Cystic fibrosis (CF) is an autosomal recessively inherited defect in the cystic fibrosis transmembrane receptor, a cell membrane chloride channel. The deficiency or absence of the channel results in thick, sticky secretions in many organs, including lung, liver, gastrointestinal tract, and pancreas. Eighty-five percent of CF patients have exocrine pancreatic insufficiency. The obstructive nature of the tenacious mucus predisposes to infection, particularly in the respiratory tract. CF was once considered a disease of childhood. However, with improvements in medical care during the past few decades, patients with CF are now living well into their third, fourth, or fifth decade of life and have a median life expectancy of 32.2 years. As survival has increased, CF-related diabetes (CFRD) has become the leading co-morbidity in this patient population, occurring in ~13% of all patients with CF. This figure is widely believed to be an underestimate because of the lack of routine screening for diabetes in the CF population. CFRD is most commonly diagnosed in patients who are between 18 and 21 years of age.

Glucose Tolerance Categories
The 1998 CFRD Consensus Committee identified four glucose tolerance categories for clinical management and research purposes (Table 1). The four categories are based on a standard glucose tolerance test: normal glucose tolerance (NGT), impaired glucose tolerance (IGT), CFRD without fasting hyperglycemia (FH), and CFRD with FH. There are important differences in medical nutrition therapy (MNT) for the various categories of glucose intolerance and other circumstances in patients with CFRD. Glycated hemoglobin (A1C) is not useful for diagnosing CFRD because increased red blood cell turnover in CF patients may falsely lower A1C levels. However, it can be useful in monitoring overall blood glucose control in established CFRD patients.

Clinical Distinctions of CFRD
The American Diabetes Association (ADA) classifies CFRD under "other specific types of diabetes" involving diseases of the exocrine pancreas. CFRD shares some features of type 1 and type 2 diabetes but has important clinical distinctions that make its medical treatment and MNT unique. Insulin deficiency is the primary defect, resulting from progressive obstruction of the pancreatic ducts. Insipid secretion causes fibrosis and fatty infiltration of the islets. Glucose metabolism is also influenced by other factors specific to CF including undernutrition, chronic and acute infection, elevated energy expenditure, malabsorption, abnormal intestinal transit time, liver dysfunction, and glucagon deficiency. Diabetic ketoacidosis is rare.

Changes in clinical status influence glucose tolerance and cause fluctuations over time. Patients in their baseline state of health are usually insulin-sensitive, whereas pulmonary exacerbations, severe chronic inflammation, and/or use of high-dose steroids make patients highly insulin resistant. Currently, insulin therapy is the only recommended treatment for CFRD. The use of oral agents is controversial and not recommended in this population until studies can confirm the safety and effectiveness of such therapy.

How MNT Differs for CFRD
Maintaining optimal nutritional status and weight in patients with CF is the goal of treatment and can dramatically improve longevity. Survival is markedly decreased in underweight patients with CF. M alnutrition in CF is the result of a combination of factors including malabsorption, declining pulmonary function, increased resting metabolic rate, anorexia, and gastrointestinal reflex leading to vomiting and food loss. Many patients require some form of nutrition support in the form of oral or gastrostomy-delivered supplements to meet the increased energy demands of CF.

CFRD profoundly affects nutritional status and weight, resulting in greater morbidity and mortality than in the general CF population. Weight loss and declining pulmonary function develop 2–4 years before the actual CFRD diagnosis, probably because of insulin deficiency. Treatment with insulin improves pulmonary function and weight parameters. Patients with CFRD or abnormal glucose tolerance are protein-catabolic; protein catabolism is not reversed entirely with insulin therapy. Diet recommendations that are often indicated for type 1 or type 2 diabetes are generally not applicable to patients with CFRD. A high-calorie, high-fat, high-sodium diet is essential to maintaining weight and nutritional status in CF.

Table 1. Glucose Tolerance Categories in CF in Response to OGTT

<table>
<thead>
<tr>
<th>Category</th>
<th>FPG (mg/dl)</th>
<th>2-h PG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>&lt;126</td>
<td>140–199</td>
</tr>
<tr>
<td>IGT</td>
<td>&lt;126</td>
<td>140–199</td>
</tr>
<tr>
<td>CFRD without FH</td>
<td>&lt;126</td>
<td>200</td>
</tr>
<tr>
<td>CFRD with FH</td>
<td>≥126</td>
<td>OGTT unnecessary</td>
</tr>
</tbody>
</table>

CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; FH, fasting hyperglycemia; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose.
restriction is never appropriate. Likewise, the risk of macrovascular disease that necessitates the typical low-fat, low-sodium diet restrictions for people with type 1 or type 2 diabetes does not apply to patients with CFRD; there is no documented risk of macrovascular complications associated with this condition. However, in a University of Minnesota study, CFRD patients had a 4% prevalence of elevated cholesterol and a 16% prevalence of elevated triglycerides, suggesting that this recommendation may change as CFRD patients live longer.

A high-sodium diet is essential in CFRD because of increased sodium losses via sweat, illness, and exercise. Hyponatremia can result in seizures and death.

Despite these differences, CFRD patients are at risk for diabetic microvascular disease, so optimal control of blood glucose is imperative to prevent these complications and to normalize metabolism of nutrients and optimize weight and nutritional status. Blood glucose targets are the same as ADA recommendations for people with type 1 or type 2 diabetes. The complexity of the daily CF regimen (pulmonary treatments at least 2 times/day; ingestion of pancreatic enzymes with each meal and snack; multiple medications; vitamins) is compounded by the demands of CFRD. Lack of adherence to complex medical regimens in patients with chronic disease has been shown to lead to unnecessary hospitalizations, increased risk for complications, and higher health care costs.

There is a paucity of data on how best to implement MNT in this population. Energy intake may vary widely from day to day depending on patients' state of health. The CFRD consensus guidelines recommend matching insulin to carbohydrates for maximum flexibility as one approach to management.

A survey of current medical practice regarding CFRD in the United States found that attainment of optimal weight was considered a top priority. Nutritional interventions varied, with 22% of providers recommending no change in dietary intervention from other patients with CF, 21% recommending no concentrated sweets, 24% using carbohydrate counting, 26% using the Exchange system, and 7% recommending other interventions.

**MNT for CFRD with FH**

CFRD patients do not usually tolerate a structured diet because their caloric intake is too variable from day to day. The most practical approach is to match insulin to carbohydrates.

Patients with CFRD with FH in their usual state of health typically produce adequate or nearly adequate amounts of basal insulin during the day but require exogenous insulin for meals and large snacks. They may also require modest doses of nighttime insulin to cover morning fasting hyperglycemia. Because the magnitude of insulin deficiency varies from patient to patient related to the loss of β-cell function, therapy must be tailored to individual needs.

A viable choice includes using a combination of insulin glargine and rapid-acting insulin in relation to meals or insulin pump therapy. However, care must be taken because basal insulin needs in CFRD are lower than in other forms of diabetes.

Most patients require ~0.5–2.0 units of rapid-acting insulin per 15 g carbohydrate consumed. Reviewing self-monitoring of blood glucose (SM BG) data and diet records is recommended to confirm the approximate carbohydrate-to-insulin ratio. Monitoring should include pre-meal and frequent 2-h postprandial glucose measurements.

Using fixed doses of insulin may not be the best approach. However, patients who do take fixed doses need to be consistent with their carbohydrate intake in conjunction with the time action of their insulin. Patients who are sick or are taking steroids often quadruple their usual insulin dose and may require additional background insulin, as well. As patients recover, their insulin needs drop dramatically and should be lowered aggressively according to their SM BG results (Table 3). Wight, nutritional status, and caloric intake should be assessed at every visit.

**MNT for CFRD Without FH**

The category of CFRD without FH is not included among current ADA diabetes classifications. There are no studies looking at best management practices in patients with CFRD without FH. One large study sponsored by the National Institutes of Health is underway at the University of Minnesota and eight other CF centers in the United States. It is comparing the use of premeal insulin lispro and that of repaglinide and will use body mass index and muscle mass as primary endpoints. A pilot study suggested that lispro use resulted in greater improvement in postmeal glucose excursion than did repaglinide.

Elevated postprandial blood glu-

### Table 2. MNT For Type 1/Type 2 Diabetes Versus For CFRD

<table>
<thead>
<tr>
<th></th>
<th>Type 1/Type 2 Diabetes</th>
<th>CFRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calories</strong></td>
<td>Calculated for maintenance, growth, or reduction diets</td>
<td>120–150% RDA</td>
</tr>
<tr>
<td><strong>Carbohydrate</strong></td>
<td>Individualized</td>
<td>Individualized</td>
</tr>
<tr>
<td><strong>Fat</strong></td>
<td>Individualized; often &lt;30% of total calories, &lt;10% saturated fat, ≤10% of calories from polyunsaturated fat</td>
<td>40% of calories; no restriction on type of fat</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>10–20% of total calories; reduction to 0.8 g/kg with nephropathy</td>
<td>10–20% total calories; no reduction with nephropathy*</td>
</tr>
<tr>
<td><strong>Sodium</strong></td>
<td>&lt;2,400 mg/day</td>
<td>&gt;4,000 mg/day</td>
</tr>
<tr>
<td><strong>Vitamins/minerals</strong></td>
<td>No supplementation unless deficiency noted</td>
<td>Routine supplementation of vitamins A, D, E, K, and multivitamin</td>
</tr>
</tbody>
</table>

* This is the recommendation of the consensus conference. In practice, a patient with severe nephropathy would require protein restriction to prevent azotemia.

CFRD, cystic fibrosis-related diabetes; MNT, medical nutrition therapy; RDA, recommended dietary allowance.

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Cystic fibrosis-related diabetes mellitus (CFRD) is a significant health concern for women with cystic fibrosis (CF). CFRD can increase the risk of microvascular and macrovascular complications, similar to those seen in type 1 and type 2 diabetes. CFRD is defined by the American Diabetes Association as fasting plasma glucose levels of 126 mg/dL or higher and/or a 2-hour plasma glucose level of 200 mg/dL or higher during an oral glucose tolerance test (OGTT). Women with CFRD are at higher risk for gestational diabetes mellitus (GDM) compared to the general population, with an estimated 14% incidence in women with CFRD. CFRD is associated with poor obstetric outcomes, including increased risk of stillbirth and preterm delivery.

Preconception counseling and normalization of blood glucose are crucial for pregnant women with CFRD. A baseline OGTT should be performed before pregnancy to assess glucose tolerance. If the OGTT results indicate IGT, the patient should be monitored closely throughout the pregnancy to ensure proper weight gain and nutritional status. Women with IGT are at high risk for developing CFRD during pregnancy, and aggressive management is necessary to prevent the progression to CFRD. Insulin needs will change throughout pregnancy, and adjustment of insulin therapy is necessary to meet blood glucose goals.

Nutritional management during pregnancy in women with CFRD includes avoiding restriction of calories or carbohydrate during pregnancy and, therefore, escalating the use of insulin. Adequate weight gain is crucial for best maternal and fetal outcomes. Diligent self-monitoring of blood glucose is imperative, as is aggressive use of insulin, if necessary, to achieve blood glucose goals. A baseline OGTT is recommended before pregnancy or once the pregnancy is confirmed and should be repeated in the second and third trimesters or earlier if weight gain is problematic.

How Other Education Topics Differ for CFRD

Exercise is encouraged for CFRD patients, but energy expenditures may be greater in these individuals because of the increased effort to breathe during exercise. In addition to the usual recommendations to monitor blood glucose before and after exercise and to carry carbohydrate while exercising, CFRD patients should be counseled to consume extra calories to avoid weight loss from exercise.

Table 3. MNT for CFRD Glucose Tolerance Categories and Pregnancy

<table>
<thead>
<tr>
<th>Category</th>
<th>Management</th>
</tr>
</thead>
</table>
| IGT                    | • Do not reduce calories.  
                          |  • Replace excessive amounts of sweetened beverages with nutrient-dense calories.  
                          |  • Spread carbohydrates throughout the day.  
                          |  • Monitor weight and nutritional status closely.                        |
| CFRD without FH        | • Do not reduce calories.  
                          |  • Replace excessive amounts of sweetened beverages with nutrient-dense calories.  
                          |  • Spread carbohydrates throughout the day.  
                          |  • Monitor weight and nutritional status closely.  
                          |  • Possibly start insulin with nutritional decline.                      |
| CFRD with FH           | • Match insulin to carbohydrates consumed.                                   
                          |  • Monitor weight and nutritional status closely.                           |
| GDM with CF            | • Do not reduce calories or carbohydrate.                                    
                          |  • Replace excessive amounts of sweetened beverages with nutrient-dense calories.  
                          |  • Start insulin if blood glucose goals are not met and weight gain is insufficient.  
                          |  • Start oral supplements, if necessary.                                   |
| Pregnancy with CFRD    | • Match insulin to carbohydrates consumed.                                   
                          |  • Adjust insulin aggressively throughout pregnancy to meet blood glucose goals.  
                          |  • Monitor weight and nutritional status closely.                           
                          |  • Replace excessive amounts of sweetened beverages with nutrient-dense calories.  
                          |  • Possibly start insulin with nutritional decline.                         |

CFRD, cystic fibrosis-related diabetes; FH, fasting hyperglycemia; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; MNT, medical nutrition therapy.
Recommendations concerning alcohol consumption should be discussed with patients’ physicians because some CF medications may interfere with alcohol and because liver disease occurs in >40% of CF patients. Otherwise, the usual recommendations to consume alcohol moderately and with food apply to CF patients. The use of nonnutritive sweeteners resulting in a decrease in total calories is not recommended.

As always, a team approach is recommended, ideally with the pulmonary team working closely with an endocrinologist and other diabetes team members who are well acquainted with CFRD.

Because of the unique nature of CFRD, the Cystic Fibrosis Foundation has published a comprehensive manual for patients with CFRD and their families that is available at no cost to all CF centers in the United States. The manual includes chapters on MNT, as well as food lists showing carbohydrate content.

References


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