Endocrine Disorders in Cystic Fibrosis

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Summary

Cystic fibrosis can cause multiple endocrine disorders including diabetes, bone disease, short stature, and male hypogonadism. The etiologies are multifactorial but may be directly related in some cases to CFTR dysfunction. Diabetes is the most common endocrine complication and can be expected to affect in almost all people with pancreatic insufficient CF but varies widely in its age of onset. Early identification and treatment of diabetes improves morbidity and mortality in CF. Short stature during adolescence can be transient if puberty is later than average, but it can also be pathologic. Inhaled and systemic steroids can slow growth and should be used at the minimum effective doses. Bone disease in CF is a frequent cause of fragility fractures and associates with worse lung disease. Bone mineral density and vitamin D levels should be monitored. Hypogonadism has been reported in 25% of men with CF. Endocrine complications can cause morbidity and mortality in CF and need to be appropriately detected and managed as part of the medical care of individuals with CF. These complications tend to occur more frequently in older individuals and may be expected to become more common as the CF population grows older.

Keywords

Diabetes; osteoporosis; short stature; hypogonadism; hypoglycemia

Introduction

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

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The relationship of CFTR genetics and complications of CF

The risks of developing complications of CF depend in part on the level and function of the CFTR protein\(^1\). Most people (~85%) with CF have two mutations resulting in essentially no CFTR function; these individuals almost always develop exocrine pancreatic insufficiency (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 non-endocrine complications such as lung disease, meconium ileus and liver disease. The remaining ~15% of people with CF have one or two copies of CFTR which result in partial function and confers delayed onset exocrine PI, or pancreatic sufficiency (PS). People with CFTR mutations in this category can have lower risk of some endocrine and non-endocrine complications (diabetes, meconium ileus, liver disease) but not others (bone disease) and still develop CF lung disease at a high rate.

CF-related diabetes

Individuals with CF are at high risk of developing a form of diabetes over time which is called CF-related diabetes (CFRD)\(^2\)–\(^4\). CFRD is distinct from type 1 and type 2 diabetes 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, hyperglycemia is due to complete or near-complete absence of insulin-producing \(\beta\)-cells in the pancreatic islets. In type 2 diabetes, 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, 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, neuropathy\(^4\). All of the CF-specific complications have been shown to improve with treatment of CFRD. Therefore, detection and appropriate treatment of CFRD is a key component of the medical care for a person with CF.

Epidemiology

As of 2014, in the U.S. CF Foundation Patient Registry, the prevalence of CFRD among all living patients was 22%, with few prepubertal children with CFRD, about 10–15% of adolescents and 30–40% of adults. However, these prevalence statistics may underrepresent the actual risk of CFRD to most people with CF. The risk of CFRD is about 5× 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 to people with PI CFTR genotypes begins to rise in adolescence and reaches >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 in the general population\(^6\).
Apart from age and CFTR genotype, a number of 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 ~4-fold variation in CFRD risk\(^8\). \(^9\). Two other potent risk factors are a family history of type 2 diabetes and CF-related liver disease, both varying the risk by about 3-fold\(^5\). \(^8\). \(^10\).

**Pathophysiology**

CFRD is characterized by reduced or delayed insulin secretion with generally normal sensitivity to insulin action. In the fasted state, insulin and C-peptide levels tend to be normal. Reduced early-phase insulin release, prolonged hyperglycemia, and reactive hypoglycemia are all seen in both CFRD and in type 2 diabetes\(^4\).

The strong correlation of CFRD with exocrine pancreatic insufficiency suggests that preexisting PI contributes to causing CFRD, initially thought to be primarily by a reduction in endocrine pancreatic mass. In CF with PI, lack of CFTR causes abnormally viscous secretions, plugging of pancreatic ducts, and a chronic pancreatitis-like picture with fatty infiltration and fibrosis of the pancreas\(^2\). \(^4\). Pancreatic islets are relatively spared in autopsy studies, but the number and mass of islets are reduced in all patients with CF regardless of whether CFRD was present\(^11\). Therefore, CFRD did not correlate with islet number or mass. However, CFRD has been reported to correlate with presence in islets of amyloid, a peptide co-secreted with insulin, also deposited in the setting of type 2 diabetes, and which may be detrimental to islet cells\(^11\). This finding suggests that factors intrinsic to the islet or beta cell also contribute to the development of CFRD.

Other studies have demonstrated defects beyond islet cell mass in development of CFRD. Mice with CF do not have pancreatic insufficiency, but are more prone to develop diabetes after a mild beta-cell injury\(^12\), suggesting that the beta cells have an intrinsic defect. In humans, the risk of CFRD is increased to people with a family history of type 2 diabetes, or who have susceptibility gene variants for type 2 diabetes\(^8\). \(^9\), indicating that some of the same glucose metabolic pathways play a role in both CFRD and in type 2 diabetes. Insulin production can be both increased and decreased in CF animal models\(^13\). \(^14\), further supporting qualitative rather than quantitative defects in insulin production. Finally, there are recent reports that CFTR is present in islets and affects insulin secretion\(^15\). \(^16\), which could help explain the qualitative alterations in insulin secretion in CF.

With the development of CFTR modulator medications such as ivacaftor and lumacaftor, the extent to which CFRD is reversible has become a clinically relevant question. So far three small studies have reported improvement of insulin secretion and hyperglycemia after treatment with ivacaftor\(^17\)–\(^19\). Anecdotal reports of hypoglycemia in people treated with CFTR modulators suggest the need for caution and perhaps increased blood glucose monitoring after beginning treatment with a CFTR modulator medication.

**Diagnosis of CFRD**

The U.S. CF Foundation and American Diabetes Association issued guidelines in 2010 which have been endorsed by the Pediatric Endocrine Society and the International Society for Pediatric and Adolescent Diabetes\(^20\). \(^21\). CFRD may be diagnosed in individuals with...
classic symptoms of diabetes (polydipsia, polyuria) with plasma glucose ≥200 mg/dl (7.0 mmol/L). In asymptomatic individuals, CFRD is diagnosed by elevated glucose on an oral glucose tolerance test or after sufficiently abnormal random glucose measurements or sufficiently elevated hemoglobin A1c. Because CFRD impacts the course of CF but may be asymptomatic, the U.S. CF Foundation and the European CF Society guidelines recommend annual screening by 2 hr oral glucose tolerance test starting at age 10 years. Alternative screening and diagnosis strategies using different provocation, identifying high- or low- risk groups, or continuous glucose monitoring are under investigation.

**Treatment of CFRD**

CFRD is a disease of insulin insufficiency, and the only treatment that has been shown to improve outcomes is insulin. A typical insulin regimen used is basal-bolus consisting of once- or twice-daily long-acting insulin injection plus extra short-acting insulin with meal or snacks. Use of basal-only regimen has been shown to be effective in some studies, perhaps in early CFRD. Insulin pumps are effective in CFRD and can simplify the intensive insulin regimen resulting in increased adherence. Tube feedings can be covered by premixed insulin of intermediate duration or with appropriate programming of an insulin pump. Use continuous subcutaneous insulin infusion (CSII, i.e., insulin pump) is an effective option for insulin delivery which can be particularly advantageous if a person with CF is requiring multiple boluses for frequent extra meals; in addition, because of the minimal risk of DKA to people with CFRD, CSII is associated with lower risk in CFRD compared to type 1 diabetes. Continuous glucose sensors have been recommended as a tool to help guide insulin therapy.²¹

There are no general restrictions on quantity of dietary carbohydrates in CFRD, in contrast to the general recommendations for type 2 diabetes. Pure sugar such as sweet sodas are not recommended, but otherwise, the same dietary recommendations for people with CF without CFRD (e.g., high-calorie, high-fat, high-protein diet) stand for those with CFRD. It is recommended to avoid large quantities of simple carbohydrate and to spread the daily intake of complex carbohydrate over all meals.

Insulin secretagogues such as repaglinide may increase insulin secretion in early CFRD. However, studies have failed to demonstrate efficacy of repaglinide in improving BMI or lung function, so this class of oral agents is felt to be inferior to insulin and would be recommended only as adjunct to insulin or in cases where insulin cannot be used. Insulin sensitizing agents such as metformin or thiazolidinediones are not generally recommended for CFRD, because insulin sensitivity is generally normal, and these medications carry associated side effects and risks as well. GLP-1 agonists (e.g. sitagliptin) or DPP4 inhibitors which indirectly increase GLP-1 levels (e.g. exenatide) are under investigation in CFRD but are not currently recommended outside of the context of a research study. Acarbose, which prevents absorption of carbohydrate, is not generally recommended for use in CFRD because carbohydrates + insulin are necessary for adequate nutrition.
Hypoglycemia

People with CF may experience hypoglycemia even in the absence of CFRD or insulin treatment, occurring either postprandially or otherwise. There is no consistent data relating hypoglycemia to later CFRD or to other CF outcomes. It is recommended that CF practitioners become familiar with symptoms of hypoglycemia and alert people with CF to the possibility of hypoglycemia. Individuals with symptoms that might be due to hypoglycemia may benefit from point-of-care (glucometer) testing at the time of symptoms.

Linear growth abnormalities in CF

Reduced linear growth has been reported in a number of studies in CF (reviewed in) with a prevalence of short stature (defined by height Z-score less than −2 standard deviations below the CDC mean) found in approximately 20% of all people with CF in 1993. A clear likely contributor to poor growth is fat and micronutrient malabsorption which may not always be completely treated using pancreatic enzyme replacement therapy. Other factors include chronic inflammation, chronic infection, and treatment with inhaled and systemic glucocorticoid medications. It has been proposed that chronic insufficiency of insulin, which itself is an anabolic hormone, may also contribute to poor linear growth in CF. Growth can appear to be poorer when parents’ heights are below average or puberty is late-normal or delayed in CF. On the other hand, at birth, average length (with or without adjustment for gestational age) and levels of insulin-like growth factor 1 (IGF-1) levels in CF are reduced in humans and animal models, suggesting that intrauterine growth abnormalities may occur before many of the above factors are likely to play a role.

The extent to which abnormalities in the growth hormone (GH)/IGF-1 axis play a role is unclear. Like insulin, GH and IGF-1 have anabolic effects and could theoretically have beneficial effects in people with CF. Many studies have associated IGF-1 levels with reduced nutrition in CF, reduced lean body mass, and one study also finding IGF-1 to predict worse nutrition in 1 year. A possible confounder is that fasting and malnutrition cause both GH resistance and reduced IGF-1 levels (reviewed in). Studies of recombinant human growth hormone (rhGH) in CF have been summarized in two recent meta-analyses and a recent review. In meta-analysis, rhGH was found to increase height by about 0.2–0.6 standard deviations and to increase lean body mass in people with CF with short stature. Also, GH has been reported to increase bone mineral content, increase forced vital capacity and reduce hospitalization rate (see), but outcomes were not consistent across studies, and other key outcomes such as forced expiratory volume in 1 second and rate of pulmonary exacerbation were not affected. More research is needed to determine whether treatment with rhGH might have clinical benefit in some people with CF and growth failure, who do not have GH deficiency.

Recommendations

At each clinic visit, height, weight, and body mass index percentiles should be calculated using WHO (for age <2 yr) and CDC (for age 2–20 yr) growth charts. Assessment of growth should be made considering the context of parental heights and of pubertal stage (as delayed puberty can mimic growth failure. Poor linear growth can manifest either as low absolute
height or as abnormal height trajectory (e.g. low growth velocity causing downward crossing of height percentiles on a growth chart). When growth failure is identified, treatable etiologies should be considered. CF disease treatments should be optimized. Inhaled and systemic glucocorticoid medications should be reduced to the lowest dose necessary to achieve therapeutic goals. Adherence and effectiveness of pancreatic enzyme replacement therapy should be monitored. Screening for CF-related diabetes should be performed. Non-CF-related diagnoses may also be considered, such as thyroid dysfunction, GH deficiency, or celiac or inflammatory bowel disease. Treatment should be directed to the etiology identified.

**Cystic Fibrosis Related Bone Disease**

**Prevalence and pathogenesis**

The causes of cystic fibrosis related bone disease are multi-factorial and include nutritional deficiencies of vitamin D, K and calcium, glucocorticoid use, sex steroid deficiency, an altered growth hormone axis, inflammation and the mutation of the CFTR gene itself\(^\text{37}\). The prevalence of fractures in children and adults with CF have been reported to occur in up to a third of patients\(^\text{38, 39}\). A recent systematic review of adults with CF found a pooled prevalence of low bone mineral density (BMD) (T-score < −1 and > −2.5) of 38% and osteoporosis (T-score < −2.5) of 23.5% by dual-energy X-ray absorptiometry (DEXA)\(^\text{40}\) and of vertebral fractures by lateral spine x-ray of 14% and non-vertebral fractures by self-report of 19.7%. More recent advanced imaging studies with high-resolution peripheral quantitative computed tomography in adults with CF demonstrate compromised cortical and trabecular bone microarchitecture compared to matched non-CF controls\(^\text{41}\). Lower bone strength and quality not only increases the risk of clinical fractures but also has been associated with lower lung function in cross-sectional studies\(^\text{42, 43}\). Furthermore, lower BMD has been associated with recurrent pulmonary exacerbation and mortality in children with CF\(^\text{44, 45}\).

Mutations in the CFTR may directly impair bone formation in rodent models\(^\text{46}\). Primary cultured human osteoblast cells indicate a potential deficit in the production of osteoprotegerin\(^\text{47–49}\). Recent studies in rodent models suggest that correction of the CFTR function may prevent deterioration of bone microarchitecture associated with CF bone disease\(^\text{50}\). CFTR correctors hold promise to improve the bone disease associated with CF; however, no data on humans have been reported\(^\text{51}\).

**Approach to screening and treatment of CFBD**

The European CF Society recommends an initial bone mineral density test by DEXA starting at about 8 to 10 years of age and repeat testing every 1 or 2 years if the Z-score is less than −2 and −1, respectively\(^\text{52}\). In adults, the European CF Society recommends DEXA testing every 5 years if the BMD Z-score is > −1, every 2 years if the Z-score is −1 to −2 and every year if the Z-score is > −2\(^\text{52}\). The Cystic Fibrosis Foundation has similar recommendations with annual BMD testing if the Z-score ≤ −2, every 2–4 years if the Z-score is between −1 and −2, and every 5 years if the Z-score is ≥ −1\(^\text{53}\).
All patients with CF, especially those with CFBD, should have adequate vitamin D status with a serum 25-hydroxyvitamin D (25(OH)D) > 30 ng/mL. All children and adults should take at least 400–800 IU of vitamin D initially with step-wise increases in vitamin D dosing to achieve an 25(OH)D in the optimal range. Typically, most children and adults with CF will require 1,000–2,000 IU of vitamin D or more to maintain optimal vitamin D status. In contrast to vitamin D, intestinal absorption of calcium does not appear to be altered in CF. Children and adults with CF should consume 1,000–1,500 mg of elemental calcium in divided doses, preferably from the diet or supplemented with pills to ensure adequate mineralization of the skeleton. Other nutrients such as vitamin K, magnesium, and phosphorus are also important for optimal skeletal health. Excessive alcohol and vitamin A intake should be avoided which may negatively impact bone.

Adults and adolescents at highest risk for fragility fractures should be considered for pharmacologic therapy for treatment of osteoporosis/CFBD. A Cochrane review of 9 randomized controlled trials conducted in individuals with CF found that oral and intravenous bisphosphonates significantly increase BMD. However, despite the increase in BMD, there was insufficient data to demonstrate a reduction in fractures. Teriparatide, an FDA approved anabolic treatment for severe osteoporosis, has been reported to improve BMD in a case series of adults with CF. Another promising therapy that has not been well studied in CF is denosumab, which is an FDA approved therapy for osteoporosis whose mechanism of action is preventing the action of RANKL on osteoclasts and thus preventing their maturation.

**Male hypogonadism in cystic fibrosis**

In cross-sectional study of young men with CF, approximately 25% had low levels of testosterone. Testosterone levels positively correlate with BMD and its deficiency has been associated with the presence of vertebral fractures documented by spine x-ray. There are no screening guidelines for hypogonadism in adult men with CF. In addition, there are no prospective randomized controlled trials evaluating treatment of hypogonadism in men with CF. Screening for low testosterone should be considered in men with symptoms of hypogonadism and as part of the evaluation of osteoporosis in men with CF. Testosterone measurements should be done in the morning and not during an acute illness. A low testosterone level should be confirmed twice before committing a patient to testosterone therapy. Finally, prior to the initiation of testosterone, the patient should be advised that testosterone therapy will diminish spermatogenesis and adversely impact the patient’s reproductive potential.

**Conclusion**

Endocrine complications of 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 CFTR modulator medications. It is essential to detect and treat endocrine complications as part of high-quality medical care for people with CF.
Reference List


