

Cystic Fibrosis-Related Diabetes and Abnormal Glucose Tolerance: Overview and Medical Nutrition Therapy

Carol Brunzell, RD, CDE, and Sarah Jane Schwarzenberg, MD

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.¹

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.² As survival has increased, CF-related diabetes (CFRD) has become the leading co-morbidity in this patient population,³⁻⁵ occurring in ~13% of all patients with CF.² This figure is widely believed to be an underestimate because of the lack of routine screening for diabetes in the CF population.⁶ CFRD is most commonly diagnosed in patients who are between 18 and 21 years of age.^{4,7}

Glucose Tolerance Categories

The 1998 CFRD Consensus Committee identified four glucose tolerance categories for clinical management and research purposes (Table 1).⁸ 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.⁸

Clinical Distinctions of CFRD

The American Diabetes Association (ADA) classifies CFRD under “other specific types of diabetes” involving diseases of the exocrine pancreas.⁹ 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. Inspissation of thick, viscous secretions causes fibrosis and fatty infiltration of the islets.¹⁰ 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.⁸ 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.⁸

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.^{11,12} Survival is markedly decreased in underweight patients with CF.¹³ Malnutrition in CF is the result of a combination of factors including maldigestion, malabsorption, declining pulmonary function, increased resting metabolic rate, anorexia, and gastroesophageal reflux leading to vomiting and food loss.¹⁴ 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.¹⁵

CFRD profoundly affects nutritional status and weight, resulting in greater morbidity and mortality than in the general CF population.^{2,16,17} Weight loss and declining pulmonary function develop 2–4 years before the actual CFRD diagnosis, probably because of insulin deficiency.^{16,17} Treatment with insulin improves pulmonary function and weight parameters.¹⁸ Patients with CFRD or abnormal glucose tolerance are protein-catabolic; protein catabolism is not reversed entirely with insulin therapy.^{19,20}

Diet recommendations that are often indicated for type 1 or type 2 diabetes are generally not applicable to patients with CFRD (Table 2). A high-calorie, high-fat, high-sodium diet is essential to maintaining weight and nutritional status in CF.²¹ Caloric

Table 1. Glucose Tolerance Categories in CF in Response to OGTT⁸

Category	FPG (mg/dl)	2-h PG (mg/dl)
NGT	<126	<140
IGT	<126	140–199
CFRD without FH	<126	≥200
CFRD with FH	≥126	OGTT unnecessary

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.^{22,23} 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.²⁴

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.^{4,5,25} 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.^{26,27}

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.⁸

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.⁶

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.⁸ 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.

Available choices include 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 (SMBG) 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.²⁸ 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 SMBG results (Table 3).²⁸ Weight, 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.²⁹

Elevated postprandial blood glu-

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

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

*This is the recommendation of the consensus conference.⁸ 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

cose caused by illness, chronic steroid use, and insulin resistance can result in malnutrition and weight loss. Nutritional status, anthropometrics, and weight should be closely monitored, and nutritional decline warrants premeal insulin therapy.

Currently, most patients who have CFRD without FH are not treated with insulin unless they are unable to maintain an appropriate weight or their pulmonary function is declining more rapidly than expected. At the University of Minnesota, the strategy for diabetes not treated with insulin is to minimize large carbohydrate loads by spreading carbohydrates throughout the day without reducing total calories. Patients obtain a blood glucose profile once a month at home to monitor status (Table 3).

MNT for IGT

CF patients with IGT are at high risk for progressing to CFRD. The IGT-related risks for cardiovascular disease in the general population do not appear to be of concern for patients with CFRD.^{22,23} The risk of microvascular disease with IGT in those with CF is not known.

Although the Diabetes Prevention Program recommended weight loss and a low-fat diet for people with IGT in the general population, recommendations for weight loss or a restriction of fat and calories would never be appropriate for CF patients. The only potentially beneficial dietary restriction may be to minimize excessive consumption of regular sodas or other sweetened beverages and to maximize intake of nutrient-dense foods to prevent weight loss. Spreading carbohydrates throughout the day may also be beneficial. CF patients with IGT should be tested yearly with an oral glucose tolerance test (OGTT) and perform more vigilant blood glucose monitoring during acute illness (Table 3).²⁸

CFRD and Pregnancy

Pregnancy in women with CF is now commonplace and considered to be generally safe, with good maternal and fetal outcomes.^{30,31} Preconception counseling and normalization of blood glucose is crucial for pregnant women with CFRD, just as it is for women with type 1 or type 2 diabetes, in order to reduce fetal and perinatal

Category	Management
IGT	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Match insulin to carbohydrates consumed. • Monitor weight and nutritional status closely.
GDM with CF	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Match insulin to carbohydrate consumed. • Adjust insulin aggressively throughout pregnancy to meet blood glucose goals. • Monitor weight gain closely. • Start oral supplements, if necessary.

CFRD, cystic fibrosis-related diabetes; FH, fasting hyperglycemia; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; MNT, medical nutrition therapy

morbidity and mortality.

Adequate weight gain is imperative for the best outcomes. Calorie needs will vary according to pulmonary function, and close monitoring of weight gain and nutritional status is imperative. The use of oral supplements may be necessary to ensure proper weight gain for women with poor pulmonary function or for those otherwise having trouble gaining weight.

Insulin needs will change throughout pregnancy, so pregnant women with CFRD should be followed closely by their diabetes team for insulin adjustment throughout their pregnancy (Table 3).

Gestational Diabetes and CF

Women with CF are at higher risk for gestational diabetes mellitus (GDM) because of CF-associated insulin deficiency.²⁸ A Toronto study noted a 14% incidence of GDM in women with CF.³¹

Few studies have been published to guide clinical management in this population. Because of the risk of poor weight gain, current practices

include 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 (Table 3).²⁸

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.³² 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.

Recommendations concerning alcohol consumption should be discussed with patients' physician 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 CFRD 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.³³

References

- Welsh MJ, Ramsey BW, Accurso F, Cutting GR: Cystic fibrosis. In *The Metabolic and Molecular Basis of Inherited Disease*. Scriver CR, Beaudet AL, Sly WS, Valle D, Eds. New York, McGraw-Hill, Inc., 2001, p. 5121-5188
- Cystic Fibrosis Foundation: *Annual Data Base Report*. Bethesda, Md., Cystic Fibrosis Foundation, 2000
- FitzSimmons SC: The changing epidemiology of cystic fibrosis. *J Pediatr* 122:1-9, 1993
- Lanng S, Thorsteinsson B, Lund-Andersen C, Nerup J, Schiøtz PO, Koch C: Diabetes mellitus in Danish cystic fibrosis patients: prevalence and late diabetic complications. *Acta Paediatr* 83:72-77, 1994
- Rodman HM, Doershuk CF, Roland JM: The interaction of 2 diseases: diabetes mellitus and cystic fibrosis. *Medicine* 65:389-397, 1986
- Allen HF, Gay EC, Klingensmith GJ, Hamman RF: Identification and treatment of cystic fibrosis-related diabetes. A survey of current medical practice in the U.S. *Diabetes Care* 21:943-948, 1998
- Rosenacker J, Eichler I, Kuhn L, Harms HK, von der Hardt J: Genetic determination of diabetes mellitus in patients with cystic fibrosis. Multicenter Cystic Fibrosis Study Group. *J Pediatr* 127:441-443, 1995
- Moran A, Hardin D, Rodman D, Allen HF, Beall RJ, Borowitz D, Brunzell C, Campbell PW, Chesrown 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 E, Zipf WB: Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. *Diabetes Res Clin Pract* 45:61-73, 1999
- American Diabetes Association: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (Committee Report). *Diabetes Care* 24 (Suppl. 1):S5-S20, 2001
- Lohr M, Goertchem P, Nizze H, Gould NS, GBould VE, Oberholzer M, Heitz PU, Kloppel G: CF associated islet changes may provide a basis for diabetes. *Virchows Archiv A Pathol Anat* 414:179-185, 1989
- Ramsey BW, Farrell PM, Pencharz P: Nutritional assessment and management in cystic fibrosis: a consensus report. *Am J Clin Nutr* 55:71-75, 1992
- Corey M, McLaughlin FJ, Williams M, Levison H: A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 41:583-591, 1988
- Kraemer R, Rudeberg A, Hadorn B, Rossi E: Relative underweight in cystic fibrosis and its prognostic value. *Acta Paediatr Scand* 67:33-37, 1978
- Pencharz PB, Durie PR: Pathogenesis of malnutrition in cystic fibrosis, and its treatment. *Clin Nutr* 19:387-394, 2000
- Levy LD, Durie PR, Pencharz PB, Corey ML: Effects of long-term nutritional rehabilitation on body composition and clinical status in malnourished children and adolescents with cystic fibrosis. *J Pediatr* 107:225-230, 1985
- Finkelstein SM, Wielinski CL, Elliott GR, Warwick W, Barbosa J, Wu SC, Klein D: Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 112:373-377, 1988
- Lanng S, Thorsteinsson B, Nerup J, Koch C: Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. *Eur J Pediatr* 151:684-687, 1992
- Lanng S, Thorsteinsson B, Nerup J, Koch C: Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Paediatr* 83:849-853, 1994
- Hardin DS, LeBlanc A, Lukenbaugh S, Para L, Seilheimer D: Proteolysis associated with insulin resistance in cystic fibrosis. *Pediatrics* 101:433-437, 1998
- Moran A, Milla C, Ducret R, Nair SK: Protein metabolism in clinically stable adult cystic fibrosis patients with abnormal glucose tolerance. *Diabetes* 50:1336-1343, 2001
- Pencharz PB: Energy intakes and low-fat diets in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2:400-402, 1983
- Schlesinger DM, Holsclaw DS, Fyfe B: Generalised atherosclerosis in an adult with CF and diabetes mellitus (Abstract). *Pediatr Pulmonol* 16 (Suppl. 14):365A, 1997
- Stewart C, Wilson DC, Hanna AK, Corey M, Durie PR, Pencharz PB: Lipid metabolism in adults with cystic fibrosis (Abstract). *Pediatr Pulmonol* 16 (Suppl. 14):366A, 1997
- Figuerola V, Milla C, Parks E, Schwarzenberg SJ, Moran A: Abnormal lipid levels in cystic fibrosis. *Am J Clin Nutr*. In press
- Sullivan MM, Denning CR: Diabetic microangiopathy in patients with cystic fibrosis. *Pediatrics* 84:642-647, 1989
- Johnson SB: Insulin-dependent diabetes mellitus in childhood. In *Handbook of Pediatric Psychology*. 2nd ed. Roberts MC, Ed. New York, Guilford Press, 1995, p. 263-285
- La Greca AM, Schuman WB: Adherence to prescribed medical regimens. In *Handbook of Pediatric Psychology*. 2nd ed. Roberts MC, Ed. New York, Guilford Press, 1995, p. 55-83
- Moran A: Cystic fibrosis-related diabetes: an approach to diagnosis and management. *Pediatr Diabetes* 1:41-48, 2000
- Moran A, Phillips J, Milla C: Insulin and glucose excursion following premeal insulin lispro or repaglinide in cystic fibrosis-related diabetes. *Diabetes Care* 24:1706-1710, 2001
- FitzSimmons SC, Fitzpatrick S, Thompson B, Aitkin M, Fiel S, Winnie G, Hilman B: A longitudinal study of the effects of pregnancy on 325 women with CF. *Pediatric Pulmonol* 13:99-101, 1996
- Gilljam M, Antoniou M, Shin J, Dupuis A, Corey M, Tullis E: Pregnancy in cystic fibrosis: fetal and maternal outcome. *Chest* 118:85-91, 2000
- Ward SA, Tomezko JL, Holsclaw DS, Paolone AM: Energy expenditure and substrate utilization in adults with cystic fibrosis and diabetes mellitus. *Am J Clin Nutr* 69:913-919, 1999
- Hardin D, Brunzell C, Schissel K, Schindler T, Moran A: *Managing Cystic Fibrosis Related Diabetes (CFRD)*. Bethesda, Md., Cystic Fibrosis Foundation, 1999

Acknowledgments

Dr. Schwarzenberg is funded in part by a grant from the Cystic Fibrosis Foundation. The authors wish to thank Dr. Toni Moran for her review of this article.

Carol Brunzell, RD, CDE, is a diabetes educator at the Fairview University Medical Center Diabetes Education and Self-Management Program, Pediatric and Adult Divisions, in Minneapolis, Minn. Sarah Jane Schwarzenberg, MD, is an associate professor of pediatrics in the Division of Pediatric Gastroenterology, Hepatology, and Nutrition at the University of Minnesota in Minneapolis.