CYSTIC FIBROSIS-RELATED DIABETES

Maria “Sukie” Rayas
PGY-6
Pediatric Endocrinology Fellow

DISCLOSURES

- I disclose the following relationships with commercial companies:
  - Grant and Research Support from: Medtronic

- I do not intend to reference the investigational use of these products in my presentation today.

LEARNING OBJECTIVES

- At the end of the presentation, the participant will be able to:
  - Identify the unique presentation and complications of CFRD
  - Understand the current limitations to screening
  - Understand the management of CFRD

CYSTIC FIBROSIS

- Most common life-threatening autosomal recessive mutation of Caucasians (1:3200)
- Morbidity and mortality mainly a result of pulmonary disease
- Life expectancy 38 years (CFF 2009)
- Caused by CFTR mutations

CFTR MUTATIONS

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Stop signal prevents CFTR from being made</td>
</tr>
<tr>
<td>Class II</td>
<td>CFTR misfolded; unable to reach apical membrane; affects 90%</td>
</tr>
<tr>
<td>Class III</td>
<td>CFTR made correctly and reaches right place, does not function properly</td>
</tr>
<tr>
<td>Class IV</td>
<td>CFTR opening faulty</td>
</tr>
<tr>
<td>Class V</td>
<td>CFTR made in smaller quantities</td>
</tr>
<tr>
<td>Class VI</td>
<td>Increased degradation of CFTR</td>
</tr>
</tbody>
</table>

A normal-functioning CFTR channel moves chloride ions to the outside of the cell while a mutant CFTR channel does not, causing sticky mucus to build up on the outside of the cell.
Cystic Fibrosis-related Diabetes (CFRD)
- Most common comorbidity
- Increase in prevalence due to increasing life expectancy of cystic fibrosis (CF) patients
- 20% of adolescents, 40-50% of adult CF patients
- Most common in patients homozygous for ∆F508 (Class II)
- Average onset of 18-21 years
- Shares features of both Type 1 and Type 2 DM

PATHOPHYSIOLOGY OF CFRD
- CF: Thick secretions → obstruction → inflammation → fibrosis of the exocrine pancreas
- CFRD: Fibrosis of endocrine pancreas → islet cell destruction and β cell loss

PATHOPHYSIOLOGY OF CFRD
- Insulin insufficiency is the primary defect
  - Severe, but not absolute -> delay and blunting of 1st phase insulin secretion
- Oxidative stress from ∆F508 mutation (Class II)
  - Misfolded CFTR protein in the endoplasmic reticulum results in oxidative stress → β cell dysfunction, and apoptosis
- Insulin resistance complicates diabetes during acute illness, stress, and systemic steroid use

SYMPTOMS
- Unexplained weight loss*
- Inability to gain weight despite aggressive nutritional intervention*
- Unexplained decline in pulmonary function*
- Poor growth
- Poor progression of puberty
- Polyuria and polydipsia (33%)*

* 2-4 years prior to diagnosis
COMPLICATIONS OF UNCONTROLLED CFRD

- Microvascular complications—evident 10 years after diagnosis
  - retinopathy (15%)
  - nephropathy (15%)
  - neuropathy (50%)

- Poor nutrition
- Pulmonary function decline
- Increased mortality

COMPLICATIONS OF CFRD

CASE #1

- 13 year old Hispanic female presented to CF clinic for regular well visit
- Patient without CF exacerbation or hospitalization in 2 years
- No recent oral steroids
- Denied weight loss, fatigue, polyuria, nocturia, polydypsia
- Stated recent weight gain
- Father has Type 2 DM

- Height 162 cm (50-75%)
- Weight 69.7 kg (90-95%)
- BMI 26.6 (95%)
- Obese
- No acanthosis nigricans

CASE #1

- FEV 1 105%
- HbA1C 6.3%
- OGTT

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>139</td>
</tr>
<tr>
<td>2 hr</td>
<td>246</td>
</tr>
</tbody>
</table>

- UA: negative for glucose and ketones

Increased sugar levels in airways increase bacterial adhesion and proliferation

Pseudomonas aeruginosa and Staphylococcus aureus cultures in high glucose mediums results in increased bacteria proliferation
SCREENING FOR CFRD
- 2 hr Oral Glucose Tolerance Test (OGTT) is the screening test of choice
- The test should be performed fasting during a period of stable health (i.e., no recent pulmonary exacerbations) using the World Health Organization (WHO) protocol
  - 1.75 g/kg of glucola (maximum 75 grams) given
  - fasting and 2 hr plasma glucose levels obtained
- Annual screening at age 10 years
- HbA1c can be falsely low in CF patients and should not be used as a screening tool

CRITERIA FOR DIAGNOSIS OF CFRD
- Fasting plasma glucose ≥ 126 mg/dl (139)
- 2 hr OGTT plasma glucose ≥ 200 mg/dl (246)
- HbA1c ≥ 6.5% (< 6.5% does not rule out CFRD) (6.3)
- Classic symptoms of diabetes (polyuria, polydipsia) in the presence of random plasma glucose ≥ 200 mg/dl
- Definitions based on the population risk of microvascular disease in non-CF patients

SCREENING FOR CFRD WITH OGTT
- Longitudinal studies demonstrate that diabetes diagnosis by OGTT correlates with CF outcomes of lung function decline, microvascular complications, and risk of early death
- In a multicenter, multinational study, OGTT identified patients who benefited from diabetes therapy

SCREENING IN OUR CF CENTER
- 34/37 (92%) children screened with OGTT in 2011
  - 59% female
  - 41% Hispanic
  - 56% homozygous for F508del mutation
  - 55% with positive family history of T2DM

FAMILY HISTORY OF T2DM AND CFRD
- TCF7L2 gene variations (gene associated with Type 2 DM in general population) evaluated in 998 patients from CF Twin and Sibling family-based study and 802 patients in an independent case-control study
- Results/Conclusion:
  - Family hx of Type 2 DM increased risk of CFRD
  - Variant in TCF7L2 gene was associated with CFRD in the family study and case-control study
  - Variation in TCF7L2 increased risk of CFRD 3-fold, and decreased the mean age of diagnosis by 7 years in the family-based study

CASE #2
- 13 yr old male presented to CF clinic for scheduled routine visit
- Pt had been stable along 75% for BMI for at least 3 years
- Had failure to gain weight with decreasing BMI towards 50% even though he was on high calorie supplements and Periactin
- Moderate obstructive lung disease; average FEV1 65% with no change
CASE #2
- CF center director referred patient to endocrinology due to decreasing BMI and patient’s abnormal OGTT

OGTT

<table>
<thead>
<tr>
<th>Time</th>
<th>Glucose</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>97</td>
<td>10</td>
</tr>
<tr>
<td>30 min</td>
<td>163</td>
<td>51</td>
</tr>
<tr>
<td>1-hr</td>
<td>232</td>
<td>86</td>
</tr>
<tr>
<td>90 min</td>
<td>150</td>
<td>90.6</td>
</tr>
<tr>
<td>2-hr</td>
<td>118</td>
<td>47.9</td>
</tr>
</tbody>
</table>

SCREENING FOR CFRD

<table>
<thead>
<tr>
<th>OGTT Category</th>
<th>Fasting Glucose</th>
<th>1-hr Glucose</th>
<th>2-hour Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Glucose Tolerance (NGT)</td>
<td>&lt;100</td>
<td>&lt;140</td>
<td></td>
</tr>
<tr>
<td>Impaired Fasting Glucose (IFG)</td>
<td>100–125</td>
<td>&lt;140</td>
<td></td>
</tr>
<tr>
<td>Impaired Glucose Tolerance (IGT)</td>
<td>100</td>
<td>140–199</td>
<td></td>
</tr>
<tr>
<td>Indeterminate Glucose Tolerance (INCGT)</td>
<td>100</td>
<td>≥200</td>
<td>&lt;140</td>
</tr>
<tr>
<td>CFRD</td>
<td>&gt;175</td>
<td>&gt;200</td>
<td>&gt;700</td>
</tr>
</tbody>
</table>

Indeterminate category
- NI fasting and 2 hr blood glucose on OGTT
- 1hr glucose ≥ 200 mg/dL
- 20% of CF patients fall into this category
- Retrospective studies have shown high risk for developing CFRD within the next 5 years

CONTINUOUS GLUCOSE MONITORING (CGMS)
- Sensor in the subcutaneous tissue measures the amount of glucose in the interstitial fluid
- A recorder analyzes the data every 10 s and reports an average value every 5 min (288 readings/day)
- The sensor can be worn for 3-7 days

OGTT UNDERESTIMATES EARLY GLUCOSE DERANGEMENTS

- Dobson and associates (2004) Figure 1. Plasma glucose values in cystic fibrosis (CF) subjects and controls during an oral glucose tolerance test (OGTT). *(CF, ▪) control. *P = 0.01, **P = 0.0003, ***P = 0.0001.

CGM FROM TYPE 1 DM
CGM IN TYPE 1 DM
- Improve HbA1c
- Reduce hypoglycemic unawareness
- Decrease hyperglycemia
- Improve euglycemia

CGM IN CF PATIENTS
- CGM has been validated in patients with CF
  - Reliable, reproducible, repeatable
- Several CF studies have shown that CGM detects early glucose derangements during daily living that is not apparent by OGTT screening
  - CGM identified episodes of hyperglycemia ≥ 200mg/dl that OGTT did not
  - CGM ≥ 140mg/dl 4.5% of time associated with declining weight and lung function during preceding 12 months

OUR CF PATIENT CGM DOWNLOAD

OUR QI CF ALGORITHM

CGM OF IMPAIRED GLUCOSE TOLERANCE
CGM OF INDETERMINATE GLUCOSE TOLERANCE

**CGM**
- CGM can be used in patients with indeterminate OGGT results to evaluate glucose fluctuations on a daily basis
- CF patients have high calorie diets often requiring frequent supplements and G-tube feeds
- In select patients, abnormal CGM results in conjunction with unexplained decline in lung function or BMI can make a case for early treatment with insulin

**MANAGEMENT**
- Insulin is the only treatment recommended for CFRD
- Cochrane review in 2008 highlighted lack of RCTs of insulin and oral agents
- Sulfonylureas not currently recommended—2001 European study concluded need for RCT; stimulating an already sick pancreas
- Metformin contraindicated in pts with hypoxia for fear of fatal lactic acidosis; also GI side effects with weight loss
- Glitazones have potential for hepatic toxicity and CF patients already have risk of liver impairment

*CGMS*

- Nathan et al. (2010)
DIFFERENT TYPES OF INSULIN

TREATMENT
- Improvement in lung function and nutritional status has been shown in small case series of patients when treated with glargine (Lantus) insulin
- 6 patients with IGT
- 22 patients with improved BMI Z score, FEV1 and decreased in pulmonary exacerbations after 12 months of treatment
- Rare episodes of hypoglycemia

MANAGEMENT
- Insulin regimen tailored to the patient’s individual lifestyle
- Long-acting insulin (0.125 u/kg/day)
- Short-acting insulin for those with continued high postprandial glucose
- NPH + Regular for those with nighttime G tube feeds

LONG-TERM EFFECTS OF INSULIN
- Reverses weight loss
- Improves PFTs
- Decreases Pulmonary Exacerbations
- Decreases Mortality

NUTRITION MANAGEMENT IN CF
- Calories: 120-150% of normal caloric intake for age and gender to meet BMI goals established by CF Foundation
- Fat: 40% of total energy
- Carbs: 45-50% of total energy
- Protein: 200% of reference nutrient intake
- Salt: Increased requirement - unrestricted intake
NUTRITION MANAGEMENT IN CFRD

- The diagnosis of CFRD should not result in any dietary restrictions, although modifications not affecting caloric intake may be made.

- Substituting simple sugars, such as juice and sodas, for high-calorie supplements containing a healthy mix of fat, protein, and carbohydrates likely reduces the peak in post-prandial blood sugar and provides greater nutritional benefit.

- Carbohydrate counting for all meals and snacks may be necessary to achieve glycemic control.

CASE #3

- 14 yr old male with a history of CFRD diagnosed in 2009 presented to the ER with blurry vision and reading of H1 on home glucometer.

- ROS positive for 10 lb weight loss in past month, fatigue, polyuria, nocturia, and polydipsia, no N/V/abd pain.

- Serum glucose 648, UA neg ketones.

- HbA1C 6.5% 6 month prior.

- This admission HbA1C 14.1%.

- Patient noncompliant with Lantus/ Humalog regimen for 2 months.

- Insulin regimen restarted and adjusted in hospital, HbA1C 10.7% with 10lb weight gain 1 mo later.

FOLLOW UP RECOMMENDATIONS

- Follow up visit every 3 months.

- HbA1c with every visit.

  - Even though falsely low, generally higher in CFRD patients.

  - Elevated levels are associated with increased microvascular complications.

  - Goal <7%.

  - For a given patient, the rise and fall in HbA1c may be a useful indicator of trends in glycemic control.

MICROVASCULAR SCREENING

- Starting at 5 years after diagnosis:

  - Nephropathy: Yearly urine microalbumin/creatinine.

  - Retinopathy: Yearly retinal eye exam.

  - Neuropathy: Yearly foot exam.

SUMMARY

- CFRD can be clinically silent.

- Insidious onset of unexplained weight loss or worsening lung function → increased mortality.

- Annual screening ≥ 10 yrs of age with 2-hr OGTT, recommend obtaining 1 hr value.

- Patient’s with family hx of Type 2 DM should be aggressively screened.

- Insulin is only treatment.

- Follow-up every 3 months in clinic with HbA1C.

- Yearly microvascular screening after 5 years of diagnosis.
FUTURE DIRECTIONS

- CGM in patients in INDET category
- Consider early therapy with long-acting insulin in select patients with abnormal CGM and worsening BMI/ lung function prior to diagnosis of CFRD on OGTT
- Multidisciplinary approach to CFRD management with collaboration between pulmonology and endocrine departments is imperative

ACKNOWLEDGEMENTS

- Jane Lynch, MD
- Dan Hale, MD
- Donna Beth Willey-Courand, MD
- Lisa Matasovsky, NP
- CF team: Ere Olvera, Susie Dorsett, Tamara Brown, Kay Vavrina

REFERENCES

- Hameed S. et al. Early glucose abnormalities in cystic fibrosis are preceded by poor weight gain. Diabetes Care. 2010; 33: 221-226
- Lk N & Li