Cystic Fibrosis Related Diabetes: A Look at the Past and the Road Ahead

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1955

- Average Cost of new house $10,950.00
- Average Monthly Rent $87.00
- Average Yearly Wages $4,130.00
- Minimum Hourly Rate $1.00
- Average Cost of a new car $1,900.00
- Cost of a gallon of Gas 23 cents
- Black and White TV $99.95

Mucoviscidosis

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During the past 15 years mucoviscidosis (pancreatic fibrosis) has become an important entity in pediatrics. Little is known about it. The interest is now shared by the clinician. We shall only attempt to review a growing literature dealing with this disease, which has now drawn on it as it pertains to our discussion concerning clinical and laboratory observations of special interest to us. In medicine, the description of a new entity is often followed by a number of descriptive papers in the nature of case reports. Then by discussions concerning nomenclature, incidence, etiology, pathogenesis, and experimental observations. Mucoviscidosis is so well established today that we seldom see individual case reports except in areas where an interest in this disease is awakening. (1-5). Further, we look forward to monographs such as Bodenner's (4), and May's (5), where an accumulated experience is reported.

K.W., a 37 year old white boy from Kona, Hawaii, was hospitalized June 29, 1953 with a chief complaint of failure to gain weight and height for a year. The story began shortly after birth when his mother noted several abnormalities: (1) voracious appetite, (2) loud, persistent rattle in his throat, (3) mild dry hacking cough, and (4) protuberant abdomen. He never had actual diarrhea, but regularly had four to five large, bulky, greasy, yellow, foul-smelling stools a day. There were no other definite changes in the respiratory or G.I. history until he was 18 months old, when he had the first of a series of severe colds. These occurred three or four times a year until his fourth birthday, lasted approximately a month and were characterized by aggravation of the chronic cough and cyanosis. At age 3 he had a polypsis of the rectum which occurred on each bowel movement and had to be replaced each time up to the time of admission.

From the third year on, growth seemed retarded and he was small and thin. During the last year he made no gain. In the fourth year, polypiasts and polyps developed. Diabetes mellitus was diagnosed, and after several months of difficulties he was regulated on regular insulin three times a day. Dosage varied between 2 and 5 units, depending on urine findings. Because of the multiple complaints and poor development, he was referred to our hospital for evaluation.

Cystic Fibrosis

- 1,700
  - Known mutations of the disease
- 30,000
  - People living with cystic fibrosis in the US
- 70,000
  - People living with cystic fibrosis worldwide
- 1,000
  - New cases of CF each year
- > 18
  - More than half of the CF population is age 18 or older

https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/
### Cystic Fibrosis

- Autosomal recessive
- Mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
- Impacts the way in which salt, bicarbonate and water move in and out of cells
- The results may be recurrent pulmonary infections and malnutrition

### History of CF

- 1936
  - Fanconi first to note bronchiectasis
- 1938
  - Dorothy Andersen in coins the term cystic fibrosis of the pancreas
- 1951
  - Andersen reports on heat prostration in her patients
- 1953
  - Paul di Sant’Agnese determined the cause of the heat prostration leading to the sweat test

### What is CFRD?

- Delayed and blunted insulin release
- Hyperglycemia
- Silent disease

### Why are CF patients insulin insufficient?

- Structural loss of islets due to fibrosis?
  - Lose about 50% of islet mass
- Type 2 diabetes related changes?
- Inefficient insulin secretion due to CFTR abnormalities
**Structural Loss of Islets Due to Fibrosis**

- “Collateral Damage”
- Non selective islet cell destruction
- CFRD islets vs CF vs Control

**Why are CF patients insulin insufficient?**

- Structural loss of islets due to fibrosis?
  - Lose about 50% of islet mass
- Type 2 diabetes related changes?
  - Inefficient insulin secretion due to CFRD abnormalities?

**Type 2 Diabetes and CFRD**

- Mechanisms leading to beta cell failure
  - Oxidative stress
  - Inflammation
  - Endoplasmic reticulum stress
- Genetic susceptibility
- Amyloid deposition

**Oxidative Stress**

- Merriam-Webster Medical Dictionary
  - Physiological stress on the body that is caused by the cumulative damage done by free radicals inadequately neutralized by antioxidants and that is held to be associated with aging
- Disturbance in the balance between the production of reactive oxygen species and antioxidant defenses
  - Chronic exposure of beta cells to elevated glucose and free fatty acids, and islet amyloid polypeptide
  - Islet cell production of reactive oxygen species
- Beta cells less anti-oxidative capacity
Triggers of β cell dysfunction impinge on intercommunicating pathways. β cell dysfunction is depicted as emanating from specific extracellular (glucotoxicity, cytokines and lipotoxicity) and intracellular (IAPP) signals, which then activate an intercommunicating network of pathways (oxidative stress, ER stress and inflammatory stress) leading to β cell dysfunction and demise. The figure is intended to be descriptive of the events observed in models in vitro and in vivo, and is not intended to suggest that those mechanisms depicted are the only mechanisms that occur. FFA, free fatty acid.
T2DM and CFRD

- Susceptibility genes for type 2 diabetes
  - TCF7L2, a susceptibility gene for type 2 diabetes, confers risk for CFRD
  - SLC26A9
    - Two SNPs on chromosome 1 associated with CFRD onset
- Common in patients with CFRD vs CF without DM
- CFRD is associated with similar intrinsic β-cell defects as are associated with type 2 diabetes

Why does CF Pre-diabetes Matter?

- Pre-DM
  - Lower BMI
  - Rapid decline in lung function
  - 4 to 6 years before overt CFRD

Early onset of Glucose Abnormalities

- Changes in insulin secretion start at least by age 6
- Five-year follow-up
  - Odds of developing diabetes were 11 times greater in children with AGT compared to those with NGT
- Ten years after study onset
  - Diabetes developed in 42% of the children with AGT at baseline compared to 3% of the NGT group.
- Average age of onset for those who developed CFRD
  - Girls 11±1 years
  - Boys 12±1 years
  - Minnesota general CF population onset at 23 years

Proposed development mechanism of CFRD

CFRD is the “Tip of the Iceberg”

OGTT Glucose Tolerance Categories

- CFRD FH+
- CFRD FH-
- IGT
- Indeterminate GT
- NGT

Impact of Hyperglycemia in CF

- Malnutrition
  - Loss of glucose and calories in the urine
- Dehydration
  - May thicken pulmonary secretions
- Catabolic state
  - Protein catabolism/loss of lean muscle mass
  - Deficiency in antiproteolytic and antioxidant protection in lung
Impact of Hyperglycemia in CF

- Intermittent Hyperglycemia
  - May promote pulmonary infection
- Increased susceptibility to infection
- Airway glucose concentrations elevated
  - Facilitating growth of respiratory pathogens
  - Creates pro-inflammatory and pro-bacteria environment in airways

Screening for CFRD

- HbA1c is less reliable
  - Decreased RBC lifespan
  - Spuriously low results
  - >6.4% is consistent with DM
- Some have suggested CGM for diagnosis
  - Not well established criteria

Criteria for the diagnosis of CFRD under different conditions.

<table>
<thead>
<tr>
<th>Healthy Individuals</th>
<th>Continuous Glucose Tracker</th>
<th>Skin Biopsy, Systemic Steroids</th>
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Onset of CFRD

- Date a person with CF first meets diagnostic criteria, even if hyperglycemia subsequently abates. (ADA-E; Consensus)
List of All Approved Therapy for CFRD

- Insulin
- Insulin
- Insulin
- Insulin
- Insulin
- Evaluate for stressors/burn out/depression

Treatment

- Insulin therapy
  - Opportunity to deliver glucose to the body’s tissue
  - Improvement
    - Weight
    - BMI
    - Protein anabolism
    - Pulmonary function
    - Survival
  - Promotes improved nutrition and pulmonary function
- Insulin as an opportunity to maximize patient’s health

Treatment guidelines

- Treatment goal of HbA1C <7%
  - Reduce the risk of microvascular complications
- Monitor HbA1C quarterly
- Ongoing DSME
- No diet restrictions

Clinical Spectrum of CF Glucose Tolerance

- Normal
- Abol CGM
- Indeterminate
- IGT
- CFRD FH-
- CFRD FH+

Complications

- Hyper/Hypoglycemia
- Monitor blood pressure
- An annual lipid profile
  - CFRD and pancreatic exocrine sufficiency
  - Obesity
  - Family history of coronary artery disease
  - Immunosuppressive therapy following transplantation
- Microvascular complications
  - Retinopathy
  - Nephropathy
  - Neuropathy
  - Related to duration of diabetes

CFRD Mortality

- Increased mortality rate age related
  - 30 and older
    - Patients with CF with diabetes had significantly higher age-adjusted mortality than those with no diabetes
  - Under age 30
    - Similar mortality rates compared with those without CFRD
- Severe genotypes higher cumulative mortality at every age over 32 than those with mild genotypes
- Mortality rate for patients with CFRD older than 30 years remains higher than that of patients with CF without diabetes
  - 1.8 per 100 person-years.
CFRD Management Goals

- Pulmonary Team
  - Pulmonologist
  - Respiratory therapist
  - Nurse
  - Social worker
  - Dietitian
  - Mental health professional

- Endocrine Team
  - Endocrinologist
  - Diabetes nurse educator
  - Dietitian
  - Mental health professional

- Patient and Family

Challenges in CFRD

- Acceptance of insulin/SBGM
  - CF care is already complicated without diabetes
- Acceptance of diabetes
  - “Just a number” on a meter
- Erratic oral intake
  - Consistent intake makes diabetes management easier
- Insulin sensitivity is a moving target
  - Varies with overall health status/infections
- Invasive nutritional support
  - Less well established paradigm in DM care

Epilogue: The Future – Cystic Fibrosis (2065)

- The first in utero trial of CF corrective stem-cell therapy has just been completed. Sally age 29 was part of the trial. Sally’s partner was found to be a CF carrier at the age of 16 when he underwent whole genome sequencing, introduced in his high school biology programme. Sally was known to be a carrier because she was conceived by in vitro fertilization pregnancy, her father Peter (born 2015) having CF with bilateral absence of the vas deferens. Peter has been on CFTR rescue molecular therapy since 6 years of age, one of over 1000 patients in the adult CF clinic, seen twice per year for surveillance. Molecular free DNA testing reveals the fetus is affected with two CFTR gene mutations. Peter holds his breath, and he has plenty of it (FEV1 88% predicted), waiting for the result of Sally’s first surveillance ultrasound. On Sally’s 20-week fetal ultrasound there is no evidence of ectopic bowel, the pancreatic ducts are normal and vas deferens patent. Bennie is born at 38 weeks gestation and the newborn screening blood spot shows two CFTR mutations. Nasal brushing reveals respiratory epithelium fully replaced by replacement CFTR. Rectal biopsy-derived artificial organ cultured shows normal electrolyte transport. Bennie leaves hospital at 34 of age (delivered by having testing). He will be seen by a molecular physician in the new 67 bed Children’s Hospital (30 ICU beds, 35 acute inpatient beds, 213 hospital-in-the-home “beds”) built on the site of a disused park, where resorts now share the use of an old children’s hospital.

Clinical Summary

- Diabetes is an expected complication of CF
- Insulin insufficiency is found in the majority of CF patients
  - Compromises nutrition by promoting a catabolic state
- Aggressive screening and early insulin therapy
  - Reverse chronic weight loss
  - Improve pulmonary function
  - Reduce mortality in CFRD
- Treatment of patients in their well state
  - Similar to treating T1D in the honeymoon phase
- Treatment during acute illness
  - Increase in insulin resistance
- CF lung function and nutrition come first—-we work around it!

Special Thanks

- Cystic Fibrosis Foundation and the Envision group
- Envision mentor Andi Kelly
- Kara Hughan and Maria “Sukie” Rayas

Questions????