Endocrine Disorders in Cystic Fibrosis

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KEYWORDS

• Diabetes • Osteoporosis • Short stature • Hypogonadism • Hypoglycemia

KEY POINTS

- Endocrine complications of cystic fibrosis (CF) tend to occur more frequently in older individuals and thus can be expected to become more common as CF medical care improves and the population grows older.
- It is unknown to what degree that these complications may be affected by treatment with CF transmembrane conductance regulator (CFTR) modulator medications.
- It is essential to detect and treat endocrine complications as part of high-quality medical care for people with CF.

INTRODUCTION

CF is caused by defects in the CF transmembrane conductance regulator (*CFTR*) gene, an epithelial chloride channel that is widely expressed. The most common complications of CF are exocrine pancreatic insufficiency (PI) and progressive lung disease, which is the most common cause of death from CF. In addition, people with CF have several important endocrine abnormalities, which are the focus of this review, including diabetes (CF-related diabetes [CFRD]), bone disease, poor linear growth, and hypogonadism.

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THE RELATIONSHIP OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR GENETICS AND COMPLICATIONS OF CYSTIC FIBROSIS

The risks of developing complications of CF depend in part on the level and function of the CFTR protein.[1] Most people (approximately 85%) with CF have 2 mutations resulting in essentially no CFTR function; these individuals almost always develop exocrine PI within the first year of life, and they are at risk of developing all of the endocrine complications of CF, including diabetes and bone disease, as well as the nonendocrine complications, such as lung disease, meconium ileus, and liver disease. The remaining approximately 15% of people with CF have 1 or 2 copies of *CFTR* with partial function, which confer delayed-onset exocrine PI or pancreatic sufficiency (PS). People with *CFTR* mutations in this category can have lower risk of some endocrine and nonendocrine complications (diabetes, meconium ileus, and liver disease) but not others (bone disease) and still develop CF lung disease at a high rate.

CYSTIC FIBROSIS–RELATED DIABETES

Individuals with CF are at high risk of developing a form of diabetes over time, which is called CFRD.[2–4] CFRD is distinct from type 1 diabetes mellitus and type 2 diabetes mellitus but has similarities to both. As is the case for all forms of diabetes, people with CFRD have elevated blood glucose (hyperglycemia). In type 1 diabetes mellitus, hyperglycemia is due to complete or near-complete absence of insulin-producing β-cells in the pancreatic islets. In type 2 diabetes mellitus, hyperglycemia is due to a combination of reduced sensitivity to insulin and insufficient production of insulin. People with CFRD tend to have normal insulin sensitivity but have reduced and abnormal production of insulin. In contrast to type 1A diabetes mellitus, in which insulin production declines rapidly and has an abrupt and symptomatic onset, in CFRD, insulin production declines gradually, and diabetes can be asymptomatic.

The main complications of CFRD are worse lung disease, poorer nutritional status, and increased mortality. In addition, CFRD can cause some of the same complications seen for other forms of diabetes, including retinopathy, nephropathy, and neuropathy.[4] All of the CF-specific complications have been shown to improve with treatment of CFRD. Therefore, detection and appropriate treatment of CFRD are key components of the medical care for persons with CF.

Epidemiology

As of 2014, in the US CF Foundation Patient Registry, the prevalence of CFRD among all living patients was 22%, with few prepubertal children with CFRD, approximately 10% to 15% adolescents, and 30% to 40% adults. These prevalence statistics may, however, under-represent the actual risk of CFRD to most people with CF. The risk of CFRD is approximately 5 times higher in people with *CFTR* genotypes that cause exocrine PI than in those with residual-function mutations that cause PS.[5] The risk of developing CFRD for people with PI *CFTR* genotypes begins to rise in adolescence and reaches greater than 80% by age 40.[6] Individuals with PS *CFTR* genotypes do develop CFRD over time at a rate that is still substantially higher than that of type 2 diabetes mellitus in the general population.[6]

Apart from age and *CFTR* genotype, several other risk factors have been identified. Genes other than *CFTR* (genetic modifiers) strongly influence the risk of CFRD,[7] and the 5 such risk variants identified so far are responsible for approximately 4-fold variation in CFRD risk.[8,9] Two other potent risk factors are a family history of type 2 diabetes mellitus and CF-related liver disease, both varying the risk by approximately 3-fold.[5,8,10]