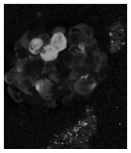
# Cystic Fibrosis Related Diabetes Mellitus (CFRD): A common rare disease



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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:

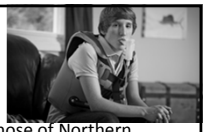
- Appreciate that diabetes is very common in people with cystic fibrosis
- Understand how CFRD is unique from Type 1 and Type 2 diabetes mellitus
- Practice CFRD care that is consistent with the official guidelines

## 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 an 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

ANDERSEN—CYSTIC FIBROSIS OF PANCREAS 357

of fat in the dried weight, of which 69 per cent was fatty acid; Siwe [3k] found 82 per cent and 96 per cent of the total fat as neutral fat on two occasions. The proportion of fatty acid to total fat was therefore within normal range in 3 cases but extremely low in 1. It is of interest that in the first 3 cases the pancreas showed cystic fibrosis, while in Siwe's case [3k] there was complete replacement of the acini with adipose tissue.

The blood sugar value was low in several cases (3 from the literature [8] and cases 37 [XVIII] and 44 [XX] from the Babies Hospital), and spontaneous attacks of hypoglycemia have been described.[9] Dextrose tolerance tests were done in 4 cases. In 2 (Siwe,[3k] case 44 [XX]) there was a rise from a low fasting level to over 200 mg. per hundred cubic centimeters in an hour, with an abrupt drop at two hours. These curves are similar to those described by Harris [19] as characteristic of

## A little more history

- First case report of diabetes in "cystic fibrosis of the pancreas" 1958[1]
- 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[2]
  - 42% of their patients (7-28 years of age) had glycemic abnormalities

[1]Caldwell DM, McNamara DH. Calif Med. 1958 Oct;89(4):280-4.
[2]Handwerger et al. N Eng J Med. 1969 Aug; 281 (9): 451-461

## 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[1]
- Current guidelines were published in 2010

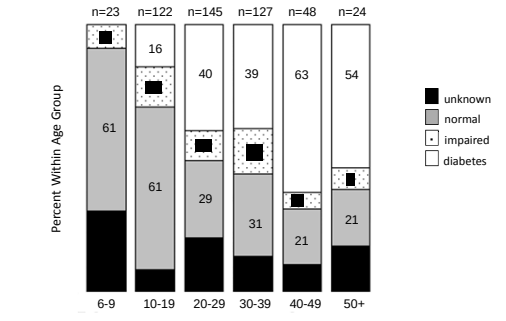
[1]Moran A et al Diabetes Res Clin Pract. 1999 Aug;45(1):61-73.

# Why do we care about CFRD?

## CFRD is common

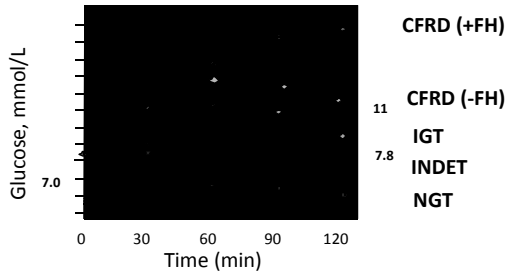
- Occurs in 15% of adolescents and 40-50% of adults (increases with age)[1]
  - In patients with "severe" mutations, up to 80% will develop diabetes with time
- In some pediatric endocrine practices 2nd most common type of diabetes seen
- A spectrum of glucose abnormalities includes and even larger percentage of the CF population[2]

[1]Moran et al Diabetes Care 2009, [2]Moran et al J Pediatr 1998




N=486; p=0.001 for trend,
Ode et al 2010, unpublished data, credit to William Thomas and Antoinette Moran for the figure

Glucose Tolerance Categories in CF



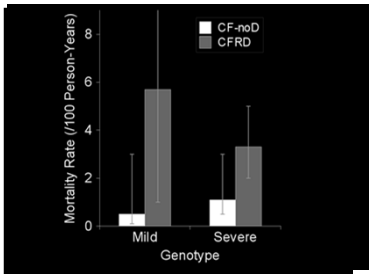

## Abnormal glucose is a problem even without CFRD

- 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[1]
- Impaired glucose tolerance (IGT)
  - Increased inflammation
  - Lower BMI SDS
  - Lower FEV1[2]
- Treatment of both states with insulin has slowed lung function decline in small studies

[1]Sheikh S. Pediatr Pulmonol 2015, [2]Lavie M. Diabetes Research Clin Pract 2015

## CFRD is deadly

- Diabetes is not just a marker of worsening CF disease
  - Independent predictor of worse lung function[1,2,3]
  - Independent predictor of increased mortality[3]




[1]Chamnan P et al Diabetes Care 2010 33:311-316 [2]Milla CE et al Am J Resp Crit Care Med 2000, [3]Lewis C et al. Am J Respir Crit Care Med, 2015

# 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**[1]
    - 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

[1]Moran et al J Pediatri 1991,

## risk factors

- Genetics[1]
  - Family history of type 2 increases risk 3x
  - Presence of type 2 genes may increase risk[1]
- 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[2]

[1]Blackman et al. Diabetologia 2009, [2]Battezzati et al J Clin Endo Metab 2015

# There are Guidelines!

Moran et al. Clinical care guidelines for cystic fibrosis related diabetes: A position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care. 2010 Dec; 33(12): 2697-2708

http://care.diabetesjournals.org/content/33/12/2697.full

Or

https://www.cff.org/Care/Clinical-Care-Guidelines/Other-CF-Related-Conditions-Clinical-Care-Guidelines/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

[1]Schwarzenberg et al Diabetes Care 2007, [2]Milla et al Diabetes Care 2005

## 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)[1]
    - Children <6 years of age have up to 40% rate of abnormality on OGTT[2]
- 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[1]
  - 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.

Self plagiarized from- Ode &Brunzell in: Nutrition and Cystic Fibrosis. Yen and Leonard Ed. Springer 2015

## 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 for 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 methylprenisolone 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