Cystic Fibrosis Related Diabetes Mellitus (CFRD): A common rare disease

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Disclosures
• I have no financial relationships to disclose
• I will discuss off-label use of medications

Objectives
By the end of this presentation I hope you:
• Appreciate that diabetes is very common in people with cystic fibrosis
• Understand how CFRD is unique from Type 1 and Type 2 diabetes mellitus
• Practice CFRD care that is consistent with the official guidelines
Objectives

By the end of this presentation I hope you can:

• Appreciate that diabetes is very common in people with cystic fibrosis
• Discuss the unique aspects of CF related diabetes
• Practice CFRD care that is consistent with official guidelines

Cystic Fibrosis

• CF is the most common severe genetic disease in those of Northern European decent
  • recessive disorder caused by a defect in a single gene
  • A mutation in the anion channel: CFTR
  • This causes thick sticky mucus in the lungs, pancreas, intestines
• CF dramatically increases risk for premature death due to respiratory failure
• Recently, there have been major advances in care and lifespans have improved dramatically

A little history 1938:

Dorothy Andersen’s original paper

• Original description of Cystic Fibrosis
• 3/4 tested had abnormal glucose tolerance
A little more history

- First case report of diabetes in “cystic fibrosis of the pancreas” 1958
- In the 1960s >20 articles published describing abnormalities of glucose metabolism in CF
- However, the first paper to argue that glucose abnormalities were intrinsic to CF was in 1969
  - 42% of their patients (7-28 years of age) had glycemic abnormalities


But-

- CF patients
  - Don’t get DKA
  - Don’t die from complications of diabetes
  - Didn’t typically live long enough to develop complications

- diabetes in CF
  - just meant the patient had “worse CF”

But then people with CF started to survive out of childhood

Re-emergence of CFRD as a clinical concern

- The Cystic Fibrosis Foundation first addressed CFRD in 1990
  - At that time there was little useful data
- First guidelines with evidence based recommendations were published in 1998
  - Included definitions of NGT and AGT for CF patients
- Current guidelines were published in 2010

Why do we care about CFRD?

CFRD is common

- Occurs in 15% of adolescents and 40-50% of adults (increases with age)
  - In patients with "severe" mutations, up to 80% will develop diabetes with time
- In some pediatric endocrine practices 2nd most common type of diabetes seen
- A spectrum of glucose abnormalities includes and even larger percentage of the CF population


N=486, p=0.001 for trend.
Nar et al 2010, unpublished data, credit to William Thomas and Antoinette Moran for the figure
Abnormal glucose is a problem even without CFRD

- Indeterminate glycemia (INDET)
  - 60 minute glucose >160 mg/dl is associated with increased risk of CFRD
  - 60 minute glucose>200 is associated with worsened lung outcomes
- Impaired glucose tolerance (IGT)
  - Increased inflammation
  - Lower BMI SDS
  - Lower FEV1
- Treatment of both states with insulin has slowed lung function decline in small studies


CFRD is deadly

- Diabetes is not just a marker of worsening CF disease
  - Independent predictor of worse lung function
  - Independent predictor of increased mortality

CFRD is unique

CFRD has unique pathophysiology

- It is not an autoimmune disease
- It is not type 1
- CF patients are insulin sensitive
  - They have very significant peripheral insulin sensitivity
  - They can have hepatic-only insulin resistance
  - It is not type 2
- Primary pathology: progressive insulin deficiency
  - Even CF patients who are “normal” have abnormal insulin secretion
    - Patients with CF have reduced insulin secretion during an OGTT even if they have normal exocrine pancreas function
    - However, we don’t yet know the pathophysiologic mechanisms that drive inadequate insulin secretion

**risk factors**

- Genetics
  - Family history of type 2 increases risk 3x
  - Presence of type 2 genes may increase risk
- unique risk factors
  - Age, female sex, CFTR genotype (ΔF508), pancreatic insufficiency, liver disease
  - Females have increased poor glucose tolerance and increased mortality from CFRD
    - Potentially due to increased insulin clearance

1Moran et al J Pediatri 1991
There are Guidelines!

http://care.diabetesjournals.org/content/33/12/2697.full
Or https://www.cff.org/Care/Clinical-Care-Guidelines/Other-CF-Related-Conditions/Cystic-Fibrosis-Related-Diabetes-Clinical-Care-Guidelines/

Screening

• In CF, diabetes is clinically silent
  • Clinical decline begins 4-5 years before the diagnosis of diabetes, and long before the presence of clinical symptoms\(^1\)
• Screening is required

\(^1\)Milla CE et al Am J Resp Crit Care Med 2000

How do we screen?

• Fasting BS?
  • No
  • Elevated fasting blood sugars are a late finding in CF
• HgA1C?
  • No
  • CF patients can have a normal A1C with a very elevated average blood sugar!
• OGTT- is the recommended modality
  • Can vary within patient from test to test
  • “worst” value correlates with long term outcomes, even if subsequent test are “better”
Screening: the guidelines

- All CF patients who do not already have known diabetes are screened
  - OGTT yearly when at baseline health, starting at 10 years of age
    - 1.75 g/kg of oral glucose solution (max 75 g)
    - Blood glucose level at 0 min 120 min
  - Diagnosis of diabetes confirmed by repeat testing or ancillary data/symptoms

What about when they are ill? (respiratory exacerbations commonly require hospitalization)

- CFRD diagnosed during illness predicts
  - Microvascular complications\(^1\)
  - Lung function decline\(^2\)
- The guidelines recommend:
  - Fasting and 2 hour post-prandial blood sugars for the first 48 hours after admission
    - If they reach diabetic range for >48 hours, treat
    - If they remain normal, discontinue testing after 48 hours

Screening: Gaps in our knowledge

- When should we start?
  - CFRD is rare prior to puberty
  - But
    - Children with abnormal OGTT 6-10 years of age have much earlier onset of CFRD (mean 12 years instead of 24-28 yrs)\(^3\)
    - Children <6 years of age have up to 40% rate of abnormality on OGTT\(^4\)
- How hard should we look for pre-diabetic glycemic abnormalities?
- Optimal modality?
  - CGM
  - Alternative OGTT

\(^1\)Ode Pediatr Diabetes 2010, \(^2\)Yi Am J Resp Crit Care Med 2016
**Guidelines: Treatment**

**Guidelines: Treatment options**

- **What has been shown to work in CF?**
  - **Insulin**
    - Reduces mortality, improves lung function, improves BMI\(^1\)
    - Potent anabolic hormone which reverses catabolic state

- **Insulin dosing**
  - Patients with CF tend to be very insulin sensitive
    - ¼-½ of the “usual” dose of a T1DM patient of similar age and weight
    - If they are sick, however, their insulin needs may quadruple

\(^1\)Raffii M et al Am J Clin Nutr 2005

**What insulin regimen?**

- **Unfortunately there is little data comparing regimens**
  - But there is data supporting insulin pumps!

- **Guidelines recommend:**
  - CFRD with fasting hyperglycemia → basal/bolus
    - MDI
    - Insulin pump
  - CFRD without fasting hyperglycemia
    - Meal coverage
    - Lantus?
What the guidelines don’t recommend

- Don’t restrict their carbohydrates
  - Maintenance of BMI is tightly linked to survival in CF
  - Weight loss is associated with increased risk of death
- They are to follow their recommended CF diet
  - Count carbohydrates
  - Take insulin with all meals and all snacks!
- The only restriction:
  - No regular pop!

Treatment- what we don’t know:

- Do we treat IGT? INDET?
  - Emerging evidence that insulin treatment may reduce FEV1 decline
- Can we use something besides insulin?
  - GLP-1 agonists?
  - Pancreatitis?
  - DPP-4 inhibitors?
    - Study is on the way!!
  - Diet?
    - Low glycemic index diet can delay need for insulin
  - Metformin?

Piechowiak K. Dev Peroid Med 2015

Questions?
I have clinical cases/example treatment regimens coming up
A clinical question

• How about a patient who presents in ketosis?

  • We have patients who have type 1 diabetes and CF
  • Both disorders are relatively common in the same ethnic group

• What if they have negative antibodies?
• This is described in the literature
  • I would recommend treating as if they had "honeymoon" stage type 1

Some sample regimens

Sample regimen fasting hyperglycemia

• 15 year old female with fasting hyperglycemia and normal BMI, weight 62 kg.
• managed with insulin pump (insulin aspart) settings of :
  • basal rate 0.5 units/hour.
  • Insulin to carbohydrate ratios:
    • 1 :10 with breakfast,
    • 1 :25 with all snacks and
    • 1 :20 with lunch and supper.
  • Sensitivity 1 :60 mg/dl.

Sample regimen - no fasting hyperglycemia

• 25 year old male without fasting hyperglycemia and normal BMI, weight 75 kg
  • Insulin lispro 1:30 grams with all meals and snacks,
  • correction dose of 0.5 /50 mg/dl his blood sugar is over 150 mg/dl
  • no long acting insulin

Sample regimen - overnight enteral feed

• 18 year old female with known CFRD without fasting hyperglycemia.
  • She is well-controlled on meal boluses of insulin lispro of 1:15 grams of carbohydrate.
  • 8-hour overnight continuous feed contains a total of 150 g of carbohydrate.
    • 10 units of insulin, given as a dose of 7 units of NPH mixed with 3 units of regular.

Sample regimen - daytime bolus feed

• 25 year old male with CFRD without fasting hyperglycemia (already on overnight feeds)
  • His previous carbohydrate ratio is 1:10 grams of carbohydrate
  • bolus feed contains 50 g of carbohydrate.
    • 5 units of insulin aspart prior to bolus feed
    • In addition to previous regimen
      • Aspart at all meals and snacks at 1:10
      • 10.5 units of NPH and 4.5 units of regular insulin prior to the 150 gram 8 hour continuous overnight feed.
Sample regimen – Not guidelines

• 19 year old female with IGT, very poor weight gain, 45 kg would like to avoid G tube placement
  • Fasting blood sugars in 110s
  • 6 units Lantus daily with close blood glucose monitoring

Sample Regimen- Not Guidelines 2

• 14 year old female – ABPA -failed Xolair-
• On twice monthly methylprednisolone
• History of diabetic range blood sugars on prednisone, normal blood sugars in daily life
  • 8 Units of NPH given at time of methylprednisolone infusion

Conclusions

• CFRD is common
• CFRD increases mortality
• Right now insulin is our only well understood treatment
• There is a lot of room to improve our knowledge
Thank You!
Questions?

CFRD Research Team

[Diagram showing the research team members and their affiliations]

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[Names and images of team members]