Endocrine Complications of Cystic Fibrosis

Marisa Desimone MD
SUNY Upstate Medical University
Syracuse, NY
• I have no conflicts of interest to disclose
Learning Objectives

1. Review the most common endocrine complications of cystic fibrosis

2. Understand proper screening for cystic fibrosis related diabetes

3. Review screening for cystic fibrosis related bone disease
Cystic Fibrosis

- Affects 30,000 people in US
  - 70,000 people worldwide
  - 10 million Americans carry a CF gene mutation

www.cff.org
Cystic Fibrosis

- Mutation in CFTR gene
  - Cystic fibrosis transmembrane conductance regulator
  - Chloride ion channel in epithelium
Cystic Fibrosis

- Single gene, autosomal recessive disorder
  - More than 1800 mutations described
  - Grouped into 6 classes

<table>
<thead>
<tr>
<th>Class of mutation</th>
<th>Molecular defect</th>
<th>Functional abnormality</th>
<th>Main mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No synthesis</td>
<td>Protein is not synthesized</td>
<td>Gly542X, Trp128X, Arg553X, 621+1G→T</td>
</tr>
<tr>
<td>II</td>
<td>Block in processing</td>
<td>Folding defect</td>
<td>Phe508del, Asn1303Lys, Ile507del, Arg560Thr</td>
</tr>
<tr>
<td>III</td>
<td>Block in regulation</td>
<td>Channel opening defect</td>
<td>Gly551Asp, Gly178Arg, Gly551Ser, Ser549Asn</td>
</tr>
<tr>
<td>IV</td>
<td>Reduced conductance</td>
<td>Ion transport defect</td>
<td>Arg117His, Arg347Pro, Arg117Cys, Arg334Trp</td>
</tr>
<tr>
<td>V</td>
<td>Reduced synthesis</td>
<td>Decreased protein synthesis</td>
<td>3849+10kbC→T, 2769+5G→A, 3120+1G→A, 5T</td>
</tr>
<tr>
<td>VI</td>
<td>Reduced half-life</td>
<td>Decreased half-life of the protein</td>
<td>4326delTC, Gln1412X, 4279insA</td>
</tr>
</tbody>
</table>
Cystic Fibrosis

• Average life expectancy has risen dramatically since the 1950s
  – Now living to their 40s
Cystic Fibrosis Complications

**Respiratory system**
- Bronchiectasis
- Chronic infections
- Nasal polyps
- Hemoptysis
- Pneumothorax
- Collapsed lung
- Respiratory failure
Systemic complications

- Nutritional deficiencies
- Diabetes
- Osteoporosis
- Blocked bile duct
- Rectal prolapse
- Intussusception
- Liver disease
- Urinary incontinence
- Portal hypertension
- Infertility
- Electrolyte imbalances
- Psychosocial
Cystic Fibrosis Complications

Extrapulmonary Complications by Age

Cystic Fibrosis-Related Diabetes (CFRD)

• Most common comorbidity in CF patients
  – 2% children
  – 20% adolescents
  – 40-50% adults

• Clinically distinct from type 1 and type 2
  – Primarily insulin insufficiency
    • Decreased AND delayed insulin secretion
    • Fatty infiltration and fibrosis of pancreas with loss of alpha and beta cells
  – Fluctuating insulin resistance
    • Varies with health status/medications

• Often Clinically Silent

CFRD

• Risk factors:
  – Older age
  – Pancreatic exocrine insufficiency
  – Delta F508 homozygous genotype
  – Female gender
  – Family history of DM-2
  – Liver disease

• Clinical symptoms:
  – Failure to gain weight / weight loss
  – Poor growth velocity
  – Delayed puberty
  – Unexplained decline in pulmonary function
  – Increased mortality

Moran A et al. Diabetes Care 2009;32:1626-1631
CFRD

- Altered glucose homeostasis in CF
  - Delayed gastric emptying
  - Abnormal intestinal motility
  - Liver disease
  - Increased caloric intake
    - High calorie/salt/fat
    - Pancreatic enzyme replacement increases incretin production

- CFTR expressed in the beta cell
  - Decreased insulin secretion in animal model

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

ANTOINETTE MORAN, MD
CAROL BRUNZELL, RD, LD, CDE
RICHARD C. COHEN, MD
MARCIA KATZ, MD
BRUCE C. MARSHALL, MD
GARY ONADY, MD, PHD

KAREN A. ROBINSON, PHD
KATHRYN A. SABADO, MPH
ARLENE STECENKO, MD
BONNIE SLOVIS, MD
THE CFRD GUIDELINES COMMITTEE

guidelines were used when available and appro
conser
also m
for top
review:
availab

ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Management of cystic fibrosis-related diabetes in children and adolescents

Moran A et al. Diabetes Care 2010; 33(12); 2697-2708.
Moran A et al. Pediatric Diabetes 2014:15;65-76
CFRD Screening

Table 1. Glucose Tolerance Categories in CF in Response to OGTT

<table>
<thead>
<tr>
<th>Category</th>
<th>FPG (mg/dl)</th>
<th>2-h PG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>&lt;126</td>
<td>&lt;140</td>
</tr>
<tr>
<td>IGT</td>
<td>&lt;126</td>
<td>140–199</td>
</tr>
<tr>
<td>CFRD without FH</td>
<td>&lt;126</td>
<td>≥200</td>
</tr>
<tr>
<td>CFRD with FH</td>
<td>≥126</td>
<td>OGTT unnecessary</td>
</tr>
</tbody>
</table>

CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; FH, fasting hyperglycemia; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose.

- Indeterminate glycemia:
  - 1 hour value >200, but 2 hour value normal

CFRD Screening

• HgbA1c:
  – Not sufficiently sensitive for screening
    • Low correlation with glucose tolerance
    • Low positive predictive value
    • Spuriously low due to inflammation causing increased RBC turnover
  – May use to follow glucose control

• Also not used for screening:
  – Fructosamine
  – Urine glucose
  – Random glucose
  – Continuous glucose monitoring
  – Fasting plasma glucose (will miss ½ of CFRD)
  – Self monitoring of glucose with home meters
CFRD Screening

• Annual 2 hour 75-g OGTT:
• Screening test of choice
  – Correlates with clinically important CF outcomes
    • Lung function, microvascular complications, early death
  – Identifies patients who benefit from insulin therapy

• Done fasting, in the morning, during a period of stable baseline health (6 weeks since exacerbation)
• Confirm on different day
• Start at age 10 at the latest
CFRD Screening

- Hyperglycemia during acute illness common
- During acute illness +/- pulse steroid tx
- Patients on continuous enteral feeding
- Pregnancy
- Pre-transplant
CFRD Diagnosis

• Few CF patients with “normal” glucose tolerance
  – Progressive deterioration with age

• Impaired fasting glucose (100-125 mg/dL) and Indeterminate glycemia (1h >200 mg/dL but normal 2h) are common
  – May be pre-diabetic conditions
  – Associated with early onset CFRD in prepubertal CF patients
    • 28% abnormal glucose tolerance age 3-5
    • 33% abnormal glucose tolerance age 6-9
  – Associated with worse pulmonary function

Moran A et al. Pediatric Diabetes 2014:15;65-76
CFRD Diagnosis

• Define CFRD onset as when patient first meets diagnostic criteria, even if hyperglycemia later corrects
  – Long term outcomes related to disease duration
    • Microvascular complications
    • Mortality
CFRD Management

• Medical therapy
  – Insulin only recommended treatment
    • Improved weight, protein anabolism, pulmonary function, survival
  – Some patients only need treatment during acute illness

• Monitoring:
  – SMBG at least 3 times daily
  – CGM has been validated in CF patients

• Glucose goals individualized

• Use HgbA1c for monitoring
CFRD Management

• CF patients are on high calorie diet
  – 120-150% of daily RDA

• CFRD does not alter dietary recommendations
  – Almost never restrict calories
  – Goal to maintain BMI

• Encourage moderate aerobic activity for 150 minutes/week
CFRD Complications

• Hypoglycemia
  – Common even in CF patients without CFRD
    • Malnutrition
    • Increased energy expenditure (inflammation/infection)
    • Postprandial (delayed insulin secretion)
  – Possible decreased responsiveness to glucagon
  – Good catecholamine response and hypoglycemic awareness
  – Counsel on SMBG, glucagon use, risks of alcohol, driving guidelines
CFRD Complications

• DKA rare
  – Should check antibodies for DM1 if this occurs
  – No routine ketone testing
CFRD Complications

• Microvascular complications
  – Have CFRD for 5 years and have fasting hyperglycemia

• Gastroparesis
  – Common in CF patient +/- CFRD
  – Unclear how CFRD may aggravate this

• Atherosclerotic vascular disease not described in CF
  – Hyperlipidemia in post-transplant or in pancreatic sufficient patients
  – Not clear if lipid elevation requires treatment
  – No efficacy/safety data
# Cystic Fibrosis-Related Diabetes

| Screening | • Annually using OGTT  
|           | • Begin by age 10 in patients with cystic fibrosis who do not have CFRD  
|           | • A1C not recommended as screening test |
| Diagnosis | Use usual glucose criteria during period of stable health |
| Treatment | Use insulin to achieve individualized glycemic targets |
| Monitoring for diabetes complications | Annually; start 5 yrs post-CFRD diagnosis |

CFRD = cystic fibrosis-related diabetes; OGTT = oral glucose tolerance test

Managing Cystic Fibrosis-Related Diabetes (CFRD)

An Instruction Guide for Patients and Families

Cystic Fibrosis Foundation
CF Bone disease (CFBD)

• Bone disease is common in CF
  – Decreased BMD and bone quality regardless of steroid use
  – 2010 meta analysis:
    • Osteoporosis 23.5%
    • Osteopenia 38%
    • Vertebral fractures 14%
    • Non-vertebral fractures 20%
  – Increased fracture rates
    • Mechanical stress contributes
  – Kyphosis
    • Angle $\geq$40° in 60% of young adults

• Risk increases with increasing age, disease severity and malnutrition
  – Seen in young children as well
CONSENSUS STATEMENT: Guide to Bone Health and Disease in Cystic Fibrosis


European cystic fibrosis bone mineralisation guidelines

Isabelle Sermet-Gaudelus\textsuperscript{a,∗}, Maria Luisa Bianchi\textsuperscript{b}, Michèle Garabédian\textsuperscript{c}, Robert M. Aris\textsuperscript{d}, Alison Morton\textsuperscript{e}, Dana S. Hardin\textsuperscript{f}, Sarah L. Elkin\textsuperscript{g}, Juliet E. Compston\textsuperscript{h}, Steven P. Conway\textsuperscript{e}, Mireille Castanet\textsuperscript{a}, Susan Wolfe\textsuperscript{i}, Charles S. Haworth\textsuperscript{j,∗}
CFBD

• Pathogenesis multifactorial
  – Decreased osteoblastic and increased osteoclastic activity
    • Even when clinically stable
  – ?mineralization defects

• Pre-transplant and post-transplant bone disease may differ

Aris RM et al. JCEM 2005; 90(3):1888-1896
CFBD

• Inadequate bone acquisition during puberty

• Subsequent BMD loss in young adulthood
  – Rates similar to postmenopausal women

• Malnutrition plays a role
  – BUT Low BMD in pancreatic sufficient CF patients

• Genetic component
  – Role of abnormal CFTR function in bone remodeling

Aris RM et al. JCEM 2005; 90(3):1888-1896
CFBD

• Vitamin D deficiency common
  – Decreased absorption and fat mass
  – Activity of 25-hydroxylase in CF is largely unknown
  – Biliary disease common
    • Possible bile salt inactivation of 25 hydroxylase
  – Increased degradation of 25OHD
    • Known increased oxidant and P450 activity in CF
CFBD

- Diabetes effects on bone in CF unknown
  - Known association with decreased BMD in non-CF patients

- Physical inactivity
  - Reduced lung function
  - Chronic illness

- Delayed puberty

- Early gonadal failure
  - Menstrual dysfunction and low T in adults
  - Unknown if sex steroid replacement is beneficial
CFBD

• Chronic infection
  – Indirect evidence linking cytokines and growth factors to BMD
  – Inverse association with bone health and courses of IV antibiotics

• Tendency of BMD to stabilize after transplant
  – BMD may increase in post-transplant CF patients with good outcomes

• Glucocorticoids
  – Intermittent treatment in 20-50% of CF patients
  – Association with BMD confounded by disease severity
CFBD

• Lung transplant
  – Immunosuppression may exacerbate BMD
  – Fracture rates 37-42% in transplant studies
  – High turnover osteoporosis
  – Rapid decline in BMD 6-12 months post-transplant
  – Studies have few CF patients ➔ can’t extrapolate
Bottom Line:

• Pain
• Debilitation
• Chest wall deformities
• Decreased lung function (lung volume and capacity)
• Inhibited cough
• Decreased airway clearance

• Possible transplant exclusion if very low BMD or prior fragility fracture
CFBD

• DXA for screening
  – T score if postmenopausal or male >50; otherwise Z score
  – Total body if age < 20; L spine and hip if age > 20

• BMD deficit overestimated in patients with short stature
  – Adjust BMD for height if < 20 years and height < 1 SD normal

• Lateral CXR for vertebral fractures
Screening (DXA) and Treatment Protocol

Screen all adults and children > 8 years old if <90% Ideal body weight, FEV1 < 50% predicted, glucocorticoids of ≥ 5 mg/day for ≥ 90 days/yr, delayed puberty, or a history of fractures

Baseline DXA

1. **T/Z score**:
   - T/Z score ≥ -1.0
   - T/Z score > -1.0 > T/Z score > -2.0*
   - T/Z score ≤ -2.0

2. **Nutrition**
   - Vitamin D Supplementation
     - See text (evidence grade III)
   - Calcium Supplementation
     - To achieve 1300-1500 mg (32-37 mmol)/day (evidence grade II)
   - Vitamin K Supplementation
     - 0.3-0.5 mg (1.7-2.9 nmol)/day (2 ADEKS)
     - Target BMI > 25th percentile (both evidence grade II-1)
     - Encourage outdoor weight bearing exercise (evidence grade I)

   - Repeat DXA every 5 years

3. **Pulmonary & Endocrine Topics**
   - Aggressive pulmonary infection treatment (evidence grade III)
   - Minimize steroid dosing (evidence grades I-II)
   - Treat CF Diabetes, delayed puberty or hypogonadism (evidence grades I-II)
   - Endocrine referral
   - If fragility fractures have occurred, patient is awaiting transplant or BMD loss is >3-5%/yr, start bisphosphonate (evidence grades I-III)

   - Repeat DXA 2-4 years

4. **Consider Bisphosphonates**
   - Oral
     - Alendronate 70mg weekly (or 10mg daily) (evidence grade I)
     - Risedronate: 35 mg weekly (or 5 mg daily) (evidence grade III)
   - IV
     - Pamidronate 30 mg in 500 ml saline infused over 3 hrs every 3 months (evidence grade I)
     - Zoledronic acid: 4-5 mg infused over 15-20 minutes yearly (evidence grade III)

   - Annual DXA
# CFBD

<table>
<thead>
<tr>
<th></th>
<th>CF related low BMD</th>
<th>Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children, adolescents, adults &lt;20</strong></td>
<td>Z score &lt; -2</td>
<td>Z score &lt; -2 AND significant low trauma fracture</td>
</tr>
<tr>
<td><strong>Adults &gt; 20</strong></td>
<td>Z score &lt; -2</td>
<td>Z score &lt; -2 AND significant low trauma fracture</td>
</tr>
<tr>
<td><strong>Postmenopausal women, and men &gt; 50</strong></td>
<td>Z score &lt; -2</td>
<td>T score ≤ -2.5 and/or significant low trauma fracture</td>
</tr>
</tbody>
</table>

CFBD

- Standard: Calcium /vitamin D /Weight bearing exercise

- Bisphosphonates
  - Increase BMD; no fracture data

- Teriparatide improved BMD in small case series

- Denosumab not studied in CF

- Treat hypogonadism

- Growth hormone considered in children with severe delay

- CF specific concerns:
  - Malabsorption of oral agents
  - IV agents with severe bone pain and phlebitis
    - Some requiring hospitalization

Conwell LS. Chochrane Database Syst Rev 2014;3:CD002010
Aris RM et al. JCEM 2005; 90(3):1888-1896
Siwamogsatham O et al. Case Rep Endocrinol 2014; 2014 893589
Bisphosphonate treatment in adults

- Low trauma fracture history
- LS or FN or TH Z/T score ≤ −2 and bone loss > 4% per year
- Solid organ transplantation awaited or done and Z/T score ≤ −1.5
- Continuous systemic glucocorticoids > 3 months and Z/T score ≤ −1.5

Bisphosphonate treatment in children and adolescents

- LS or WB Z score ≤ −2 and low trauma vertebral compression fracture or extremity fracture history
- Continuous systemic glucocorticoids > 3 months and low trauma fracture history And/or Z score ≤ −2
- Solid organ transplantation awaited or done and Z score ≤ −2
Vitamin D and CF

• CFF vitamin D update, 2012

  An Update on the Screening, Diagnosis, Management, and Treatment of Vitamin D Deficiency in Individuals with Cystic Fibrosis: Evidence-Based Recommendations from the Cystic Fibrosis Foundation

• Check 25(OH)D levels annually

• No consensus on minimum goal level
  – 20 -30 ng/ml

• \( \text{D}_3 \) (cholecalciferol) may be superior to \( \text{D}_2 \) (ergocalciferol)

Khazai NB et al. JCEM 2009;94:2037-2043
In Summary:

• Annual
  – Screening OGTT starting at age 10
  – 25 (OH) D level
  – Calcium, phosphorus and PTH

• DXA
  – Q 5 years if normal
  – Q2 years if borderline
  – Yearly if low
Thanks!