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Nutritional Management of the Adult with Cystic Fibrosis – Part II

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Medical advances, research discoveries, and an interdisciplinary healthcare environment have led to a dramatic improvement in the life expectancy and quality of life for individuals with cystic fibrosis (CF). Advanced age with CF can lead to complications, but it also means that individuals can develop careers, get married, and start a family. This is part II of a two part series, which serves to present the nutritional challenges of adults with CF and to provide tools to prevent or manage these nutritional concerns. Part II will address cystic fibrosis related diabetes, fertility, and pregnancy with cystic fibrosis.

INTRODUCTION

As the most common co-morbidity in people with CF, cystic fibrosis-related diabetes (CFRD) occurs in approximately 40-50% of adults.[1] Although CFRD shares characteristics with both type 1 and type 2 diabetes, it is clinically distinct and thus requires a unique management approach.[2] This additional diagnosis instills both a therapeutic burden on the patient while having a negative impact on survival and lung function.[2]

With CF individuals living into the third, fourth, and even fifth decade, discussions regarding family planning are part of standard adult CF care. Ideally, CF patients should discuss pregnancy options with their adult CF team prior to conception. This allows the members of the health care team to provide guidance regarding the safety of conception for both the mother and the fetus and to discuss recommendations to optimize the health status of the mother prior to conception. Patients with CF who are pregnant benefit from nutrition counseling regarding appropriate weight gain, vitamin and mineral supplementation, and optimum blood sugar control.

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Cystic Fibrosis-Related Diabetes

Due to the progressive destruction of the pancreas and specifically to insulin-producing β-cells, CFRD is primarily caused by progressive insulin deficiency.[3] However, acute and chronic illness can cause some level of insulin resistance.[2] CF patients also intermittently receive systemic glucocorticoids, which can further exacerbate hyperglycemia. The typical macrovascular complications seen in patients with uncontrolled type 1 and type 2 diabetes are not of primary concern for patients with CF. In fact, despite the increasing life expectancy for CF patients, there has yet to be a report of a CF patient dying from atherosclerotic cardiovascular disease.[3] Declining lung function, weight loss, protein catabolism, and increased mortality are all

associated with the CFRD diagnosis thus warranting regular screening for CFRD among the CF population.[2] In 2010, the Cystic Fibrosis Foundation (CFF), the American Diabetes Association (ADA), and the Pediatric Endocrine Society (PES) published clinical care guidelines for the screening, diagnosis, and medical management of CFRD.[2]

Screening

Classic symptoms of diabetes include polyuria and polydipsia, but these often go unnoticed in the CF population. Frequent respiratory treatments can cause dry mouth for CF patients, causing them to drink more, and subsequently urinate more frequently than the general population. Other symptoms of diabetes in the CF population include fatigue, unexplained decline in lung function, unexplained weight loss, or the inability to gain weight despite best efforts. Clinicians should evaluate for these symptoms and trends among their adult CF patients.

Starting at age 10, annual screening for CFRD should be performed on all patients, regardless of whether the patient is pancreatic sufficient or insufficient.[2] The gold standard for CFRD screening is the 2-hour 75-gram oral glucose tolerance test (OGTT). Using hemoglobin A1C or fasting blood glucose is not recommended since these are not sufficiently sensitive for CFRD diagnosis.[2]

Additional screening criteria have been established to assess for CFRD during acute illness, while a patient is on continuous enteral drip feedings, and during pregnancy. When CF patients are treated for a pulmonary exacerbation, they are placed on intravenous antibiotics and/or systemic glucocorticoids. During the first 48 hours of treatment, fasting plasma glucose levels and 2-hour postprandial plasma glucose levels should be checked.[2] If after 48 hours, glucose levels do not meet diagnostic criteria, testing is no longer necessary.[2] For CF patients receiving supplemental continuous enteral pump feeding, blood glucose should be monitored mid-feeding and immediately after the completion of enteral feeding.[2] Any elevated glucose level identified by self-monitoring of blood glucose (SMBG) should be confirmed by a certified laboratory.[2]

Women with CF who are pregnant should be screened for gestational diabetes at 12-16 weeks and again at 24-28 weeks gestation.[2] For those diagnosed with gestational diabetes, further screening for CFRD should be done 6-12 weeks after delivery.[2]

Diagnosis

Similar to screening criteria for CFRD, diagnostic criteria for CFRD is delineated into categories of healthy patients, those being treated for acute illness, those on continuous drip enteral feedings, and those who are pregnant. These guidelines can be found in Figure 1.

Unfortunately, most CF patients, even those with normal 2-hour OGTT results and normal fasting glucose levels, have some degree of glucose abnormality. Individuals may demonstrate hyperglycemia in the middle of the 2-hour OGTT or may have elevated fasting glucose levels. These individuals are said to have indeterminate glycemia (INDET) or impaired fasting glucose (IFG), respectively.[2] Those whose blood glucose levels are between 100-199 mg/dL after the 2-hour OGTT are said to have impaired glucose tolerance (IGT). The clinical significance of these glucose abnormalities has not yet been defined, but CF patients who meet these criteria will often develop CFRD in the future. The diagnostic criteria presented in Figure 1 are based on the risk for microvascular complications for which patients with CFRD are also at risk.[2] Previous CFRD guidelines required a diagnostic distinction between those with fasting hyperglycemia (FH+) and those without fasting hyperglycemia (FH-). However, studies treating both FH+ and FH- patients with insulin therapy showed similar results and the 2010 guidelines state that distinguishing between FH+ and FH- individuals is no longer necessary.[1, 2, 4]

Management

At this time, insulin is the only recommended medical therapy for the treatment of CFRD.[2] Studies comparing oral diabetes agents to insulin therapy in the CFRD population demonstrate that insulin is more effective in improving nutritional and metabolic outcomes.[2, 4, 5] No specific insulin regimen has been established for CFRD patients and insulin therapy should be individualized. The majority of CFRD patients follow a basal-bolus insulin regimen requiring multiple daily subcutaneous injections of intermediate or long-acting insulin along with rapid-acting insulin at meal times. Insulin-infusion pumps are also gaining popularity among this population to provide the needed insulin without frequent injections. Patients with CFRD are counseled to perform SMBG at least three times per day and to monitor for signs and symptoms of hypo- and hyperglycemia. Guidelines for blood glucose

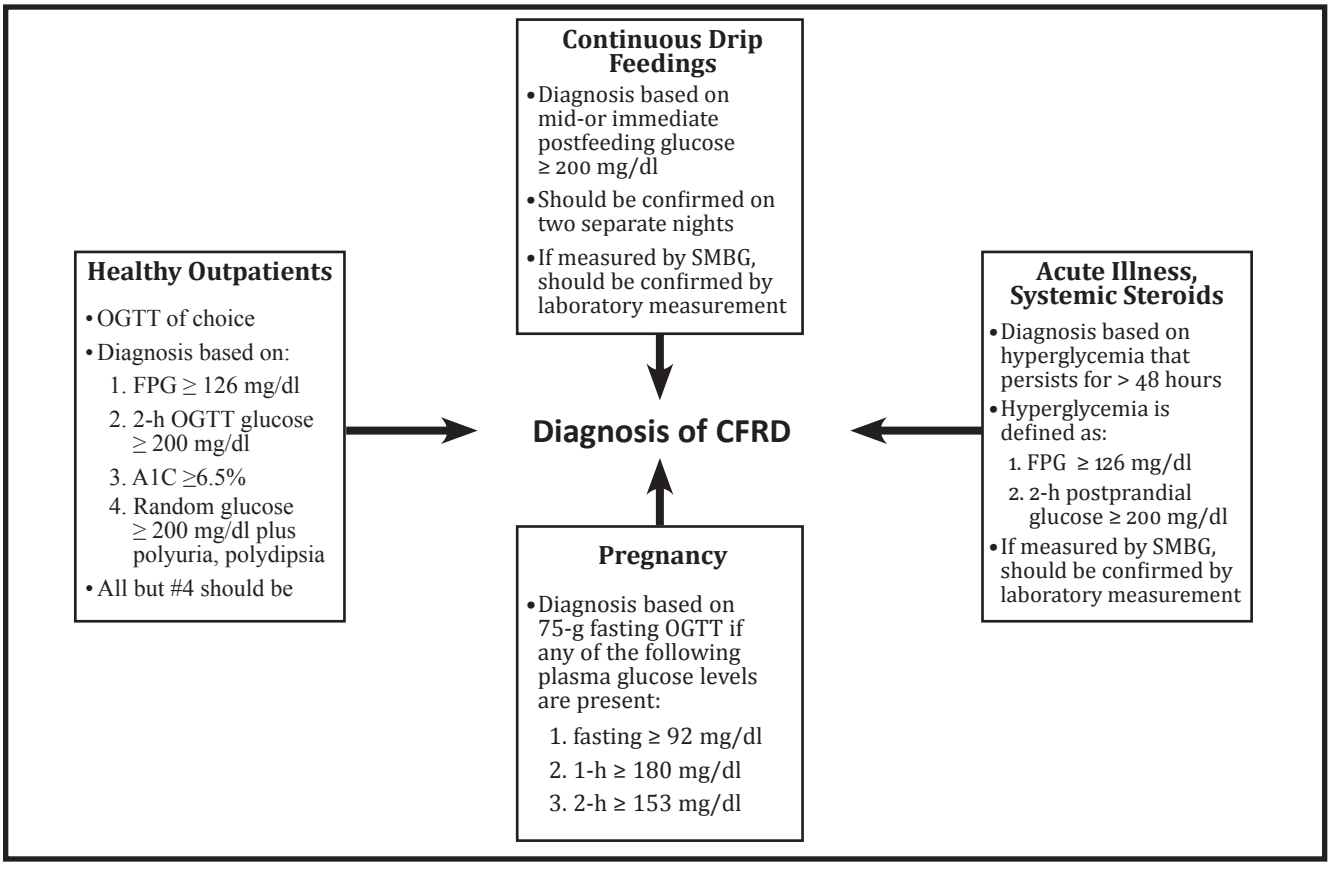

Figure 1.

goals can be found in "Managing Cystic Fibrosis-Related Diabetes: An Instruction Guide for Patients and Families, 5th Edition".[6] This manual, released by the Cystic Fibrosis Foundation in 2011, is free in print or online from the Cystic Fibrosis Foundation website: www.cff.org.[6]

During times of pulmonary exacerbation, insulin needs may greatly increase and remain elevated several weeks after antibiotic and/or glucocorticoid administration ceases.[2] Consequently, CFRD patients on elevated insulin regimens following illness should closely monitor for hypoglycemic events as the need for increased insulin tapers.

Exercise is an important component to the overall health of CF patients and is frequently encouraged. Patients with CFRD should be counseled about the hypoglycemic effects of exercise and that extra carbohydrate and/or decreased insulin doses prior to intense physical activity may be necessary. Adults with CFRD should also be counseled on the use of insulin with alcohol intake. Patients taking insulin should never drink on an empty stomach, are encouraged to consume adequate carbohydrates while drinking, and to monitor blood glucose while drinking. The hypoglycemic effects of alcohol, and the potential hyperglycemic effects of drinks that are commonly mixed with alcohol, should be discussed.

Unlike patients with type 1 or type 2 diabetes, patients with CFRD are not encouraged to follow a low-fat, low-salt, or low-calorie diet. Instead, they should continue to follow a high-fat, high-salt, high-calorie well-balanced diet and use a carbohydrate-to-insulin ratio to dose their rapid-acting insulin with meals and snacks. This diet prescription requires close coordination between the endocrinologist, the diabetes educator, and the multidisciplinary cystic fibrosis care team. CFRD patients must learn to accurately count carbohydrates and to monitor and document their blood glucose so that their basal insulin or their insulin-carbohydrate ratio can be adjusted if necessary.

Pregnancy and Fertility

Fertility

Almost all men with CF struggle with infertility. Males with CF do not typically have issues with testicular

Table 1. Safety of Commonly Used Medications During Pregnancy and Breastfeeding [8]

Medication/Class	Risk in 1st Trimester	Risk in 2nd Trimester	Recommendation	Breastfeeding
Proton pump inhibitors (PPIs)	Probably no risk	No risk	Probably safe	Compatible – low concentration in milk
Insulin/insulin analogues	No risk	No risk	Human insulins preferred, can be used without risk	Compatible – reduce dose in lactation
Bisphosphonates Risedronate	Fetal damage expected	Fetal damage expected	Contraindicated	Avoid – no data
Pancreatic enzymes	Probably no risk	Probably no risk	Probably no risk	Compatible
Vitamin A	In prophylactic doses probably safe	In prophylactic doses probably safe	Doses <10,000IU/ day are considered safe	Compatible – at prophylactic dose
B vitamins	Probably safe	Probably safe except for high doses of B6 associated with neonatal convulsions	Probably safe. High does B6 contraindicated	Compatible
Vitamin C, E, K	Probably safe	Probably safe	Probably safe. High dose Vitamin C may cause paradoxical neonatal deficiency	Compatible
Vitamin D	Probably safe in prophylactic doses	Cholecalciferol or ergocalcipherol probably safe in prophylactic doses	Probably safe in prophylactic doses	Compatible – in prophylactic dose; high dose may cause hypercalcemia in infant

Adapted with permission from *Guidelines for the management of pregnancy in women in cystic fibrosis.* Journal of Cystic Fibrosis, 2008, S2-S32.

spermatogenesis, but bilateral absence or obstruction of the vas deferens is common.[7] Consequently, although adequate sperm for fertilization may be present internally, it is not sufficiently present in the semen. Options for infertile men with CF include microsurgical epididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), or testicular sperm harvesting.[7] Extracted sperm is then used for in vitro fertilization.

Unlike men with CF, the majority of women with CF are able to conceive without issue. However, women with CF may reach menarche late and even after reaching menarche may experience stretches of amenorrhea or anovulation.[7] These causes of infertility may be related to the CFTR mutation, poor health, or malnutrition.[7] Women with CF can also have thicker cervical mucus, which leads to obstruction of the reproductive organs making it difficult for sperm to penetrate and subsequently fertilize.[7] These obstacles

(continued on page 23)

(continued from page 16)

can also be overcome using in vitro fertilization. Although in vitro fertilization is an option for both men and women with CF infertility, patients with CF are also turning to adoption and surrogacy as a means for having children.

Medications During Pregnancy and Breastfeeding

Adults with CF often spend their days juggling a complicated therapy schedule involving: oral and inhaled antibiotics, pancreatic enzyme replacements, insulin injections, and respiratory physiotherapy. In general, medications are not tested on pregnant women and information known about their safety during pregnancy or breastfeeding is established from animal studies, clinical experience, or known mechanism of action.[7] Women with CF who are pregnant should discuss their entire medication list, both prescriptive and over-the-counter, with their CF physician, dietitian, and respiratory therapist. See Table 1 for a list of nutritionally relevant commonly used medications and their suggested use during pregnancy and breastfeeding.[8]

Weight: Before and During Pregnancy

Concrete recommendations for pre-pregnancy weight in CF patients are not currently available. However, case series have demonstrated that CF women with higher pre-pregnancy BMIs deliver babies closer to full term.[9, 10] Additionally, those with a BMI < 20 kg/m^2 have an increased risk of adverse fetal outcomes. General CF guidelines advise a pre-pregnancy BMI of at least 19 kg/m^2. If patients cannot achieve this pre-pregnancy BMI goal with increased calorie intake and the use of oral supplements, it is not unreasonable to suggest gastrostomy tube placement for supplemental nocturnal feeding. In this population, a variable length gastrostomy tube rather than a fixed length balloon gastrostomy tube is preferred so that the feeding tube can remain in place as the abdomen stretches after pregnancy is achieved.

Guidelines for adequate weight gain for CF patients mimic those for the general population and are based on pre-pregnancy BMI. Malabsorption from pancreatic insufficiency and increased energy and protein requirements of CF patients can make what appears to be a modest weight gain quite challenging (see Table 2 for weight gain recommendations based on BMI).[11] An additional 300 to 800 calories per day may be required to support pregnancy for a CF patient. Importantly, this caloric requirement will vary from patient to patient, dependent on disease severity, degree of malabsorption, and sometimes results in needs greater than the general guidelines. It is often helpful to show patients their pre-pregnancy weight on a prenatal weight gain chart. This provides a visual for an appropriate weight gain goal and a copy of this chart can be sent home with the patient so that she can track her success.

Table 2. Weight Gain Recommendations for Pregnancy[11]

- Underweight (BMI < 18.5 kg/m2)
  - > 28-40 lbs total
  - > 1 lb per week during the 2nd and 3rd trimester
- Normal Weight (BMI 18.5-24.9 kg/m2)
  - > 25-35 lbs total
  - > 1 lb per week during the 2nd and 3rd trimester
- Overweight (BMI 25-29.9 kg/m2)
  - > 15-25 lbs total
  - > 0.6 lb per week during the 2nd and 3rd trimester
- Obese (BMI ≥ 30 kg/m2)
  - > 11-20 lbs total
  - > 0.5 lb per week during the 2nd and 3rd trimester

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Vitamins During Pregnancy

Vitamin supplementation during pregnancy with CF is similar to that of the general population. Due to chronic fat malabsorption, fat soluble vitamin levels (A, D, E and K) should be checked prior to conception and throughout pregnancy. Suboptimal levels should be corrected with additional supplementation (See Part I for "Vitamins Supplementation" guidelines). Folic acid deficiency can result in neural tube defects. Therefore, women with CF who are well nourished should take 400 mcg of folic acid daily while trying to get pregnant. Those at high risk for deficiency, or with a history of poor compliance, should take 4000 to 5000 mcg per

day prior to conception and during the first trimester.[8] Iron deficiency anemia should be prevented or corrected prior to conception and throughout pregnancy. Iron stores should be assessed by checking serum ferritin levels each trimester and supplementing accordingly. Excessive vitamin A supplementation is often a concern during pregnancy since high doses of vitamin A can be teratogenic and standard CF multivitamins contain higher than recommended doses of vitamin A for pregnancy. However, low levels of vitamin A can also be teratogenic and some CF centers have continued high dose vitamin A supplementation throughout pregnancy without a resultant increase in serum vitamin A levels. Consequently, it is recommended to check vitamin A levels prior to pregnancy and if within normal limits, to continue routine high dose vitamin A supplementation. Vitamin A levels should be subsequently checked during each trimester with a decrease in dosage if serum levels become elevated.

Nutrition After Delivery

The delivery of a healthy baby, while maintaining a healthy mother with CF, is certainly a cause for celebration. However, the work to maintain maternal weight and lung function has just begun. Compound the work of new motherhood with the burden of CF therapy regimens and it is easy to understand how the mother may lose sight of her own health during those first few months with a newborn. Discussion about this challenging time should begin prior to delivery and follow-up with the multidisciplinary CF team shortly after pregnancy is helpful.

Similar to the general population, women with CF are encouraged to breastfeed and have done so successfully.[12] As previously mentioned, information regarding the transfer of medications from mother to infant via breastmilk is often lacking and patients should review their entire medication list with the CF team when considering breastfeeding. Refer to Table 1 for a list of nutritionally relevant medications and their use during breastfeeding. A more extensive list of common CF medications and their use during pregnancy and breastfeeding can be found in the "Guidelines for the management of pregnancy in women with cystic fibrosis".[8]

Due to increased calorie and protein requirements, women with CF typically do not struggle to lose the weight gained during pregnancy and will often return to pre-pregnancy weight within one to two months after delivery. Breastfeeding increases calorie needs and women with CF who decide to breastfeed should be counseled to consume at least an additional 500 calories per day and to take 1200 mg calcium per day. Continue to routinely check fat-soluble vitamins (A, D, E and K) and replete to maintain normal levels (see Part I).

CONCLUSION

The advances in CF care have led to improved life expectancy, which can mean additional complications, but can also mean an enhanced quality of life. As a common co-morbidity of CF, CFRD must be diagnosed early and managed appropriately to minimize long-term consequences of inadequate blood glucose control. Healthy pregnancy is now a safe and feasible option for patients with CF. Practitioners can improve pregnancy outcomes by counseling patients before, during, and after delivery about the importance of nutrition and pregnancy. This is a challenging patient population, but the motivation and teamwork of the CF community make it equally rewarding. ■

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