CYSTIC FIBROSIS (CF) COMPLICATIONS BEYOND THE LUNGS

A Resource for the CF Center Care Team

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Overview:

CF complications beyond lung disease continue to emerge as patients age

- Patients require care from CF multidisciplinary teams and their complications change over time[1-3]
- Such complications include[1-3]:

Loss of pancreatic exocrine and endocrine function

CF-related diabetes

CF liver disease

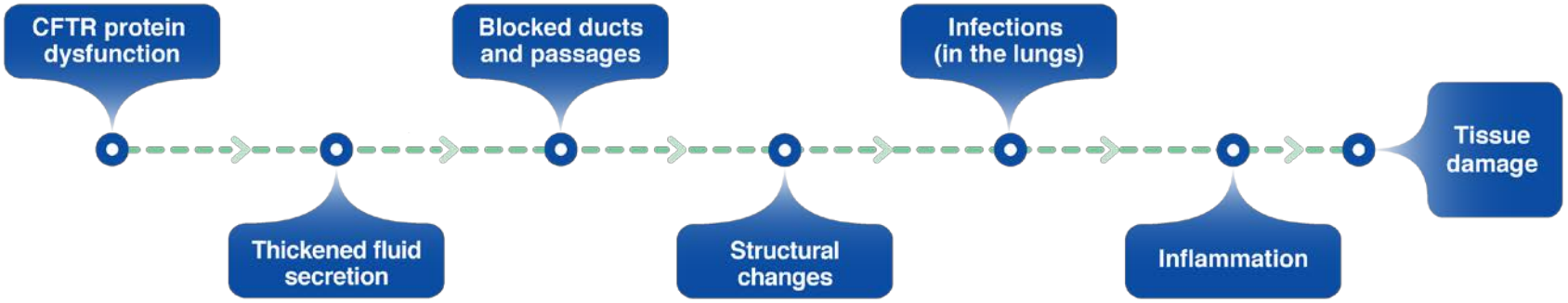
CF-related bone disease

Depression and anxiety

- Monitoring for these complications can help detect their emergence and progression[1-5]
- Other less prevalent complications may also occur such as pancreatitis in 10-15% of pancreatic-sufficient patients[1,2]

References: 1. Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **2.** Ronan NJ et al. *Presse Med*. 2017;46(6 Pt 2):e125-e138. **3.** Kobelska-Dubiel N et al. *Prz Gastroenterol*. 2014;9(3):136-141. **4.** Marquette M, Haworth CS. *Paediatr Respir Rev*. 2016;20:Suppl(2-5). **5.** Quittner AL et al. *Thorax*. 2016;71(1):26-34.

CFTR protein abnormalities begin a cascade leading to structural damage in several organs[1-4]



References: 1. Elborn JS. *Lancet*. 2016;388(10059):2519-2531. **2.** Cantin AM et al. *J Cyst Fibros*. 2015;14(4):419-430. **3.** Sathe MN, Freeman AJ. *Pediatr Clin North Am*. 2016;63(4):679-698. **4.** Kobelska-Dubiel N et al. *Prz Gastroenterol*. 2014;9(3):136-141.

CF affects both the exocrine and endocrine functions of the pancreas

- In the healthy pancreas, CFTR channels regulate chloride and bicarbonate secretion, which, in turn, affects the composition of pancreatic fluids that carry enzymes into the intestine[1]
- In CF, these processes are altered due to CFTR dysfunction[1]

Blocked pancreatic ducts

Exocrine: CFTR dysfunction causes clogged pancreatic ducts. Enzymes to digest food are unable to pass into the intestines, and instead they break down the pancreas itself[1,2]

Endocrine: Islet β cells, which regulate insulin secretion, are largely spared early in life but can be lost over time due to a variety of mechanisms, leading to CF-related diabetes[1,3]

References: 1. Gibson-Corley KN et al. *J Pathol.* 2016;238(2):311-320. **2.** Davis PB. *Am J Respir Crit Care Med.* 2006;173(5):475-482. **3.** Rana M et al. *Nat Rev Endocrinol*. 2010;6(7):371-378.

CF-related diabetes may occur as the pancreas is progressively damaged

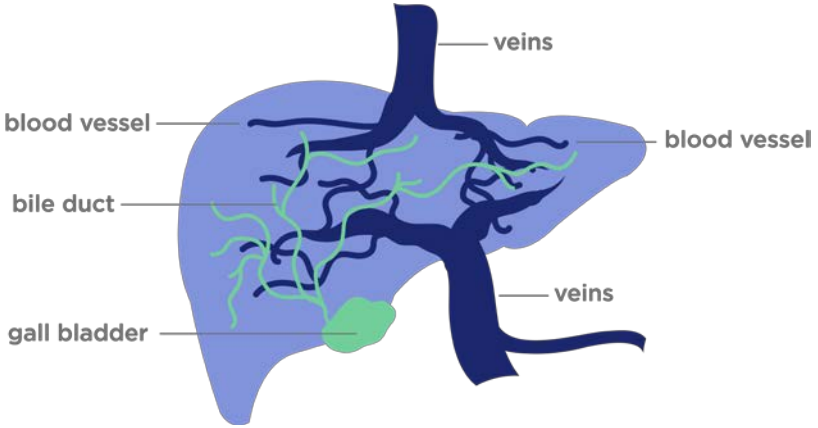
- β-cells in the pancreas regulate insulin production, carbohydrate metabolism, and blood sugar levels[1,2]
- β-cell dysfunction and destruction can occur in CF through a variety of mechanisms, many of which are mediated by CFTR function[1,2]
- The result can be a range of blood sugar problems and, eventually, CF-related diabetes[1]

The prevalence of CF-related diabetes increases with age[3,4]

Patients with CF-related diabetes can experience more rapid declines in lung function compared with those who do not[5,6]

References: 1. Rana M et al. *Nat Rev Endocrinol*. 2010;6(7):371-378. **2.** Kayani K et al. *Front Endocrinol*. 2018;9(20):1-11. **3.** Moran A et al. *Diabetes Care*. 2009;32(9):1626-1631. **4.** Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **5.** Terliesner N et al. *J Pediatr Endocrinol Metab*. 2017;30(8):815-821. **6.** Brennan AL et al. *J Cyst Fibros*. 2004;3(4):209-222.

CF liver disease is associated with scarring, inflammation, and abnormal liver function



- Altered secretions due to CFTR dysfunction can clog small bile ducts, reduce gallbladder size, increase bile viscosity, and increase the risk of gallstones[1]

AGE ≤15 YEARS

- Patients may have abnormal liver function tests[2]
- Patients with CF are at risk for cirrhosis, which is clinically apparent in only 5% of patients and usually presents by age 15[3]

ADULTHOOD

- 3.1% of adults with CF may develop liver cirrhosis[4]

Liver transplants can be necessary beginning in childhood[5,6]

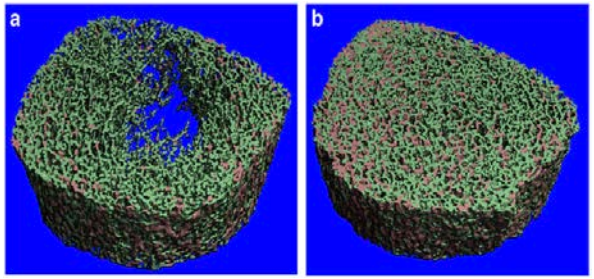
References: 1. Kobelska-Dubiel N. *Prz Gastroenterol*. 2014;9(3):136-141. **2.** Elborn JS. *Lancet*. 2016;388(10059):2519-2531. **3.** O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. **4.** Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **5.** Jonas MM. *Liver Transpl*. 2005;11(12):1463-1465. **6.** Lamireau T et al. *Can J Gastroenterol*. 2006;20(7):475-478.

Low bone mineral density (BMD) increases in prevalence with age

The risk of fractures also increases[1-3]

- 1.5% of patients with CF <18 years and 21% ≥18 years have osteopenia[3]
- 0.6% of patients with CF <18 years and 8.9% ≥18 years have osteoporosis[3]
- Poor nutritional status along with chronic infections and inflammation due to CF disease, among other factors, can affect bone formation and resorption[4]
- Patients with CF may have insufficiencies of essential vitamins (such as vitamin D), as well as calcium malabsorption, which contribute to low BMD[4]
- Delayed puberty and physical inactivity, amongst others, may also contribute towards low BMD[4]
- CFTR dysfunction also affects the process of bone remodeling[5,6]

a. 28-year-old woman with CF[7]



b. Healthy 28-year-old woman[7]

Reprinted from Putman MS. *Osteoporos Int.* 2016;27(8):2497-2505, with permission.

References: 1. Jacquot J et al. *Osteoporos Int*. 2016;27(4):1401-1412. **2.** Nishiyama KK et al. *Bone*. 2018;107:181-187. **3.** Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **4.** Marquette M, Haworth CS. *Paediatr Respir Rev*. 2016;20(Suppl):2-5. **5.** Velard F et al. *Am J Respir Crit Care Med*. 2014;189(6):746-748. **6.** Sermet-Gaudelus I et al. *J Cyst Fibros*. 2011;10(Suppl 2):S16-S23. **7.** Putman MS et al. *Osteoporos Int.* 2016;27(8):2497-2505.

Rates of anxiety and depression are high among adolescents and adults with CF

Prevalence peaks in early adulthood[1]

- In ages <18, the prevalence of depression is 3.3%[1]
- In ages ≥18, the prevalence of depression is 25.3%[1]
- In ages <18, the prevalence of anxiety is 3.2%[1]
- In ages ≥18, the prevalence of anxiety is 17.6%[1]
  - Of patients reporting anxiety or depression, 36% report both
- Depression and anxiety symptoms have been associated with[2]:
  - Decreased lung function
  - Lower BMI
  - Worse adherence
  - Reduced health-related quality of life
  - Increased hospitalizations

References: 1. Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **2.** Quittner AL et al. *Thorax*. 2016;71(1):26-34.

Tests are available to detect and monitor CF-related complications that emerge as a patient ages

Organs	Selected Tests
Pancreas[1-3]	• Nutritional status (e.g., BMI, overall health) • Glucose monitoring (beginning at age 10)
Liver[4-6]	• Liver function blood tests • Physical examination • Ultrasound
Bone[2]	• Bone mineral density scan (every adult with CF should be screened once, subsequent follow-up depends on the baseline scan) • Vitamin D levels
Depression/Anxiety[2,7]	• Annual depression and anxiety screenings (age 12 and older)

References: 1. Rana M et al. *Clin Endocrinol*. 2013;78(1):36-42. **2.** Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **3.** Moran A et al. *Diabetes Care*. 2010;33(12):2697-2708. **4.** Kobelska-Dubiel N et al. *Prz Gastroenterol*. 2014;9(3):136-141. **5.** Debray D et al. *J Cyst Fibros*. 2011;10(Suppl 2):S29-S36. **6.** Sokol RJ, Durie PR. *J Pediatr Gastroenterol Nutr*. 1999;28(Suppl 1):S1-S13. **7.** Quittner AL et al. *Thorax*. 2016;71(1):26-34.

CF complications beyond lung disease emerge as patients age

- Systems and organs affected include:
  - The pancreas (CF-related diabetes, pancreatitis in pancreatic sufficient patients)[1,2]
  - The liver (biliary cirrhosis)[3]
  - The bones (low bone mineral density, risk of fractures)[1,4]
  - The mental health (anxiety, depression)[5]

Patients require care from CF multidisciplinary teams as their complications evolve over time[1-3]

References: 1. Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. **2.** Ronan NJ et al. *Presse Med*. 2017;46(6 Pt 2):e125-e138. **3.** Kobelska-Dubiel N et al. *Prz Gastroenterol*. 2014;9(3):136-141. **4.** Nishiyama KK et al. *Bone*. 2018;107:181-187. **5.** Quittner AL et al. *Thorax*. 2016;71(1):26-34.