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Diagnosis and Treatment of Endocrine Co-Morbidities in Patients with Cystic Fibrosis

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Abstract

Purpose of review—The aim of this review is to provide an update on various relevant endocrine aspects of care in adolescents and adults with cystic fibrosis (CF).

Recent findings—As life expectancy in CF has continuously improved, endocrine complications have become more apparent. The common endocrine complications include cystic fibrosis related diabetes (CFRD), cystic fibrosis related bone disease, vitamin D deficiency and poor growth and pubertal development. Thyroid and adrenal disorders have also been reported, although the prevalence appears to be less common.

Summary—Endocrine diseases are an increasingly recognized complication that has a significant impact on the overall health of individuals with CF. This review summarizes the updated screening and management of endocrine diseases in the CF population.

Keywords

cystic fibrosis; cystic fibrosis related diabetes; cystic fibrosis related bone disease; vitamin D; thyroid

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Conflicts of interest

There are no conflicts of interest

Introduction

Cystic fibrosis (CF), caused by mutations in the CF transmembrane conductance regulator (CFTR) protein, is the most common lethal autosomal recessive disease in Caucasians, with a worldwide prevalence of 1 in 2,500 live births [1]. Mutations in the CFTR result in loss of chloride transport in epithelial cells causing the accumulation of thick, viscous secretions that ultimately result in multi-organ dysfunction. Advances in both nutritional and medical care have resulted in an increased life expectancy in patients with CF. The median predicted survival age has risen from 31.3 to 41.1 over the last 10 years [2]. With increasing age, a larger number of patients with CF are developing disease-related co-morbidities, including endocrine diseases such as cystic fibrosis related diabetes (CFRD), cystic fibrosis related bone disease, vitamin D deficiency, short stature, hypogonadism, and hypothyroidism. The purpose of this review is to provide an update on appropriate endocrine care in adolescents and adults with CF.

Cystic Fibrosis Related Diabetes

Pathophysiology

CFRD involves pathophysiological features of both type 1 and type 2 diabetes [3]. CFRD primarily results from insulin deficiency, but insulin resistance also plays a contributory role, and can become acutely severe during infection, pulmonary exacerbation and glucocorticoid usage [3]. Abnormal function of chloride channels leads to accumulation of thick viscous secretions and causes obstructive damage to the exocrine pancreas with progressive fibrosis, fatty infiltration and amyloid deposition in the islets. This results in loss of beta, alpha and pancreatic polypeptide cells [4, 5]. Recently, it has been proposed that a combination of increased oxidative stress and an accumulation of misfolded CFTR proteins in the endoplasmic reticulum (ER) that may lead to ER stress and eventual apoptosis of the beta cell [6].

Genetic factors may also influence the risk of developing CFRD [7]. CFRD mainly occurs in patients with CF who have severe disease, and is also related to the severity of exocrine pancreatic insufficiency [7, 8]. In addition, type 2 diabetes susceptibility genes such as tumor necrosis factor, heat shock protein, calpain 10 and *TCF7L2* have been linked to risk of CFRD [9–11].

The primary defect in CFRD is severe, but not absolute, insulin deficiency [12–14**]. Fasting insulin and C-peptide concentrations may be normal but there is a delay and blunting of peak insulin secretion during a standard OGTT related to loss of the first phase of insulin secretion, which can be found even in CF patients with normal glucose tolerance [12–14**]. The secretion of other islet hormones is also impaired, in particular loss of glucagon responses [12, 13]. Impaired macronutrient utilization has been described in CF patients with glucose intolerance, specifically an impaired ability of insulin to appropriately suppress hepatic glucose production, lipolysis, and proteolysis [15–17].

Prevalence and Risk of Increased Mortality

CFRD is the most common co-morbidity in CF, occurring in 9% of patients between 5–9 years of age, 26% of 10–20 year olds and up to 50% by the age of 30 [8, 18, 19]. The reported prevalence of CFRD varies depending on the monitoring and diagnostic criteria utilized [18, 20, 21]. The presence of CFRD is associated with worsening pulmonary function, poorer growth and nutritional status and lower rate of survival compared to CF patients without diabetes [22–24].

Screening and Recommendations

CFRD is usually clinically silent and patients may remain asymptomatic for years [25, 26]. It is important to identify patients before the onset of symptoms because the presence of CFRD is associated with adverse outcomes. HbA1C should not be considered as a routine screening test for diagnosis of CFRD because levels are often normal at the time of diagnosis of CFRD [27, 28]. However, HbA1C can be used as an effective test to monitor disease progression and adherence to diabetes treatment [29, 30]. The oral glucose tolerance test (OGTT) is the standard test for screening of CFRD and is recommended by the CF Foundation [28, 31, 32]. Annual screening for CFRD should begin by age 10 years using a 2-h 75-g OGTT (1.75 g/kg glucose, maximum 75 g) during a period of stable baseline health [28]. The OGTT should also be performed prior to lung transplantation, pre-pregnancy planning and during pregnancy [28]. Based on the OGTT, patients are classified as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT), CFRD and indeterminate glycemia as shown in Table 1 [33**, 34]. If the OGTT result is normal or borderline abnormal and diabetes is suspected on clinical symptoms, a period of home glucose monitoring (pre- and 2-h postprandial and mid-way through an overnight tube-feeding) or continuous glucose monitoring may provide additional useful information [32, 35]. Furthermore, fasting and 2-h postprandial plasma glucose levels of CF patients with acute pulmonary exacerbation requiring intravenous antibiotics and/or systemic glucocorticoids should be monitored at least in the first 48 hours. A diagnosis of diabetes should be made if the FPG concentration is greater than or equal to 126 mg/dL or postprandial plasma glucose levels are greater than or equal to 200 mg/dL [28, 32, 36].

Treatment Goals and Options

Insulin is the only recommended medical therapy for CFRD [32]. In addition to glycemic control, insulin therapy may also help to stabilize pulmonary function and improve nutritional status in patients with CFRD [26, 32]. Basal-bolus insulin regimens, either by multiple daily subcutaneous injections or by continuous subcutaneous infusion (insulin pump), are recommended in CFRD [28]. Oral hypoglycemic agents such as repaglinide, sulphonylureas, metformin and thiazolidinediones are currently not recommended in CFRD due to limited effectiveness and unacceptable gastrointestinal side effects [32, 37, 38].

Nutritional therapy is important in CFRD. Individuals with CFRD normally require a higher calorie consumption of 120–150% or more of the recommended intakes for the general population [21, 39] to maintain body weight and a goal BMI of 23 kg/m^2 in men (ages >20 yr), 22 kg/m^2 in women (ages >20 yr), and 50th percentile for BMI for adolescents (<20 yr).

yr) [28, 40]. Caloric restriction is generally not recommended. However limiting intake of simple sugars and the use of carbohydrate counting and insulin-carbohydrate ratio can help to optimize glycemic control [28, 32, 33**]. Protein intake in CF is typically recommended to be 1.5 to 2 times the dietary reference intake for the general population [21], and fat should comprise 35–40% of total energy intake [28]. As with all patients with CF, routine supplementation with fat-soluble vitamins is recommended due to fat malabsorption.

The goals of CFRD treatment are to reverse protein catabolism, maintain normal weight and decrease the risk of acute and chronic diabetic complications [34, 41]. Self-monitoring of blood glucose (SMBG) at least 3–5 times a day is recommended in all patients on insulin therapy to safely achieve goals. The plasma glucose goal for patients with CFRD is shown in Table 2 [28]. Although HbA1C levels may be spuriously low in CF and may not provide the actual measure of true glycemic control, the HbA1C trend may be a useful indicator of glycemic control [29, 30]. Thus, quarterly HbA1C measurement is recommended [28, 41].

Chronic Complications

Microvascular complications occur in CFRD, although the prevalence appears to be less than that found in other forms of diabetes [42]. Microalbuminuria and diabetic retinopathy have been reported in 4–21% and 10–23% of patients with CFRD, respectively [42, 43]. Neuropathies, including autonomic neuropathy and gastroparesis, are commonly found and have been reported in up to 50% of CFRD patients [42]. Thus, annual monitoring for microvascular complications of diabetes is recommended, beginning 5 years after the diagnosis of CFRD [28]. Atherosclerotic vascular disease is not typical of CF; however, hypertension has been reported and increases the risk for diabetic nephropathy [43]. Therefore, blood pressure measurement at every routine CFRD visit is recommended [28].

Cystic Fibrosis Related Bone Disease

Pathophysiology

Major contributing factors for CF-related bone disease include vitamin D and vitamin K malabsorption, poor nutritional status, physical inactivity, chronic inflammation, glucocorticoid therapy, delayed puberty and early hypogonadism [44, 45]. Recently there have been several studies demonstrating the direct impact of CFTR on bone mineral density in CF [46–48]. Furthermore, abnormalities in glucose and insulin regulation can also aggravate bone loss in patients with CF [49].

Prevalence of low bone density/osteoporosis and fractures

Osteopenia, osteoporosis and fracture are commonly found in patients with CF, starting at a young age and continue into adulthood. The pooled prevalences of osteoporosis, osteopenia, radiographic vertebral fractures and nonvertebral fractures were 23.5% (95% CI, 16.6–31.0), 38% (95% CI, 28.2–48.3), 14% (95% CI, 7.8–21.7) and 19.7% (95% CI, 6.0–38.8), respectively [50]. The prevalence of CF-related bone disease appears to be associated with severity and progression of CF, severity of lung disease and malnutrition [45, 51].

Screening recommendations

Dual-energy X-ray absorptiometry (DXA) is the gold standard method to measure BMD in CF [52–54**]. All adults at the age of 18 years and children older than 8 years old who have a body weight less than 90% of ideal body weight, FEV1 <50% predicted, high-dose glucocorticoid treatment of longer than 90 days/year, delayed puberty or a history of fractures should have a baseline BMD, using Z-scores for children <18 years old and T-scores for patients aged 18 years or older [53]. If the results are normal (T or Z-score ≥ -1), DXA should be repeated every 5 years. If the results show T or Z-score between -1.0 and -2.0 , DXA should be repeated in 2–4 years. If T or Z-score ≤ -2.0 or documented significant reduction in BMD (defined as $>3\%$ in the lumbar spine or $>5\text{--}6\%$ in the proximal femur), pharmacologic therapy should be considered and DXA should be performed annually [53].

Treatment goals and options

Prevention, early recognition and treatment are the most effective strategies for optimal bone health to maintain the quality of life in individuals with CF [53]. All CF patients should be encouraged to maintain an optimal BMI ($\geq 23 \text{ kg/m}^2$ in men ages >20 yr, $\geq 22 \text{ kg/m}^2$ in women ages >20 yr, and 50th percentile for BMI for adolescents ≥ 20 yr [40]) through adequate calorie and macronutrient consumption. Supplementation of vitamin D, vitamin K and calcium supplementation, as well as participation in an exercise program that incorporates routine weight bearing exercises [52–54**, 55], should also be encouraged. Vitamin D recommendations are described in detail below. To maximize bone health in adults with CF, daily calcium intake should achieve at least the recommended Dietary Reference Intakes of 1,000–1,300 mg [52, 56]. Higher dietary or supplemental calcium intakes of up to 1500 mg have also been recommended in CF [53]. Recommendations for vitamin K supplementation are inconsistent and range from a dose of 0.3–0.5 mg/day [53] to 1–10 mg/day [52]; annual monitoring of bone turnover markers and/or proteins induced by vitamin K absence or antagonism may be useful in guiding individual recommendations in CF [52, 57].

Bisphosphonates are the first line medical treatment in CF patients with osteoporosis [52, 53, 58]. They reduce bone resorption by inhibiting the recruitment and function of osteoclasts, shortening the osteoclast lifespan and slowing osteoblast apoptosis. To date, bisphosphonates, either in the oral form or intravenous form, have been used widely and have shown to be efficacious for treating bone disease in CF [51, 59–62]. Despite the promising effects of bisphosphonates, concerns about the safety and tolerability of this medication still exist [53, 63]. An anabolic agent such as teriparatide, a recombinant human parathyroid hormone analogue, has been approved as an anabolic drug for use in osteoporotic postmenopausal women [64, 65]. This medication has been shown to increase bone mineral density (BMD) and reduce fracture rate by increasing the production of new bone via the anabolic effects on osteoblasts [66]. Randomized controlled trials evaluating teriparatide and bisphosphonate therapy in postmenopausal women with osteoporosis have suggested that both medications are effective in increasing BMD and reducing fracture risk in postmenopausal women [67, 68]. However, there is no data regarding the effectiveness of teriparatide in patients with CF. We demonstrated improvement in bone density with

teriparatide therapy in a small case series of patients at our CF center [69*]. Teriparatide therapy for 2 years followed by bisphosphonate therapy may be an attractive treatment option for patients with CF.

Vitamin D Deficiency

Pathophysiology

The multi-factorial etiology of vitamin D deficiency in CF patients has been described in several studies [53, 70]. Eighty-five to 90% of patients with CF have exocrine pancreatic insufficiency, which is a major contributing factor for malabsorption of ingested dietary or supplemental vitamin D [70, 71]. CF patients may also exhibit impaired hepatic hydroxylation which may decrease circulating concentrations of the major metabolite of vitamin D, 25-hydroxyvitamin D (25(OH)D) [70, 72]. In addition, low vitamin D binding protein (DBP) may affect the dispersal, availability and circulating half-life of vitamin D in CF patients [70, 72].

In addition to the malabsorption and abnormal metabolism of vitamin D, additional hypothesized contributions to vitamin D deficiency in CF include impaired conversion of previtamin D₃ into vitamin D₃ secondary to known phospholipid membrane composition abnormalities, CFTR dysfunction in the epidermis and/or intentional sun exposure avoidance secondary to increased drug-induced photosensitivity [70, 72].

Prevalence of vitamin D deficiency

Despite routine vitamin D supplementation in patients with CF, suboptimal vitamin D status remains common. Surveys of patients with CF reported a prevalence of vitamin D deficiency in 25–90% of the CF population [70, 73, 74]. Even with a near doubling of vitamin D intake by oral supplementation, serum 25-hydroxyvitamin D (25(OH)D) concentrations only increased modestly in our CF center [75*]. This suggests that patients with CF may need even higher doses of vitamin D to overcome fat malabsorption, or there are issues with adherence to a daily supplement [75*].

Screening recommendations

The circulating serum level of total 25(OH)D is the best index of vitamin D nutritional status in both the CF population and the general population [76**]. A serum 25(OH)D level should be checked annually at the end of winter in all patients with CF and rechecked 3 months after the dose of vitamin D has been changed [76**].

Treatment goals and options

The CF Foundation recommends that all individuals with CF should be treated with vitamin D₃ (cholecalciferol), either once daily or its weekly equivalent, to maintain serum 25(OH)D levels of at least 30 ng/mL [76**]. The initial vitamin D₃ dose in infants (birth to 1 year), children (1–10 years) and adults are 400–500 IU/d, 800–1,000 IU/d and 800–2,000 IU/d, respectively [76]. If the serum 25(OH)D concentration is still suboptimal with confirmed

adherence to the prescribed regimen, the dose of vitamin D₃ can be increased to a maximum dose of 2,000 IU/d in infants, 4,000 IU/d in children and 10,000 IU/d in adults [76**].

Growth Failure

Pathophysiology

Malnutrition from malabsorption, inadequate intake and increased calorie requirements, chronic inflammation, dysglycemia and glucocorticoid usage have been clearly shown to contribute to a poor longitudinal growth in patients with CF [77]. However, the impairment in longitudinal growth cannot be explained entirely by these factors. Normal spontaneous and stimulated growth hormone (GH) levels coupled with low insulin-like growth factor 1 (IGF-I) and insulin-like growth factor-binding protein 3 (IGFBP-3) concentrations, indicates potential growth hormone resistance in CF patients [78]. Furthermore, a recent 3-center observational study has demonstrated an increased prevalence of GH deficiency in CF patients [79].

Prevalence of Growth Failure

Growth impairment in CF can be observed in infants from the age of 6 weeks and is more severe during adolescence [77, 80]. According to the US National CF Patient Registry, 14.6% of patients with CF were <5% of percentile for height-for-age according to the Centers for Disease Control and Prevention's (CDC) growth charts [77].

Screening Recommendations

Growth should be monitoring during routine follow-up visit in children and adolescents with CF [81]. Weight and height should be accurately measured at each visit and should be charted to track growth according to age-expected reference values [82].

Treatment goals and options for treatment

The goals are to promote normal growth and nutritional status [77]. Multiple studies have demonstrated significant improvement in weight and height in children with CF treated with recombinant human growth hormone (rhGH) [83–86]. In addition to growth effects, rhGH treatment resulted in increased accrual of bone mineral, decreased hospitalization rates and improved pulmonary function [83–86]. These data suggest that rhGH treatment should be considered as an adjuvant to nutritional therapy for children and adolescents with CF.

Puberty and Fertility

Previous studies reported that children with CF had delayed puberty and attenuated peak height velocity compared to the general population especially in those who had poor nutritional status, abnormal OGTT results and diminished lung function [87–89]. However, a recent study demonstrated that the delay of puberty and attenuation of peak height velocity are less severe than previously described [90]. This may be because of improved nutrient absorption through the use of pancreatic enzymes, increased caloric intake and the introduction of specialized care centers [90].

The mean age of menarche in girls with CF occurs at the age of 14.4 to 14.6 years, which is higher than 12.9 years as reported in healthy adolescents [91, 92]. Menstrual irregularities have been reported in 52% of adolescents with CF [91]. Infertility has been reported in 50% of women with CF and over 98% of men with CF [93]. The cause of infertility in men is classically due to the absence of the vas deferens [94]. Furthermore, up to 1/3 of men with CF have hypogonadism [95].

Females with CF should be queried on pubertal development and strategies should be employed to provide optimal estrogen levels for optimal peak bone mass in early adulthood. Women with CF and infertility should be referred to a reproductive specialist. Males with CF should be counseled on reproductive options and screened for hypogonadism. Males with hypogonadism may be candidates for testosterone therapy; however, long term data regarding testosterone treatment in CF is lacking.

Thyroid disease

Iodide-induced goiter, with or without hypothyroidism, has been reported in the past in patients with CF receiving pulmonary expectorants containing iodides [96]. However, the prevalence of underlying thyroid dysfunction in patients with CF remains controversial with some studies reporting normal thyroid function while others found subclinical hypothyroidism [97–99]. Serum T3 values are often decreased due to the impaired conversion of T4 to T3 secondary to acute and chronic illness often present in patients with CF. A recent study has demonstrated a high prevalence of subclinical hypothyroidism (11.6%) and iodine deficiency (83.7%), which were unrelated to age, malnutrition or pulmonary function [100]. Relatively low iodine dietary intake, reduced iodine absorption due to pancreatic insufficiency and high iodine loss through sweat could explain the high prevalence of iodine deficiency in the CF population [100]. Thus, clinicians should be alert to the potential risk of hypothyroidism, especially in patients who receive iodide-containing expectorant therapy. Furthermore, iodine status evaluated by urine iodide excretion should be considered, and iodine supplementation should be started in individuals with suboptimal iodine status.

Adrenal Function

Increased volume of distribution and increased clearance rate of glucocorticoids due to enhanced biotransformation have been observed in patients with CF [101]. Alterations in glucocorticoids metabolism may modify the clinical response, higher doses may be required to obtain the same results as in non-CF patients. The use of systemic or inhaled corticosteroid in conjunction with azole-derivates or macrolides can lead patients with CF to develop iatrogenic Cushing's syndrome [102, 103]. Azole-derivates and macrolides are inhibitors of CYP3A4 and can inhibit corticosteroid metabolism, leading to increased corticosteroid levels [102, 103]. Prolonged use of these medications has been reported to induce hypothalamic-pituitary-adrenal (HPA) axis suppression due to chronic suppressions of the HPA axis [104, 105]. Moreover, azole-derivates also play a direct role in the development of adrenal suppression by inhibiting cortisol synthesis [102]. The degree of suppression varies from mild symptoms to classic adrenal crisis [105]. Thus, in CF patients

who are chronically treated with the combination of glucocorticoid and azole-derivates or macrolides, adrenal function should be monitored.

Conclusion

Advances in CF care have led to improved survival and quality of life in patients with CF; however, many chronic endocrine diseases have emerged as a result of potential endocrine complications by routine screening and a high index of suspicion is imperative for patients with CF to receive timely treatment. The addition of an endocrine specialist to the CF care team is important to continue to improve health outcomes in CF.

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Key points

- Annual screening for CFRD should begin by the age of 10 years, using 2-h 75-g OGTT (1.75g/kg glucose, maximum 75 g)
- HbA1C is not recommended as a screening test for CFRD. However, the HbA1C trend is a useful indicator of glycemic control
- DXA should be performed in all adults at the age of 18 years and children older than 8 years old who are at risk of low bone density
- Vitamin D status should be evaluated with an annual serum 25(OH)D concentration at the end of winter in all patients with CF
- Nutritional status and growth should be monitored at each routine follow-up visit

Table 1

Oral glucose categories in CF

Category	FPG, mg/dL (mmol/L)	2-h PG, mg/dL (mmol/L)
NGT	<126 (7.0)	<140 (7.8)
Indeterminate *	<126 (7.0)	<140 (7.8)
IGT	<126 (7.0)	140–199 (7.8–11.1)
CFRD without hyperglycemia	<126 (7.0)	200 (11.1)
CFRD with hyperglycemia	126 (7.0)	NA

* Mid-OGTT 200 mg/dL (11.1 mmol/L)

Table adapted from [34]

Table 2

Plasma glucose goals for patients with CFRD

	Fasting and pre-meal, mg/dL (mmol/L)	2–3 h post-prandial, mg/dL (mmol/L)	Bedtime, mg/dL (mmol/L)
Adults	70–130 (3.9–7.2)	<180 (10.0)	90–150 (5.0–8.3)
Adolescents	90–130 (5.0–7.2)	<180 (10.0)	90–150 (5.0–8.3)
School-age children	90–180 (5.0–10.0)	<200 (11.1)	100–180 (5.6–10.0)
Children <6 years	100–180 (5.6–10.0)	<200 (11.1)	110–200 (6.1–11.1)
Pregnant women	95 (5.3)	120 (6.7)	60–99 (3.3–5.5)

Table adapted from [28]