Screening and Diagnosis of CFRD

- Describe the clinical impact of the early diagnosis of glucose abnormalities in people with CF.
- Summarize the limitations of alternative modalities for screening and diagnosing CFRD.
- Identify the current recommendations for the management of CFRD.

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MEET THE AUTHOR

Andrea Granados, MD
Instructor in Pediatrics
Division of Pediatric Endocrinology and Diabetes
Washington University School of Medicine
St. Louis, Missouri

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Director, Adult Cystic Fibrosis Program
Associate Professor of Medicine
The Johns Hopkins University
Baltimore, Maryland

Suzanne Sullivan, RN, BSN
Senior Clinical Nurse
Johns Hopkins Hospital
Baltimore, Maryland
BOB BUSKER: Welcome to this eCysticFibrosis Review podcast.

I’m Bob Busker, managing editor of the program. We’re here today with Dr. Andrea Granados, Instructor in Pediatrics, in the Division of Pediatrics, at Washington University School of Medicine in St. Louis. And our topic is: Screening and Diagnosis of CFRD: Cystic Fibrosis Related Diabetes.

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Learning objectives for this audio program include:

- Describe the clinical impact of the early diagnosis of glucose abnormalities in people with CF.
- Summarize the limitations of alternative modalities for screening and diagnosing CFRD.
- Identify the current recommendations for the management of CFRD.

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She has also indicated that her discussion today will not reference the unlabeled or unapproved use of any drugs or products.

MR. BUSKER: Dr. Granados, thank you for joining us today.

DR. GRANADOS: Thank you, Bob, very much for the invitation and the opportunity to discuss this topic today.

MR. BUSKER: CFRD — Cystic Fibrosis Related Diabetes. In your newsletter issue, you presented current research that describes how this most prevalent extrapulmonary complication of cystic fibrosis is associated with a decline in pulmonary function, poor nutritional status, and greater mortality. Our focus today is to translate how some of that new information can impact CF management in the clinic. So please start us out with patient scenario.

DR. GRANADOS: Our first case is a 12-year-old female CF patient with pancreatic insufficiency who is clinically stable and had a routine screening oral glucose tolerance test (OGTT) that was abnormal. She has normal lung function for her age. She is on a routine medication regimen including pancreatic enzymes for all her meals and snacks, multivitamins, and CF specific vitamins.

The results of the OGTT show that fasting glucose was 92, the one-hour was 202, and the two-hour glucose was 177. The findings are consistent with diagnosis of impaired glucose tolerance. She denies polyuria or polydipsia. She has had excellent longitudinal growth at the 50th percentile, with growth velocity typical of a pubertal growth spurt. She has not gained weight since her previous CF visit three months ago, dropping from the 50th to the 40th percentile.

MR. BUSKER: Her oral glucose tolerance test results indicate IGT — impaired glucose tolerance. What are the clinical implications of IGT for this patient?

DR. GRANADOS: The available evidence supports a significant decline in pulmonary function and weight for as long as six years before the diagnosis of CFRD, so there is a clear association between poor health outcomes such as nutritional status and lung function, with early glucose abnormalities including impaired glucose tolerance, impaired fasting glucose, and indeterminate glycemia or INDET.

In addition, there is evidence that the degree of impairment of glucose tolerance and the degree of deficiency in insulin secretion correlate with the rate of lung function decline in patients with CF, suggesting a direct cause and effect relationship between insulin deficiency and clinical decrease.

Coriati and colleagues, reviewed in this newsletter, reported that subjects with CF and INDET displayed a reduced pulmonary function similar to that seen in patients with CFRD.

MR. BUSKER: When should treatment be initiated? Do you hold off treating until the diagnostic criteria of CFRD appear? Do you treat as soon as the glucose abnormalities are identified? What's the best thought here?

DR. GRANADOS: For people with earlier glucose abnormalities such as in this case, there are no good data on whether early institution of insulin outweighs the disadvantages of intervention. So unfortunately, we don’t have an answer to this question.
Insulin therapy is invasive and requires regular blood glucose monitoring. Furthermore, there is a risk of hypoglycemia, and it is expensive. However, small studies suggest that there might be an improvement in BMI or nutritional status and lung function in patients treated with small doses of insulin without any reports of hypoglycemia.

Two large multicenter studies going on right now will help answer this question. In the meantime, I believe the diagnosis of abnormal glucose tolerance represents an excellent opportunity to provide education to the family and explain the risk of CFRD in the near future and the negative impact in lung function and nutrition.

MR. BUSKER: What would be the key things to communicate?

DR. GRANADOS: Families need to understand that an earlier diagnosis and treatment of CFRD will have a positive impact in their patient’s overall health. We also use this opportunity to teach patients about carbohydrate counting. We do not ask them to restrict carbohydrate intake, with the exception of sodas or sugary drinks, but rather to spread the carbohydrates throughout the day. This reduces swings in blood glucose levels and also starts preparing them for the future when they will likely get diabetes and have to do this as part of an insulin regimen.

They also need to know that patients with CF progress to diabetes at the time of acute illness because of increased insulin resistance and during this time treatment with insulin will be indicated.

MR. BUSKER: The current guidance recommends an annual OGTT as part of the screening test for CFRD in patients 10 years or older. Why is that the recommended age?

DR. GRANADOS: CFRD is rare in CF patients younger than 10 years, with a prevalence of roughly 1% to 5%. CFRD prevalence increases with age, with diabetes occurring in about 15% of adolescents and 50% of adults with cystic fibrosis. This is why the current guidelines recommend screening at this age.

However, a study showed that while diabetes, per se, is not common in children between 6 to 9 years of age, abnormal glucose tolerance is seen in almost half, and these children were at risk of developing diabetes in the next three to four years. This is important because we know that early intervention may help prevent an expected decline in pulmonary and nutritional status.

It is possible that when the guidelines get updated, a younger age for screening will be recommended.

MR. BUSKER: An oral glucose tolerance test is inconvenient and time-consuming for both the patient and the clinician. Are there alternative diagnostic tests? What’s been studied?

DR. GRANADOS: In recent years researchers have been trying to answer this question, and special attention has been put to the performance of HbA1c, continued glucose monitoring, and intermediate time points in the OGTT.

MR. BUSKER: Let’s look at those one at a time. HbA1c?

DR. GRANADOS: HbA1c tends to underestimate the degree of hyperglycemia. This may be because red blood cells in patients with cystic fibrosis have a shorter lifespan from chronic inflammation, which affects the degree of glycosylation.

Also, in early CFRD, intermittent hyperglycemia might not be high enough or long enough to raise HbA1c levels. A couple of studies used different cutoffs to try to predict CFRD, but the findings were not reproducible, and this test failed to discriminate patients with early glucose abnormalities that have clinical relevance for us, given its association with poor clinical outcomes. HbA1c is not recommended as a screening tool, but it is recommended to monitor patients with an established diagnosis of CFRD.

MR. BUSKER: What about CGM — continuous glucose monitoring?

DR. GRANADOS: Continuous glucose monitoring is another method that has been studied as a screening tool in CF, although it should be noted that the American Diabetes Association does not recommend it as a screening tool for any type of diabetes. CGM provides detailed 24-hour glycemic profiles under free living conditions. While the OGTT involves consumption of a specific amount of carbohydrate to make sure it is comparable between individuals, CF patients at home often consume carbohydrates far in excess of the OGTT 75 gm.

CGM gives information on multiple glucose parameters not validated in CFRD like average 24-hour blood glucose levels, and fluctuation indices. These parameters have not been studied in subjects with CF. We don’t have longitudinal data on their impact on health outcomes in CF, including lung function or weight deterioration.

The biggest problem is that a majority of CF adults, regardless of OGTT findings, have intermittent high glucose levels that are seen in CGM 24-hour glucose monitoring. For instance, one of the articles in the newsletter commentary suggesting that CGM be used for diabetes screening, found that 16 of the 17 CF patients they studied had an abnormal CGM.
MR. BUSKER: And that last one you mentioned? Intermediate time points in the OGTT. What’s that about?

DR. GRANADOS: Intermediate time point elevation during OGTT has been a focus of several research investigations. In normal individuals, glucose levels start to rise after consumption of carbohydrates at the beginning of the OGTT, but because of a strong early insulin response they peak at 30 to 60 minutes and then normalize. In CF, because of an absent early insulin secretion, glucose levels continue to rise and peak at 60 to 90 minutes before falling. Sometimes because of a latent disorder in insulin secretion, they fall too far and the patient experiences reactive hypoglycemia two to three hours after the carbohydrate intake.

In CF, an elevated one-hour glucose over 200 mg/dL with a normal two-hour glucose, which is also called INDET, is considered an early stage of glucose dysregulation. Glucose profiles in INDET are associated with a marked reduction in lung function at the level usually observed in patients with newly diagnosed CFRD.

One study presented in the newsletter suggested alternative one-hour cutoff, such as a one-hour glucose over 160 mg/dL as a value that predicts risk of diabetes. However, there is a lack of perspective longitudinal studies to support one-hour glucose as a screening test for diabetes, and also it is not clear if the test would increase adherence to testing compared to the gold standard two-hour OGTT.

MR. BUSKER: Thank you for that case and discussion. We’ll continue with Dr. Andrea Granados from Washington University School of Medicine in just a moment.

DR. GRANADOS: The second case is a 15-year-old male admitted to the hospital for CF exacerbation. He has a delta-F508 heterozygous genotype. He also has fairly well-preserved lung function and has not had any lung exacerbations in the past two years until now. He is on pancreatic enzymes with meals and snacks, multivitamins, and an antacid to be taken once a day. He has not had a diagnosis of CFRD and has no CF liver complications.

Prior to admission he had respiratory symptoms and a decline of his lung function. Initially he was advised to start oral antibiotics at home but in follow-up there was no evidence of improvement, so he was admitted to the hospital for IV antibiotics. During the current hospitalization his blood glucose levels were monitored. Endocrinology was consulted because glucose levels had been ranging from 100 to 150 fasting and two-hour postprandial glucoses in the low 200s for more than 48 hours. He denies polyuria or polydipsia.

MR. BUSKER: So, an adolescent is admitted to the hospital for a pulmonary exacerbation. As he’s being treated, you find his glucose levels are elevated. In this setting of an acute illness, can you legitimately make a diagnosis of CFRD?

DR. GRANADOS: Based on the current CFRD guidelines, a diagnosis of CFRD can be made during the acute illness if the elevation of the glucose levels persists over 48 hours. The criteria included fasting glucoses of over 126 or two hours postprandial over or equal to 200 milligrams per deciliter. The 48-hour time point was chosen because for many patients, hyperglycemia resolves quickly after IV antibiotics treatment, while for others it persists and 48 hours generally differentiates between these two groups.

MR. BUSKER: So persistent glucose elevation for 48 hours or longer can indicate CFRD. What then would be the recommended treatment for this patient?

DR. GRANADOS: The only recommended therapy for CFRD is insulin. For CFRD with fasting hyperglycemia, the CF
Foundation recommends basal/bolus insulin therapy with multiple daily injections of short-acting insulin before each meal, and a single daily dose of long-acting insulin. This regimen can be also delivered by insulin pump.

Basal/bolus therapy allows flexibility with diet, since insulin dose is adjusted to the carbohydrate content of each meal and snack. The benefits on insulin in CFRD have been studied to a limited degree, but the available evidence suggests improvement in HbA1c, BMI or nutritional status, lung function, and number of pulmonary exacerbations and survival. The average adolescent with CFRD receives roughly 0.4 units/kg/day of insulin, which is less than prescribed for most adolescents of similar age with type 1 diabetes.

Patients with CF generally have persistence of endogenous insulin secretion and in this sense, are much like a patient with type 1 diabetes in the honeymoon phase. In our experience, we recommend starting meal coverage with insulin to carbohydrate ratio of 1/2 unit/15 gm to 1 unit/15 gm of carbohydrate, and a correction scale usually starting at 1 unit for every 50 mg/dL over 150.

In the presence of fasting hyperglycemia, we also recommend long-acting basal insulin, at roughly 0.25 units/kg/day, with subsequent adjustments of the dose based on fasting glucose concentration. Patients who are acutely ill or on steroids need much higher doses because they are insulin resistant, but this is rapidly reduced as the illness resolves.

MR. BUSKER: Have any oral antihyperglycemic agents been studied in patients with CFRD?

DR. GRANADOS: Oral diabetes agents are not currently recommended in CFRD. Repaglinide stimulates insulin secretion and has been shown to increase insulin release and reduce glucose concentrations in people with CFRD in short-term. But in one study, after six months all weight gain achieved with repaglinide was lost because a failing beta cell can only respond to stimulation for a limited time.

A recent Cochrane review found no significant conclusive evidence that long-acting and short-acting insulins or repaglinide have a distinct advantage over one another in controlling hyperglycemia or clinical outcomes associated with CFRD.

DPP-4 inhibitors and GLP-1 analogs are used to treat patients with type 2 diabetes and are currently being studied in CF. GLP-1 is an incretin hormone released from the intestinal L cells in response to eating. It works by stimulating insulin and inhibiting glucagon. It is quickly deactivated by the serine protease dipeptidyl-peptidase-4, DPP-4. Incretin hormones account for 70% of the release of insulin from the pancreas in response to food. We know that subjects with CF have reduced levels of GLP-1, so there is a potential therapeutic use in CF, although there are still concerns that stimulating a failing beta cell mass may not have a durable effect.

MR. BUSKER: What about an oral agent like metformin to increase insulin sensitivity or reduce insulin resistance?

DR. GRANADOS: Metformin is not currently recommended in CFRD. The primary etiopathogenic factor in CFRD is insulin deficiency and not insulin resistance, which is what metformin treats. Furthermore, metformin has significant gastrointestinal side effects that might be particularly problematic in CF.

MR. BUSKER: What about the CFTR correctors, doctor? Patients on CFTR correctors or potentiators have shown significantly improved overall lung function. Are there any findings about improvements in hyperglycemia or insulin secretion in patients with CFRD who are on CFTR correctors?

DR. GRANADOS: Results from several studies show that the CFTR itself is essential for beta cell function. In a small study of patients with cystic fibrosis aged 6 to 52 years given ivacaftor, a CFTR corrector approved by the FDA, restoration of the CFTR function for one month improved the insulin response to oral glucose significantly. All patients but one showed improvement in first phase insulin secretion after ivacaftor. These data are promising, and we hope to have data in the near future from larger studies looking at other CFTR corrector potentiators and their effects on glucose abnormalities in patients with CF.

MR. BUSKER: Thank you. We've got time for one more patient scenario.

DR. GRANADOS: Our final patient is an 18-year-old male with cystic fibrosis and pancreatic insufficiency. He has relatively mild lung disease and is currently on continuous regimen of inhaled antibiotics, alternating monthly between inhaled tobramycin and inhaled aztreonam. He has been on this regimen for a couple of years. He’s on pancreatic enzymes, multivitamins, nutritional supplements, and oral azithromycin three times per week.

He has had a five-pound weight loss since last visit. He reports worsening of respiratory symptoms. He recently started college and a new job. He admits that it has been difficult for him to keep up with all his medications. CFRD was diagnosed a couple of months ago, and he was started on basal and bolus regimen. He heard from a relative that diabetes can be treated with diet, so he decided to stop his insulin, to limit the sugar in his diet, and to eat more protein. He also stopped checking his blood sugars.

During the visit his HbA1c is 7.6%, up from 6.7% at the time of diagnosis.
MR. BUSKER: This 18-year-old has stopped his insulin and his glucose monitoring — essentially all his recommended CFRD treatments — because a relative told him he can control his cystic fibrosis related diabetes through diet. Is there a simple way to explain how inappropriate that choice is?

DR. GRANADOS: Yes. The dietary management of CFRD is very different from that in type 1 or type 2 diabetes. Unlike in type 2 diabetes, calorie and carbohydrate restriction is usually not appropriate in CFRD. The recommendation for caloric intake in individuals with CF ranges from 110% to 120% of the estimated average intake. The majority of patients with CF rely on refined sugary foods as a source of energy. Restriction of those may impact their nutritional status. We usually emphasize a balanced and healthy diet. Both the dietary change and stopping the insulin therapy are likely contributing factors to the weight loss in this patient.

In CFRD, normalization of blood glucose levels should be achieved by balancing insulin requirements with sufficient caloric intake. Patients with CFRD need continuous education in diabetes management and nutrition. Because their needs are different from those of people with type 1 and type 2 diabetes, they definitely benefit from multidisciplinary CF team experienced in CFRD.

Importantly, when insulin therapy is first instituted or when a patient has a change in living circumstances, it is critical that the patient have good access to the team for insulin dose adjustment.

MR. BUSKER: So, in patients with CFRD, continuing follow-up becomes very important. What follow-up do you recommend to your patients?

DR. GRANADOS: We recommend quarterly follow-up with a specialized multidisciplinary team with expertise in diabetes and CF. The reason for the quarterly visit is that this population requires ongoing insulin adjustments as well as ongoing diabetes education with teaching on insulin dosing and administration, hypoglycemia, blood glucose monitoring, carb counting, glucagon, and complications from diabetes. We also perform a quarterly HbA1c level, which helps monitor the diabetes control.

MR. BUSKER: A few moments ago, you noted that dietary management in cystic fibrosis related diabetes is different than in type 1 or type 2 diabetes. But, and particularly since people with CF are living longer, should people with CFRD be concerned about the common micro- and macro-complications of diabetes?

DR. GRANADOS: Yes, definitely. Subjects with CFRD are at increased risk of microvascular complications and they should be screened annually. Assessments should include fundoscopy, measurement of urinary albumin concentration, blood pressure, and foot examination for peripheral sensory neuropathy.

While people with type 1 and type 2 diabetes die from atherosclerotic cardiovascular disease, this does not seem to be the case in CF. To date there have been no reports of deaths from macrovascular complications in CF.

MR. BUSKER: How extensive a problem have you found patients not adhering to their recommended CFRD therapies?

DR. GRANADOS: People with CF have complex and time consuming daily treatment regimens of up to two hours a day. Therefore, the new diagnosis of CFRD adds a significant amount of stress and work to our patients. Patients need to check blood glucose four times a day, including before the three big meals of the day and at bedtime. They also need to count carbohydrate content of their meals to be able to calculate their insulin doses. This process takes time. Poor adherence is a common problem in CFRD, as in any other chronic disease.

As presented in previous newsletters from the eCysticFibrosis Review, the adherence rate to CF treatment has been reported as low as 50%. In subjects with type 1 and type 2 diabetes, adherence to oral or insulin regimen varies from 36% to 93%. We don’t have data on adherence to CFRD treatment, but we find this is a particular struggle of adolescents. They want to be independent from their families and their families also want to try not to micromanage the adolescent’s daily activities.

Diabetes is generally relatively asymptomatic, so the adolescent doesn’t feel any changes if they miss insulin doses. Furthermore, adolescents feel invulnerable and they don’t think about long-term consequences of poor diabetes control.

When I have patients with poor adherence I try to provide more education and empower them to understand the reasons for our recommendations. We provide a schedule and a routine. Many times, reminders help with compliance to the diabetes regimen. They can use alarms in their smart phones to remember to get their insulin.

Most young men and women are concerned about body image and more are motivated to increase their muscle mass than they are motivated to gain weight. In this patient in particular, we would stress that taking insulin and getting the dose right will help him build muscle mass. Also, we tell them that patients with poorly controlled diabetes usually think they feel fine but once the diabetes is under good control, they realize that they have better energy and concentration and just feel better.
I also encourage communications with their families and continued parental involvement in the medical care of our patients. Studies addressing this issue are definitely needed, and studies that focus on intervention to improve individual adherence barriers.

MR. BUSKER: Thank you, Dr. Granados, for today’s cases and discussion. To wrap things up, let’s review what we’ve been talking about today in light of our learning objectives. So, to begin: the clinical impact of the early diagnosis of glucose abnormalities in people with cystic fibrosis.

DR. GRANADOS: There is a clear association between poor health outcomes such as nutritional status and lung function with early glucose abnormalities, including impaired glucose tolerance and fasting glucose and INDET, or indeterminate glycemia.

It is important for the clinician to screen all patients with CF 10 years or older, to be able to identify early glucose dysregulation abnormalities.

MR. BUSKER: And our second learning objective: the limitations of alternative modalities for screening and diagnosing CFRD.

DR. GRANADOS: Recent studies have looked at the performance of HbA1c, continuous glucose monitoring, and intermediate time points in the OGTT as a screening method for CFRD. HbA1c tends to underestimate the degree of hyperglycemia. A couple of studies used different cutoffs to try to predict CFRD, but the findings were not reproducible.

Continuous glucose monitoring in CF patients has demonstrated that regardless of OGTT findings, the majority of patients have intermittent high glucose levels, and we do not completely understand its clinical impact. In addition, close to half of the patients who have hyperglycemia on CGM do not develop CFRD, making it an imperfect screening tool.

A recent study has suggested alternative cutoffs such as one-hour glucose over 160 mg/dL as a value that predicts risk of diabetes. However, there is a lack of prospective longitudinal studies to support the one-hour glucose as a screening test.

MR. BUSKER: And finally: the current recommendations for the management of CFRD.

DR. GRANADOS: Management of CFRD is currently limited to insulin, but alternative oral hypoglycemic agents are being studied. It is important to continue to educate our patients; therefore, quarterly visits with a multidisciplinary team with expertise in CFRD is currently recommended.

MR. BUSKER: From the Division of Pediatrics at Washington University School of Medicine, Dr. Andrea Granados, thank you for participating in this eCysticFibrosis Review podcast.

DR. GRANADOS: Thank you, Bob, very much, it was a real pleasure for me to be part of this eCysticFibrosis Review Podcast today.

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