

# 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<sup>1-3</sup>
- Such complications include<sup>1-3</sup>:



Loss of pancreatic exocrine and endocrine function



CF-related diabetes



CF liver disease



CF-related bone disease

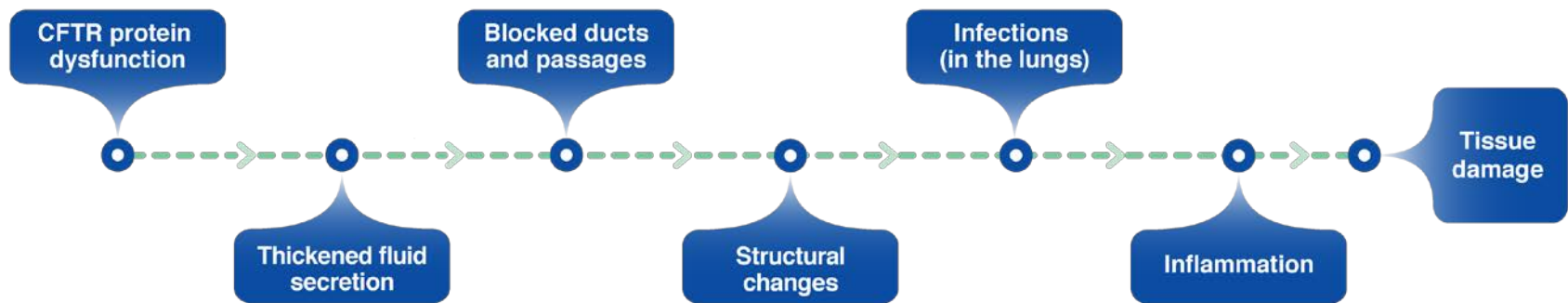


Depression and anxiety

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

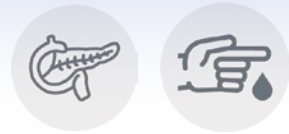
**References:** 1. Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016*. Bethesda, MD. Cystic Fibrosis Foundation; 2017. 2. Ronan NJ et al. *Presse Med*. 2017;46(6 Pt 2):e125-e138. 3. Kobelska-Dubiel N et al. *Prz Gastroenterol*. 2014;9(3):136-141. 4. Marquette M, Haworth CS. *Paediatr 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<sup>1-4</sup>

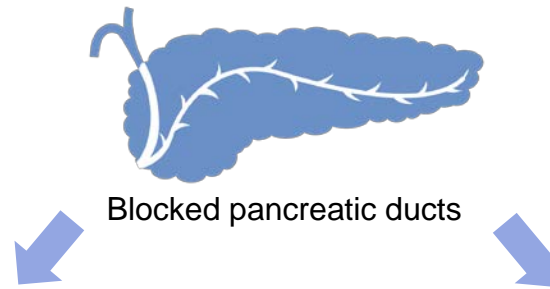


**References:** 1. Elborn JS. *Lancet*. 2016;388(10059):2519-2531. 2. Cantin AM et al. *J Cyst Fibros*. 2015;14(4):419-430. 3. Sathe MN, Freeman AJ. *Pediatr Clin North Am*. 2016;63(4):679-698. 4. Kobelska-Dubiel N et al. *Prz Gastroenterol*. 2014;9(3):136-141.

# 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<sup>1</sup>
- In CF, these processes are altered due to CFTR dysfunction<sup>1</sup>



**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<sup>1,2</sup>

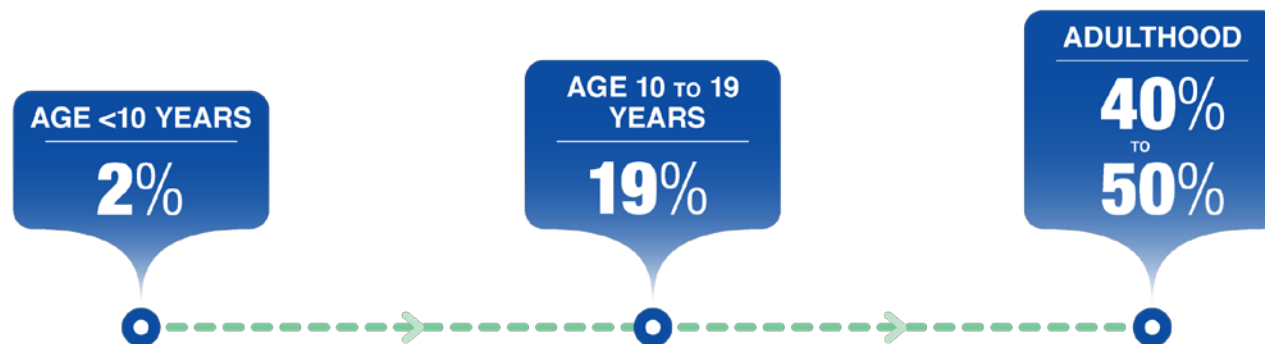
**Endocrine:** Islet  $\beta$  cells, which regulate insulin secretion, are largely spared early in life but can be lost over time due to a variety of mechanisms, leading to CF-related diabetes<sup>1,3</sup>

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



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

*The prevalence of CF-related diabetes increases with age<sup>3,4</sup>*

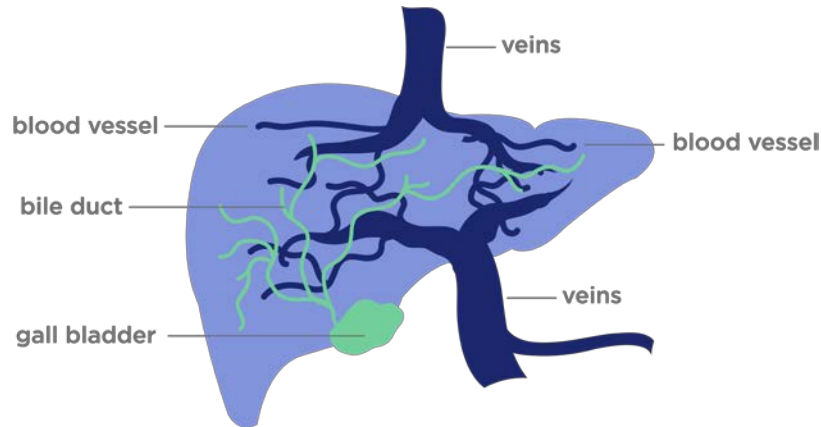


*Patients with CF-related diabetes can experience more rapid declines in lung function compared with those who do not<sup>5,6</sup>*

**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<sup>1</sup>

## AGE $\leq$ 15 YEARS

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

## ADULTHOOD

- 3.1% of adults with CF may develop liver cirrhosis<sup>4</sup>



Liver transplants can be necessary beginning in childhood<sup>5,6</sup>

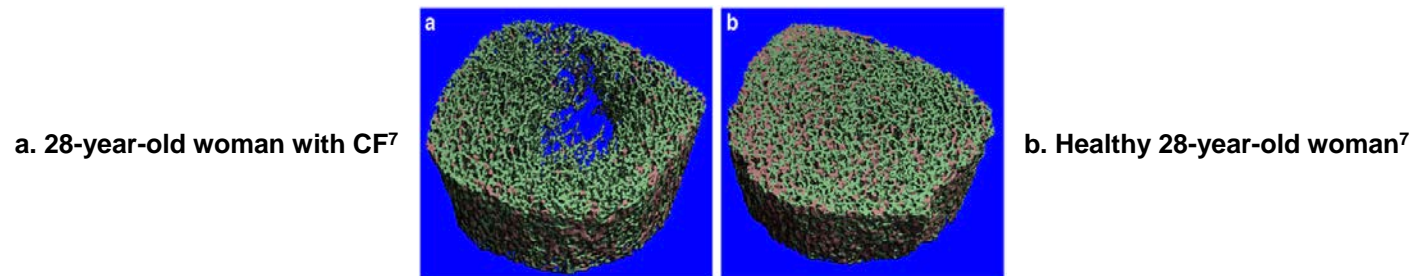
**References:** 1. Kobelska-Dubiel N. *Prz Gastroenterol.* 2014;9(3):136-141. 2. Elborn JS. *Lancet.* 2016;388(10059):2519-2531. 3. O'Sullivan BP, Freedman SD. *Lancet.* 2009;373(9678):1891-1904. 4. Cystic Fibrosis Foundation. *Patient Registry Annual Data Report 2016.* Bethesda, MD. Cystic Fibrosis 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<sup>1-3</sup>

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



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<sup>1</sup>

- In ages <18, the prevalence of depression is 3.3%<sup>1</sup>
- In ages ≥18, the prevalence of depression is 25.3%<sup>1</sup>
- In ages <18, the prevalence of anxiety is 3.2%<sup>1</sup>
- In ages ≥18, the prevalence of anxiety is 17.6%<sup>1</sup>
  - Of patients reporting anxiety or depression, 36% report both
- Depression and anxiety symptoms have been associated with<sup>2</sup>:
  - 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
<b>Pancreas</b> <sup>1-3</sup>	<ul style="list-style-type: none"> <li>• Nutritional status (e.g., BMI, overall health)</li> <li>• Glucose monitoring (beginning at age 10)</li> </ul>
<b>Liver</b> <sup>4-6</sup>	<ul style="list-style-type: none"> <li>• Liver function blood tests</li> <li>• Physical examination</li> <li>• Ultrasound</li> </ul>
<b>Bone</b> <sup>2</sup>	<ul style="list-style-type: none"> <li>• Bone mineral density scan (every adult with CF should be screened once, subsequent follow-up depends on the baseline scan)</li> <li>• Vitamin D levels</li> </ul>
<b>Depression/Anxiety</b> <sup>2,7</sup>	<ul style="list-style-type: none"> <li>• Annual depression and anxiety screenings (age 12 and older)</li> </ul>

**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)<sup>1,2</sup>
  - The liver (biliary cirrhosis)<sup>3</sup>
  - The bones (low bone mineral density, risk of fractures)<sup>1,4</sup>
  - The mental health (anxiety, depression)<sup>5</sup>

*Patients require care from CF multidisciplinary teams as their complications evolve over time<sup>1-3</sup>*

**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.