands. The common pathological finding in these organs is accumulation of thick, viscous secretions associated with progressive obstruction, scarring and destruction; 84% of CF patients die from respiratory disease [2]. Improvements in pulmonary and nutritional care over the last few decades have led to dramatic improvements in the mortality rate, and now many patients with CF live into their third, fourth or fifth decades. The median life expectancy for CF patients at present is 31.3 years [2]. As CF patients

live longer, glucose intolerance and cystic fibrosis related diabetes (CFRD) are common complications.

Diabetes requiring insulin is the leading comorbidity in approximately 21,000 CF patients reported to the National CF Patient Registry, a national database of CF patients maintained for more than 30 years [2]. Approximately 5–6% of CF patients in North America and Europe are reported to have diabetes [2,3]. Because of the insidious nature of diabetes in CF and the lack of routine diagnostic screening, these figures may grossly underestimate the true prevalence of the full spectrum of CFRD. In Denmark, where annual oral glucose tolerance testing (OGTT) is performed, 50% of the CF population older than 30 years of age is reported to have diabetes [4]. Based on OGTT screening, one large United States CF Center found a CFRD prevalence of 9%, 26%, 35% and 43% in patients age 5–9, 10–19, 20–30 and > 30 years, respectively [5] (Fig. 1).

CFRD shares features of both type 1 and type 2 diabetes, but is a distinct clinical entity. The primary cause is insulin deficiency, but glucose metabolism is strongly influenced by factors unique to CF, including undernutrition, chronic and acute infection, elevated energy expenditure, glucagon deficiency, malabsorption, abnormal intestinal transit time and liver dysfunction. These factors are not static, and glucose tolerance may fluctuate over time in CF.

Understanding the nature of CFRD is critical for patients with CF, because the additional diagnosis of diabetes is associated with greater nutritional failure, worse pulmonary disease and earlier death [6–8]. Retrospective studies have shown that pulmonary decline and weight loss begin 2–4 years before diagnosis of CFRD [6–8], and mortality is dramatically higher in CF patients with diabetes than in the general CF population. In one study of 448 patients, nearly 60% of the non-diabetes CF population was alive at age 30 years, while only 25% of patients with diabetes reached this age [6]. Recent analysis of the National CF Patient Registry data shows that the mortality rate was 6-fold greater in patients with

CFRD (S. FitzSimmons, unpublished analyses, National CF Patient Registry).

The etiology of clinical deterioration in CFRD is unknown. This association may simply reflect a propensity for diabetes in the sickest of patients. The finding that insulin therapy appears to reverse negative changes in weight and lung function [7], however, suggest a cause and effect relationship between insulin deficiency and clinical decline. Muscle mass is often reduced in CF [9,10], and many of these patients are in a state of chronic protein catabolism [11]. Insulin deficiency may promote negative protein balance, contributing to CF morbidity and mortality [11]. Furthermore, hyperglycemia may directly damage the lung since chronic abnormalities in pulmonary function have been reported in both type 1 and type 2 diabetes [12,13].

In 1990 the Cystic Fibrosis Foundation convened the first consensus conference on diabetes in CF. At that time there were few data available to guide the conference participants. Since then,

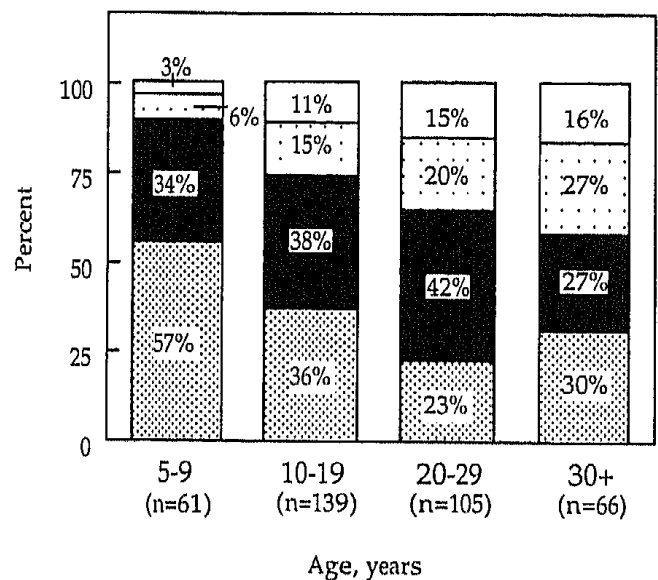


Fig. 1. Glucose tolerance categories in CF, expressed as percent prevalence within age groups (n = total number of patients studied within that age group). Patients with CFRD and fasting hyperglycemia include those who chronically required insulin to prevent fasting hyperglycemia and those who intermittently required insulin during periods of stress. From [5]. ■ = NGT, ■ = IGT, ▨ = CFRD without fasting hyperglycemia, □ = CFRD with fasting hyperglycemia.

our understanding of CFRD has increased greatly. Because considerable confusion still exists over the diagnostic criteria for diabetes in CF, however, it is difficult to interpret or to generalize findings from much of the CFRD literature.

In February 1998, the CF Foundation gathered a group of individuals with expertise in CF, diabetes, and nutrition to review the scientific literature on CFRD and to accomplish the following tasks:

- Establish clear and appropriate terms to define the various states of glucose tolerance in CF as we know them today and agree on a unified nomenclature for the disease.
- Provide guidelines for screening procedures to diagnose diabetes in CF.
- Develop a protocol for the inpatient and outpatient management of CF patients with diabetes.
- Set priorities for CFRD research funding.

Whenever possible, the recommendations set forth in this document are based upon well-documented research findings. In areas where no data are yet available, suggestions represent expert opinion and consensus, and are stated as such. This document is meant to reflect our understanding of CFRD at this point in time, and will need to be updated and changed as new data become available.

2. Description and pathophysiology of CFRD

CFRD has an average age of onset of 18–21 years [3,4,6]. There is a slight female predominance [3,6] and the disease may be more common in patients homozygous for the most frequent CF gene mutation, $\Delta F508$ [3]. Patients do not have the immunological serum markers or HLA-DR profiles typical of type 1 diabetes [14–16]. A minority of CF patients do not have pancreatic exocrine insufficiency; these patients have much milder malnutrition and pulmonary disease than other patients with CF, and they are not prone to develop diabetes [17].

Microvascular complications of diabetes occur in CF, with prevalence reports of 5–16% retinopathy, 3–16% nephropathy and 5–21%

neuropathy [4,18,19]. The risk of diabetic macrovascular complications does not appear to be significant. Cholesterol and triglyceride levels were normal in Canadian adult patients with CFRD [20]. There is a case report of a single patient with CF and long-standing diabetes who had diffuse atherosclerosis noted on autopsy following death from chronic pulmonary disease [21]. The absence of other reports suggests that this is a rare problem, but as patients with CFRD live longer we may need to revise this assumption.

Insulin deficiency is the hallmark of CFRD. First phase insulin secretion in response to intravenous glucose and other stimulatory agents is impaired in exocrine insufficient adult CF patients and the insulin response to oral glucose is significantly delayed [22–26]. The absolute amount of insulin secreted over time is normal in CF patients with impaired glucose tolerance (IGT), but is diminished in patients with CFRD [24]. Glucagon and pancreatic polypeptide secretion are also decreased [22] while somatostatin levels may be elevated [27].

The islet secretion data correlate with autopsy findings, which demonstrate fibrosis and fatty infiltration of the exocrine pancreas, disruption of the islet architecture and destruction of many, but not all, of the islets [28–30]. Not only is the absolute number of pancreatic islets diminished in CF, but the cellular composition is altered, with a significantly decreased percentage of beta, alpha and pancreatic polypeptide cells and relatively increased delta cells [28–30].

There is a discrepancy between the islet pathology described at autopsy and the occurrence of diabetes in CF. Patients with CFRD do not appear to have greater beta cell destruction than patients without diabetes, suggesting that diabetes in CF is not simply related to the severity of fibrosis-induced islet damage. Islet amyloid deposition is a feature of CFRD [31]. Islet amyloid accumulates in type 2 diabetic patients but not in patients with type 1 diabetes or pancreatitis [32–34]. It is not clear whether amyloid accumulation is simply a by-product of the disease process or if it contributes to beta cell dysfunction [35]. It has been hypothesized that abnormal glucose tolerance is nearly universal in CF adults secondary to

Table 1
Oral glucose tolerance categories in cystic fibrosis^a

Category	FPG, mg/dl (mM)	2-h PG, mg/dl (mM)
Normal glucose tolerance (NGT)	< 126 (7.0)	< 140 (7.8)
Impaired glucose tolerance (IGT)	< 126 (7.0)	140–199 (7.8–11.1)
CFRD without fasting hyperglycemia	< 126 (7.0)	≥ 200 (11.1)
CFRD with fasting hyperglycemia	≥ 126 (7.0)	OGTT not necessary

^a The OGTT is performed by giving an oral glucose load of 1.75 g/kg body weight (maximum 75 g) to fasting patients. FPG and 2-h PG are measured. The patient should have consumed at least 150 g/day of carbohydrate during the 3 days prior to testing (600 kcal). Most CF patients consume much more carbohydrate than this on a daily basis.

structural fibrotic damage to the islet, but progression to overt diabetes may primarily occur in patients who also have the type 2 diabetes gene defect(s) [31].

Insulin sensitivity must also be considered in the etiology of diabetes in CF. Patients with CFRD have modest insulin resistance [36–40]. Insulin sensitivity is more controversial in CF patients without diabetes, in whom it has been reported to be increased [36,41], normal [25,38,40], or decreased [38,39].

3. Diagnostic criteria for CFRD

The terms type 1 and type 2 diabetes are not appropriate to describe the patient with CFRD. The new classification scheme of the American Diabetes Association (ADA) places CFRD in the category of 'Other specific types [of diabetes]...diseases of the exocrine pancreas' [42]. The consensus committee recognized four glucose tolerance categories in CF, based on the results of the 1.75 g/kg (maximum 75 g) OGTT (Table 1):

- Normal glucose tolerance (NGT).
- Impaired glucose tolerance (IGT).
- CFRD without fasting hyperglycemia.
- CFRD with fasting hyperglycemia.

The only difference between this classification and that of the ADA is that CFRD categories differentiate whether or not fasting hyperglycemia is present [42]. The ADA definition of diabetes is based upon the glucose threshold levels beyond which complications are likely [43]. In type 2 diabetes-prone populations, fasting plasma glucose (FPG) > 126 mg/dl and 2-h glucose > 200 mg/dl are equally and independently associated with microvascular complications, and thus they are considered equivalent in terms of defining the diabetic state [43]. In general, individuals prone to type 2 diabetes are also likely to suffer from additional abnormalities including obesity, severe insulin resistance, hypertension and hyperlipidemia—factors which might themselves play a role in the pathogenesis of diabetes complications. CF patients are metabolically very different from patients with type 2 diabetes, and they are not likely to experience these other risk factors. There are no existing data from which to determine whether elevation of the OGTT 2-h glucose level, in the absence of fasting hyperglycemia, carries the same risk for microvascular complications in CFRD as in type 2 diabetes.

In addition to the two OGTT categories, acceptable criteria for diagnosis of CFRD include (Table 2):

- Fasting plasma glucose (FPG) ≥ 126 mg/dl (7.0 mM) on two or more occasions.
- FPG ≥ 126 mg/dl (7.0 mM) plus casual (without regard to time of day or last meal consumed) glucose level ≥ 200 mg/dl (11.1 mM).
- Casual (previously called random) glucose levels ≥ 200 mg/dl (11.1 mM) on two or more occasions with symptoms.

Table 2
Criteria for the diagnosis of CFRD^a

2-h PG ≥ 200 mg/dl (11.0 mM) during a 75-g OGTT
FPG ≥ 126 mg/dl (7.0 mM) on two or more occasions
FPG ≥ 126 mg/dl (7.0 mM) plus casual glucose level ≥ 200 mg/dl (11.1 mM)
Casual glucose levels ≥ 200 mg/dl (11.1 mM) on two or more occasions with symptoms

^a CFRD should be identified as 'with fasting hyperglycemia' or 'without fasting hyperglycemia'. CFRD may be chronic or may be intermittent with stress.

Table 3
Clinical symptoms^a of diabetes in CF

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

^a These symptoms may indicate the presence of CFRD.

Potential symptoms of diabetes in CF include polydipsia and polyuria, weight loss or inability to gain weight despite aggressive nutritional intervention, poor growth, poor progression of puberty or unexplained chronic decline in pulmonary function (Table 3).

CFRD, with or without fasting hyperglycemia, may be chronic or may be intermittent. Patients with intermittent CFRD repeatedly require insulin therapy to control hyperglycemia when they are physically stressed with infection, with intensive nutritional intervention such as high calorie overnight gastrostomy feedings or with glucocorticoid treatment of pulmonary disease. Blood glucose levels normalize between periods of stress in patients with intermittent diabetes. Women with CF are at high risk for gestational diabetes mellitus (GDM).

4. Screening criteria

4.1. Fasting blood glucose levels

The ADA recommends FPG as the screening test of choice for diabetes, with a value > 126 mg/dl (7.0 mM) considered diagnostic [42]. Casual glucose levels are generally measured annually in CF patients as part of routine management [44]. If this level is < 126 mg/dl (7.0 mM), it is unlikely that fasting hyperglycemia is present and there is no need for further work-up unless symptoms of CFRD are present (Table 3). FPG levels should be measured on all patients with casual glucose levels ≥ 126 mg/dl (7.0 mM). FPG ≥ 126 mg/dl (7.0 mM) is diagnostic for CFRD when confirmed by a second FPG test or if it occurs in association

with a casual glucose level > 200 mg/dl (11.1 mM).

4.2. OGTT testing

For a several reasons, the ADA does not recommend the routine use of the OGTT for diabetes screening [42]. It is, however, the most sensitive method presently available for diagnosing diabetes without fasting hyperglycemia. Although the FPG and the 2-h plasma glucose (2-h PG) do not correlate perfectly with each other, they give the same prevalence of diabetes when either is used alone as a diagnostic criterion in type 2 diabetes prone populations [45,46]. These glucose levels may be less closely related in CFRD. Over a 3-year period at the University of Minnesota, 74 patients were diagnosed by OGTT with CFRD without fasting hyperglycemia [5]. Their average FPG was 98 ± 11 mg/dl (5.4 ± 0.6 mM) and their average 2-h PG was 254 ± 25 mg/dl (14.1 ± 1.4 mM). During the same time period, 36 patients were diagnosed with CFRD with fasting hyperglycemia. Thus, FPG levels alone would not have identified more than two-thirds of CF patients with diabetes.

Because little is known about the risk of future microvascular or nutritional complications due to insulin deficiency in patients with CFRD without fasting hyperglycemia, the consensus committee felt it was important to separate the two CFRD categories for research purposes and for making treatment decisions. It was decided that OGTT screening of the entire CF population was not practical or justified at present, but that the OGTT should be strongly considered to rule out CFRD without fasting hyperglycemia in patients with potential diabetes symptoms (Table 3).

4.3. Other screening tests

Hemoglobin A_{1c} should not be used as a screening test for CFRD.

This test is commonly used to monitor patients with established diabetes (including those with known CFRD), since, when it is elevated, it indicates poor glycemic control. Hemoglobin A_{1c} has been shown by several investigators to be unreli-

able in the diagnosis of new CFRD because it is usually normal [6,47–49]. It may be, early in the course of CFRD, that intermittent hyperglycemia is not intense or prolonged enough to raise hemoglobin A_{1c} levels. Alternatively, one could speculate that red blood cell survival time is shortened in CF due to the effects of chronic inflammation, which would spuriously lower the hemoglobin A_{1c} level.

Casual blood glucose levels are affected by time of day, last meal and gastric emptying time. When persistently elevated ≥ 200 mg/dl (11.1 mM) in the presence of symptoms, the diagnosis of diabetes can be made. FPG levels should also be measured in this situation. Normal casual glucose levels do not exclude a diagnosis of CFRD.

Classical clinical symptoms are not sensitive enough to be used alone as a screening test for diabetes in CF. Like type 2 diabetes, CFRD has an insidious onset and clinical symptoms occur relatively late in its course. Only one-third of patients with CFRD had symptoms of polyuria or polydipsia at the time of diagnosis in a prospective Danish study of 191 patients [47].

CFRD is rare in children with CF younger than 10 years of age. Measurement of other diabetes associated antibodies may help differentiate CFRD from type 1 diabetes in young CF children with diabetes.

5. Management of the outpatient with CFRD and fasting hyperglycemia

5.1. Outpatient office management

Patients with CFRD should be seen quarterly by a medical team experienced in their management. Suggested team members include, but are not limited to, physicians, diabetes nurse educators, dietitians with experience in both diabetes and CF, and mental health professionals. The goals of treatment are:

1. Maintain optimal nutritional status, including normal growth and development in children and adolescents, and achievement/maintenance of normal weight in adults.

2. Control hyperglycemia to reduce acute and chronic diabetes complications.
3. Avoid severe hypoglycemia.
4. Promote the optimal psychological, social and emotional adaptation to living with diabetes.
5. Be as flexible as possible within the framework of the patient's lifestyle and CF.

As for all types of diabetes, age-appropriate diabetes education should be provided initially and on an ongoing basis, to provide the patient with the skills necessary for independence in self-management of diabetes and problem solving.

5.2. Routine glucose monitoring

All patients with diabetes should have a home glucose meter for self-monitoring of blood glucose levels (SMBG). For insulin treated patients, it is recommended that glucose levels be measured at least three or four times per day. Two-hour postprandial glucoses can be useful in adjusting the insulin dose, particularly if the patient is treated with insulin lispro. Early morning (01:00–03:00 h) glucose levels should be checked at least monthly to exclude unrecognized nocturnal hypoglycemia. The patient should be taught to recognize glucose patterns related to insulin dose, diet and activity. Glucose targets are the same as those recommended by the ADA for type 1 and type 2 diabetes [42].

5.3. Insulin versus oral diabetes agents

Because patients with CF are insulin deficient, insulin is the standard medical treatment. Most patients primarily need supplemental insulin for meal coverage and require very little insulin during the night unless they are receiving continuous nocturnal nasogastric or gastrostomy feedings. Multiple daily injections of short-acting insulin before each meal, with the dosage adjusted to match the carbohydrate content of the meal, is a useful method for many patients because it provides considerable flexibility in the timing and content of meals. Many different physiologically based insulin regimens are possible, however, and that which best fits the patient's lifestyle and needs should be selected.

Little useful information exists regarding therapy with oral diabetes agents in CFRD. The literature consists primarily of abstracts with small subject numbers [50–54]. Deriving conclusions from these data is problematic because of the lack of uniformity in defining diabetes. The responses of patients with fasting hyperglycemia may be very different than those of patients without fasting hyperglycemia, and the responses of patients who begin therapy during acute illness must be interpreted with caution since many of these patients have intermittent diabetes and will recover glycemic control independent of medical therapy.

There are potential problems in CF with existing FDA approved oral agents. Drugs which improve insulin sensitivity do not address the primary problem of insulin deficiency in CF. Metformin is contraindicated in patients with hypoxia because of the risk of fatal lactic acidosis, and it has multiple gastrointestinal (GI) side-effects which are unacceptable for most CF patients. The potential for serious hepatic toxicity with troglitazone may be greater in CF than in the general population because of underlying liver problems. Acarbose, which reduces post-prandial glucose and insulin excursion by limiting intestinal absorption of glucose, causes diarrhea, anorexia and abdominal discomfort. The use of a drug which inhibits energy absorption in malnourished individuals is questionable.

Sulfonylureas enhance insulin secretion by acting on a specific islet beta cell receptor. In the few studies measuring the effect of these drugs on insulin secretion in CF, minimal improvement, if any, was found [51–54]. Concern about use of sulfonylureas in CF has emerged because of evidence that they bind to and inhibit CFTR [55]; this may assume greater clinical importance as new drugs designed to improve CFTR function become available. Glyburide is not a good drug choice in this population because 50% of its elimination is in the bile.

The consensus committee felt strongly that, until further data were available, oral diabetes agents should only be considered within the context of a controlled research trial in CFRD.

5.4. Treatment of acute and chronic complications

Ketoacidosis is rare in CF, perhaps because of glucagon deficiency or because enough endogenous insulin secretion is retained to inhibit ketogenesis. Ketosis was reported in 4% of Danish patients with CFRD [47]. Hypoglycemia is a common acute complication of intensive insulin therapy. Patients and their family members must be taught to recognize its symptoms and to provide appropriate treatment (dietary management, glucagon). Patients with CF are not able to mount a glucagon response to hypoglycemia, but they are generally able to compensate for glucagon deficiency with an exuberant catecholamine response [22].

Recommendations for screening for chronic diabetes complications are similar to those for type 2 diabetes, including regular measurement of blood pressure and examination of the feet, annual dilated eye examinations and annual urine albumin measurement [42]. Screening should begin at the time of initial diagnosis, because unrecognized diabetes may have been present for several years. A baseline fasting lipid profile is recommended after metabolic control is achieved in the patient with CFRD. If it is normal and there is not a family history of dyslipidemia or cardiovascular disease, there does not appear to be a need for further routine lipid screening.

The frequency of gastrointestinal complications related to autonomic neuropathy in CFRD is unknown, but anecdotal case reports suggest they exist. These complications may exacerbate other CF symptoms, impair administration of adequate nutrition and compromise blood glucose control. Many of these complications may be mistaken for complications of CF. Because of the significant overlap in the GI manifestations of these two diseases, consultation with a gastroenterologist familiar with both CF and diabetes is essential.

6. Nutritional management of CFRD

Nutritional therapy is an integral component of the management of both cystic fibrosis and diabetes. Malnutrition in CF is associated with

stunted growth, pubertal delay, deterioration of lung function and early death. Dietary therapy in diabetes is necessary to achieve glycemic control. The challenge to CF caregivers is to combine the nutritional principles of these two diseases in such a way as to normalize growth and weight and maintain near normal blood glucose levels. Management of diabetes should enhance rather than interfere with the achievement of optimal nutritional status in CF.

Dietary strategies for type 1 and type 2 diabetes seek to normalize blood glucose levels to protect the patient from future microvascular complications and prevent acute episodes of life-threatening hypoglycemia. These same principles apply to CFRD. Other factors which usually influence the dietary management of diabetes are not pertinent in the patient with CF. Differences in the dietary approach to CFRD compared to that of type 1 or type 2 diabetes are summarized in Table 4. Achievement of weight loss or prevention of weight gain are often important treatment issues for people with type 1 and type 2 diabetes but not CFRD. The majority of deaths in type 1 and type 2 diabetes are due to cardiovascular disease; at present, macrovascular disease does not appear to be a complication of CFRD and thus there is no reason to restrict fat intake. When discrepancies exist between the dietary approaches to the two diseases, the recommendations given for the general CF population take precedence. The goals of medical nutrition therapy in CFRD are as follows:

Table 4
Ways in which CFRD medical nutrition therapy differs from that of type 1 and type 2 diabetes

High energy intake is necessary for survival; caloric restriction is never an appropriate means of glycemic control
High fat intake is recommended (40% of total calories) to provide increased calories and because macrovascular disease does not appear to be a concern
Protein reduction may not be appropriate in diabetic nephropathy because of the potential for malnutrition
Salt restriction is almost never indicated
Frequent intercurrent illness necessitates constant adjustment of the meal plan

1. Sufficient calories, frequently in excess of that required by healthy individuals, must be provided to ensure normal weight gain, growth and development in children and adolescents and normal weight in adults [56].
2. Maintenance of near normal blood glucose levels must be sought to protect the patient from acute and chronic complications of diabetes.
3. The dietary plan must include strategies for managing exercise and episodes of illness, and for prevention and treatment of hypoglycemia.
4. Flexibility in meal planning is necessary in order to accommodate the patient's lifestyle, variability in energy intake, fluctuations in clinical status and pulmonary treatment regimen.
5. Nutritional therapy must take into consideration the patient's psychosocial circumstances, economic issues, education level and cultural or religious beliefs, as well as evaluation of the patient's motivation or ability to learn and potential for making changes.

Achieving these goals requires the efforts of a coordinated team of care providers experienced with both CF and diabetes. The patient is an important member of this team.

6.1. *The individual meal plan*

Principles for assessment of nutritional status, calculation of energy requirements and management of dietary intake are, for the most part, no different than those recommended for all patients with CF [56]. Energy needs are considerably higher in CF than in the general population, and failure to maintain a normal weight is associated with poor survival [57]. For this reason, calorie restriction is never an appropriate means of glycemic control in individuals with CFRD. The weight goal in CF is 100–110% ideal body weight.

The meal plan should be based on the patient's usual food intake and eating patterns as determined by dietary recall. Flexibility in meal planning is important to optimize intake and to allow for normal eating patterns. Any number of different meal plan options are available depending on the patient's individual circumstances. Because di-

etary carbohydrate intake can vary considerably from day to day in the patient with CF, one common strategy is to teach the patient to adjust their pre-meal short-acting insulin dose to match the carbohydrate content of the meal. This is based on the insulin to carbohydrate ratio, or the number of units of insulin needed per unit of carbohydrate to achieve a post-prandial glucose in the target range. This ratio must be individually determined.

Measurement of blood glucose levels, together with documentation of food intake and activity, help both the care provider and the patient understand individual responses to specific foods and to other circumstances affecting blood glucose such as stress, illness, medications and time of day. This information is useful for continuously updating and adjusting the individual meal plan.

7. Management of CFRD without fasting hyperglycemia

Because patients with CFRD without fasting hyperglycemia are at high risk for development of fasting hyperglycemia, they should be followed closely so that progression to fasting hyperglycemia, if it occurs, is detected and treated promptly. Glucose levels should be measured more frequently during acute illness. Management goals and practices for CFRD without fasting hyperglycemia, including medical nutrition therapy, exercise recommendations and screening for chronic complications, are no different than those outlined above for management of patients with CFRD with fasting hyperglycemia.

There are no data available at present to determine whether patients with CFRD without fasting hyperglycemia require insulin therapy to prevent malnutrition or microvascular complications. In many of these cases, the patient will have undergone the diagnostic OGTT test because of clinical concerns about failure to gain or maintain weight, poor growth, delayed pubertal progression, or unexplained chronic decline in pulmonary function. In these symptomatic patients, a trial of insulin therapy may be considered. Oral diabetes agent therapy should, in general, only be consid-

ered within the context of placebo-controlled research studies.

8. Management of the CF patient with impaired glucose tolerance

Impaired glucose tolerance is found in 18–47% of CF patients who undergo oral glucose tolerance testing [5,47]. The nutritional and metabolic consequences of this condition in CF are unknown. At present, there are no specific guidelines for management of the CF patient with impaired glucose tolerance. Because these patients are at risk for progression to diabetes [47], they should be followed carefully for development of potential clinical symptoms.

9. Inpatient management of CFRD

For CF patients with established diabetes on insulin therapy, it is not unusual for insulin needs to substantially increase during acute illness. Care providers must be ready to aggressively increase the insulin dose. Conversely, as the illness subsides, rapid reduction of the insulin dose to baseline levels is often necessary (usually within 2–8 weeks of the acute illness). Sometimes a dramatic increase in insulin requirements is the first sign that an illness the patient perceives as minor is really more serious and requires intervention. Many patients with CFRD only need insulin therapy during periods of acute illness.

Acute illness is associated with severe insulin resistance. In this setting, diabetes often first becomes apparent in CF. Thus, it is important that hospitalized CF patients be screened for diabetes.

10. Pregnancy

Increasing numbers of women with CF are becoming pregnant each year. Early fears that pregnancy would shorten survival appear to be unfounded for most of these patients [58]. National CF Registry data demonstrate, however, that women with CF who have diabetes during

pregnancy experience unusually rapid deterioration of pulmonary function in the years following pregnancy compared to non-pregnant CF controls matched for age, weight and baseline pulmonary function [58]. There are no data about fetal outcome in CF pregnancies.

All women with CFRD should be counseled about the risks of pregnancy, the importance of careful metabolic control prior to pregnancy and methods of birth control. If possible, diabetes care should be optimized before conception for the woman wishing to become pregnant. As in other forms of diabetes, aggressive normalization of blood glucose levels is sought for pregnant women with CFRD. In addition to reducing perinatal morbidity, tight control of diabetes may improve overall nutrition in the pregnant CF woman, since normal weight gain is often difficult in CF pregnancies. Dietary restriction is not an acceptable method for reducing glucose levels. Monitoring for microvascular disease is important in all pregnant women with diabetes [42].

Women with CF who are not known to have diabetes are at high risk for developing gestational diabetes because of compromised beta cell function. The optimal timing for performing screening in CF pregnancies is not known. Diabetes may develop earlier in these patients or may be present before the pregnancy even begins. Until studies better define this, it seems most prudent to do a baseline OGTT prior to conception, if possible, or at the time the pregnancy is confirmed. This should be repeated in the middle of the second and third trimesters (20–24 weeks and 30–34 weeks), or earlier if maternal weight gain is inadequate.

11. Adherence issues in adolescents and adults with CFRD

There is growing recognition that lack of adherence to treatment regimens in patients with chronic illness is an important clinical problem that can lead to unnecessary hospitalizations, in-

creased risk for illness-related complications and increased health care costs [59,60]. The treatment of CF presents particularly difficult challenges for patients and their families because it involves a time-consuming, complex daily medical regimen. Although there is little empirical evidence addressing how a second diagnosis of CFRD affects patients, it clearly increases the complexity of the daily medical cares.

Adherence is particularly problematic as children move into adolescence. This is related to many factors including lack of developmentally appropriate information, misconceptions about what constitutes adequate treatment, struggles for control and independence, striving for normality, stressors in the home environment and anxiety. Multiple elements can also combine to hinder adherence in adults with CFRD.

Several strategies can be used to overcome adherence problems. The most important is utilization of a multi-disciplinary team approach. A comprehensive psychosocial evaluation should be performed at the time CFRD is diagnosed and on an annual basis thereafter, with a goal of identifying factors which compromise the patient's ability to adhere to the prescribed regimen. If psychological dysfunction is apparent in the patient or an immediate family member, referral to a mental health professional is recommended because of its potential impact on adherence and disease management.

Patients and their families should be given detailed, developmentally appropriate information on an on-going basis, including a rationale for why treatment is important. Each component of the treatment regimen should be discussed and prescribed in writing. Expectations should be clear, with sensitivity to religious and cultural issues and with as much flexibility as is medically acceptable.

Finally, while a central goal of both adult and adolescent CF care is independence for the patient, the patient's family should be incorporated into the education and treatment plan to ensure that an appropriate level of support is available in the home.

12. Future research directions

One of the goals of this consensus conference was to identify and prioritize areas of future research effort. Studies involving patients with CFRD without fasting hyperglycemia were seen to be the most critical. Specific issues in this group included exploring their risk for malnutrition and protein catabolism secondary to insulin deficiency, identifying whether they are at risk for microvascular disease, evaluating their prognosis compared to CF patients without diabetes or patients with CFRD with fasting hyperglycemia, and examining the role of insulin or oral diabetes agent therapy in these patients. Other research topics given high priority were the effect of pregnancy on morbidity and mortality in women with CFRD, the psychosocial impact of diabetes on patients with CF and their families, the relationship between glycemic control and pulmonary function, the risk of macrovascular disease in CFRD, and the role of chronic inflammation and infection in CFRD.

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