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Cystic fibrosis related liver disease and endocrine considerations

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ABSTRACT

Cystic fibrosis-liver disease (CFLD) is one of the most common non-pulmonary complications in the CF population, is associated with significant morbidity and represents the third leading cause of mortality in those with CF. CFLD encompasses a broad spectrum of hepatobiliary manifestations ranging from mild transaminitis, biliary disease, hepatic steatosis, focal biliary cirrhosis and multilobular biliary cirrhosis. The diagnosis of CFLD and prediction of disease progression remains a clinical challenge. The identification of novel CFLD biomarkers as well as the role of newer imaging techniques such as elastography to allow for early detection and intervention are active areas of research focus. Biliary cirrhosis with portal hypertension represents the most severe spectrum of CFLD, almost exclusively develops in the pediatric population, and is associated with a decline in pulmonary function, poor nutritional status, and greater risk of hospitalization. Furthermore, those with CFLD are at increased risk for vitamin deficiencies and endocrinopathies including CF-related diabetes, CF-related bone disease and hypogonadism, which can have further implications on disease outcomes and management. Effective treatment for CFLD remains limited and current interventions focus on optimization of nutritional status, identification and treatment of comorbid conditions, as well as early detection and management of CFLD specific sequelae such as portal hypertension or variceal bleeding. The extent to which highly effective modulator therapies may prevent the development or modify the progression of CFLD remains an active area of research. In this review, we discuss the challenges with defining and evaluating CFLD and the endocrine considerations and current management of CFLD.

CFLD overview

Definition: Cystic fibrosis related liver disease (CFLD) comprises a broad collection of pathologies including cholelithiasis, cholangitis, hepatic steatosis and cirrhosis. Defining CFLD is complicated by our incomplete understanding of CFLD pathophysiology and absence of a reliable, non-invasive diagnostic test for CFLD. Additionally, diagnostic criteria for CFLD are not uniformly accepted. DeBray (2011) proposed CFLD diagnosis when two of three of the following are present: (1) hepatomegaly or splenomegaly, (2) abnormal serum AST, ALT or GGT for 1 year, (3) abnormal ultrasound [1]. Flass and Narkewicz (2013) proposed a more narrow definition of CFLD defined by the presence of cirrhosis and/or portal hypertension, with other forms of CFLD described as CFLD without cirrhosis and portal hypertension or preclinical [2] (Table 1).

Pathophysiology: As with other causes of cirrhosis, the pathophysiology of CFLD is poorly understood [3]. Classically, absent cystic fibrosis transmembrane conductance regulator (CFTR) in the bile duct epithelium was felt to cause biliary stasis and patchy periportal inflammation and fibrosis, which in some cases progresses to cirrhosis. This theory is consistent with the current understanding that the CFTR is highly expressed in the bile ducts and not expressed in hepatocytes. Recently, alternative theories of CFLD pathogenesis have emerged. The gut-liver-axis theory proposes that intestinal dysbiosis results in

Abbreviations: CFLD, Cystic fibrosis-liver disease; CFTR, cystic fibrosis transmembrane conductance regulator; ULN, upper limit of normal; APRI, aspartate aminotransferase to platelet ratio; Fib-4, Fibrosis-4; UDCA, ursodeoxycholic acid; BMI, body mass index; IGF-1, insulin-like growth factor-1; GH, growth hormone; CFBD, CF bone disease; CFRD, CF related diabetes; FFA, free fatty acids.

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Table 1
Proposed Diagnostic Criteria for CFLD.

European Criteria (DeBray)[1] 2 of the following:	North American Criteria (Flass and Narkewicz) [2]
1) Abnormal physical exam -Hepatomegaly OR -Splenomegaly	1) CF Liver Disease with cirrhosis and/or portal hypertension
2) Abnormal liver serologies -AST, ALT, or GGT elevated above 1x upper limit of normal (ULN) 3 times in one year	2) Liver involvement without cirrhosis and portal hypertension a. Persistent AST, ALT, GGT > 2 times ULN b. Intermittent elevations of the above labs c. Steatosis (histologic determination) d. Fibrosis (histologic determination) e. Cholangiopathy (based on US, MRI, CT, ERCP) f. Ultrasound abnormalities consistent with cirrhosis
3) Abnormal Ultrasound	

1. Debray, D., et al., *Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease.* J Cyst Fibros, 2011. **10 Suppl 2**: p. S29-36.
2. Flass, T. and M.R. Narkewicz, *Cirrhosis and other liver disease in cystic fibrosis.* J Cyst Fibros, 2013. **12**(2): p. 116–24.

increased endotoxin delivery to the liver where altered endothelial immune function leads to bile duct inflammation [4]. Considerable doubt was shed on the classic understanding of CFLD as a biliary disease when multiple explant CF livers demonstrated no cirrhosis on careful histologic examination. Instead, liver histology demonstrated obliterative portal venopathy and nodular regenerative hyperplasia [5,6]. Similar histologic findings were described in 17 liver explants from youth [7]. Because nodular regenerative hyperplasia shares ultrasonographic features with cirrhosis, biopsy and expert pathology examination is needed to distinguish these entities.

Epidemiology: The prevalence of CFLD is highly dependent on the definition used. Asymptomatic elevation in liver serologies are common, with 85% of youth demonstrating persistent (>6 month) elevation in ALT by age 20 years [8]. Despite the frequency of abnormal liver laboratory tests, only 10% of CF patients have clinical evidence of cirrhosis and only 2–3% progress to portal hypertension [9]. CFLD is classically described as a childhood onset disease, with most cases presenting in the first two decades [9–11], although adult onset CFLD is increasingly recognized [12]. Multiple studies demonstrate higher rates of CFLD and more severe disease among males [10,11,13]. Biliary disease in CF (neonatal cholestasis, cholangiopathy, microgallbladder, gallstones, and cholecystitis) is generally not considered a risk factor for progression to cirrhosis [2]. Although hepatic steatosis can progress to cirrhosis in the general population, hepatic steatosis in CF, which is present in 15–30% of CF patients, has not been proven to progress to cirrhosis [14].

CFLD presents primarily in pancreatic insufficient individuals with two copies of a severe CFTR variant, but most such patients will not develop severe liver disease [10]. Genome wide association studies have identified that heterozygosity for the SERPIN1A Z allele, the variant associated with alpha-1-antitrypsin deficiency, confers an odds ratio of ~5x for developing CFLD with portal hypertension [9]. Importantly, this is present in only 9% percent of severe CFLD cases, so it does not explain population heterogeneity in CFLD [9]. Furthermore, a study of 101 sibling pairs with CF demonstrated only 27.8% concordance for the presence of CFLD, suggesting environmental factors play a large role in CFLD pathogenesis [15] (Table 2).

Diagnosis: Diagnosis of CFLD requires evaluation of clinical history, physical exam, laboratory findings, imaging, and sometimes liver biopsy. Hepatomegaly is a classic feature of CFLD and is defined as liver enlargement above age specific normal ranges [1,16]. Elevation of liver enzymes AST, ALT and GGT are often used to screen for CFLD, with

Table 2
Risk Factors for the Development of CFLD.

Male sex
Youth aged
Pancreatic insufficiency
Severe CFTR variant
SERPIN1A Z allele

persistent elevations of >1.5 - >2x the upper limit of normal (ULN) suggesting possible CFLD (Table 1) [1,17]. While elevated liver serologies alone have relatively low specificity for severe CFLD, a low or falling platelet count, low albumin, and prolonged clotting time suggest advanced liver disease [18]. Surrogate markers for CFLD, the aspartate aminotransferase to platelet ratio (APRI) and Fibrosis-4 (Fib-4), can be useful in identifying CFLD. In 67 youth with CFLD confirmed by dual pass biopsy, APRI > 0.264 had a 73% sensitivity and 70.1% specificity for diagnosing CFLD. Fib-4 > 0.358 predicted the presence of portal hypertension with 78% sensitivity and 93% specificity in the same cohort [19].

Ultrasound is often the imaging test of choice in initial evaluation for liver involvement, with a nodular ultrasound suggesting the presence of cirrhosis. The multi-center PUSH study (Prediction by Ultrasound of the Risk of Hepatic Cirrhosis in Cystic Fibrosis) demonstrated that a heterogenous pattern on ultrasound predicts progression to a nodular pattern. A homogenous pattern, felt to represent hepatic steatosis, was not predictive of progression to nodularity [20]. Transient elastography, a non-invasive ultrasound measure of liver stiffness, is increasingly used to monitor progression of CFLD [21] and to improve detection of CFLD in children when combined with APRI [22]. Magnetic resonance elastography provides a 2-D characterization of focal liver changes, though cost and availability limit its use [21]. Liver biopsy is the gold standard for diagnosing CFLD, but is invasive and subject to sampling error given the patchy nature of CFLD [23]. The recent recognition of portal venopathy and nodular regenerative hyperplasia as types of CFLD highlights the need for improved diagnostic modalities for CFLD.

Treatment: Treatment for CFLD is limited to ursodeoxycholic acid (UDCA), a natural bile acid that thins bile to prevent cholestasis. UDCA is believed to reduce peri-portal inflammation and slow progression to cirrhosis, but has shown limited benefit in clinical trials [24]. A retrospective analysis of the French CF Gene Modifier Study found no benefit from early UDCA treatment in preventing progression of CFLD [25]. Furthermore, emerging evidence that severe CFLD often results from portal venopathy rather than biliary dysfunction suggests a limited role for UDCA. Treatment of CFLD with portal hypertension frequently involves variceal banding and eventual liver transplantation, with or without simultaneous lung transplant [25]. Portal hypertension due to portal venopathy is commonly associated with intact synthetic function and may be better treated with shunting procedures. With the pathogenesis of CFLD tied to CFTR dysfunction and as early evidence suggests that CFTR modulator therapy may improve biliary dilatation and hepatic steatosis in CF [26], it is reasonable to anticipate lower incidence and severity of CFLD in modulator-treated individuals [27]. The Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function (PROMISE) (*NCT04038047)* will evaluate the 2-year impact of modulator therapy on liver function and CFLD. Long-term studies are needed to evaluate the effect of modulator therapy on those with preexisting CFLD and the progression and or development of liver disease in those with CF.

Modulator Therapy Dosing and CFLD: It is estimated that ~90% of the CF population are eligible for treatment with elexacaftor/tezacaftor/ivacaftor (Trikafta). Adverse effects of Trikafta therapy include hepatotoxicity with elevated bilirubin and transaminase levels. Prior to commencement of therapy, baseline liver function assessment including AST, ALT, and bilirubin are recommended and serial monitoring of liver function is suggested every 3 months for the first year and then annually

[28]. If liver enzymes become elevated greater than five times the ULN or ALT/AST three times the ULN with bilirubin greater than two times the ULN, dosing should be discontinued. Liver function should be monitored after discontinuation and risks and benefits of resuming with an alternate dosing strategy can be considered after liver function normalizes [28].

Clinical Implications of CFLD: The development of CFLD is associated with higher all-cause mortality compared to those with CF without liver disease and is the third leading cause of death among those with CF [29]. CFLD is associated with decline in lung-function (decreased FEV1), poor nutritional status, low body mass index (BMI), and increased risk of pulmonary exacerbation [30]. In pediatric studies, CFLD is associated with poor linear growth and weight status [31,32]. Effective treatment for CFLD remains limited and current interventions focus on optimization of nutritional status and identification and treatment of comorbid conditions.

CFLD and general endocrine considerations

CFLD is associated with multiple endocrinopathies (Fig. 1), some directly related to liver dysfunction and some a consequence of liver dysfunction. People with severe CFLD are known to have endocrine comorbidities compared with matched people with CF without liver disease [33].

Vitamin D deficiency: A variety of factors affect vitamin D absorption and metabolism contributing to vitamin D deficiency in those with CFLD [34,35]. Malabsorption of vitamin D is common in those with CF due to pancreatic insufficiency and is further exacerbated in those with underlying CFLD due to biliary stasis. Furthermore, patients with severe liver disease have impaired 25-hydroxlyase activity, resulting in impaired vitamin D synthesis. People with CF are known to have increased oxidant and P450 enzyme activity, which leads to increased degradation of 25-hydroxy vitamin D [34]. Severe liver disease also affects hepatic synthetic function and can lead to decreased levels of vitamin-D binding protein and albumin, the major binding proteins of circulating vitamin D, which can result in lower measured total 25-OH vitamin D levels [36]. Dihydroxy vitamin D levels (1,25-OH vitamin D) are normal in liver disease, possibly due to activity of parathyroid hormone which tends to be high normal or high [34].

Vitamin K deficiency: Vitamin K plays a role in the synthesis of coagulation factors. Vitamin K also mediates carboxylation of osteocalcin which has been implicated in CF related bone disease [37]. In addition to vitamin D deficiency, CFLD is associated with vitamin K deficiency due to malabsorption. Severe deficiency may result in signs of coagulopathy including mucosal or subcutaneous bleeding. Vitamin K deficiency is more prevalent in those with CFLD with cirrhosis and is associated with lower levels of vitamin K despite oral supplementation [38]. High dose vitamin K supplementation is recommended for all pediatric and adult patients with CFLD [39,40].

BMI/Nutritional status: Since nutritional status is associated with linear growth, maintenance of BMI, pulmonary function and survival in those with CF [41], optimization of nutrition is a crucial component of CFLD care. Hepatic involvement in CF with steatosis is often associated with malnutrition, deficiency of essential fatty acids, and a lack of carnitine and choline [42]. Nutritional approaches involve optimizing caloric content up to 150% of estimated daily calories with emphasis on a high fat diet [43,44], dietary supplementation of fat-soluble vitamins and medium chain fatty acids, and pancreatic enzyme supplementation [1]. Protein supplementation can be a balancing act because increased protein in severe CFLD patients can precipitate decompensation [45]. During periods of undernutrition, oral calorie supplements in conjunction with a meal or as a snack between meals [46] can prove vital in rehabilitation. However, there is no clear evidence favoring routine supplements for weight gain. The challenges in this aspect of CFLD care includes providing adequate nutrition education and setting targets for calorie intake and monitoring weight, particularly in children [47]. Chronic loss of appetite may improve with transient use of cyproheptadine, but idiosyncratic liver damage associated with cyproheptadine requires it be used cautiously in patients with CFLD [48,49].

Hypogonadism: Hypogonadism is common within the CF population with underlying etiologies being multifactorial. These include chronic inflammation, recurrent infections and high dose glucocorticoid therapy, which can impact the hypothalamic-pituitary axis. Hypogonadism has been reported in up to one quarter of males with CF and oligomenorrhea and secondary amenorrhea in one quarter to one half of women with CF [50,51]. In the general population, liver cirrhosis is associated with an increased risk of hypogonadism in men, with an incidence as high as 90% in those with severe disease [52]. In addition to the mechanisms discussed above, the pathogenesis of hypogonadism in cirrhotic liver disease includes decreased hepatic clearance of estrogens as well as alterations in sex hormone-binding globulin binding, with increased binding of estrogen relative to testosterone [53].

IGF-1/Growth hormone resistance: Cystic fibrosis is associated with low levels of insulin-like growth factor-1 (IGF-1) that is produced in the liver [54]. Severe liver disease and cirrhosis as well as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis are also associated with decreased IGF-1 [55,56]. Circulating IGF-1 levels decrease as liver disease progresses, related to reduced synthetic liver capacity, with normal to elevated growth hormone (GH) levels related to impaired pituitary negative feedback and GH resistance [57]. IGF-1 is the major mediator of the anabolic effects of GH and lack of IGF-1 is thought to contribute to malnutrition as well as low bone mineral density seen in patients with liver disease [58]. There is some evidence that treatment with recombinant GH therapy in those with liver cirrhosis may overcome the GH resistance state as well as improve nitrogen balance [59]. There are no randomized controlled trials for the use of GH therapy specifically in CFLD, but case reports have described possible benefit [60]. Further data is needed to determine if routine use of recombinant GH therapy in CFLD is indicated.

Bone disease/osteoporosis: Osteoporosis is the predominant bone

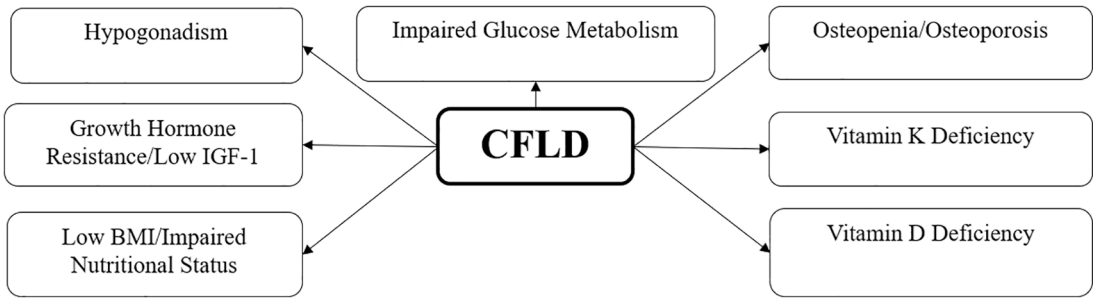

Fig. 1. CFLD and Endocrine Manifestations Fig. 1. CFLD and Endocrine Manifestations: CFLD is associated with increased risk of the development of endocrinopathies including impaired glucose metabolism/CFRD, CF-related bone disease and hypogonadism, growth hormone resistance, impaired nutritional status and vitamin deficiencies.

disorder seen in patients with CFLD. Those with CFLD have a 1.8 fold higher frequency of CF bone disease (CFBD) compared to matched controls with CF [33]. The increased risk of CFBD in those with liver disease is multifactorial and is associated with low BMI, IGF-1 deficiency, hypogonadism, vitamin D and vitamin K deficiencies. Bone disease does not resolve with liver transplantation [61]. The treatment remains correction of the hormonal deficiency (hypogonadism, GH), nutritional rehabilitation and vitamin D, vitamin K and calcium supplementation as indicated. Pharmacologic therapy with bisphosphonates, RANK ligand inhibitor and anabolic bone agents is recommended based on the patient's age.

Liver disease and glucose metabolism

The liver plays a central role in glucose metabolism and homeostasis through several dynamic processes including glucose storage in the form of glycogen and glucose release via glycogen breakdown (glycogenolysis), and glucose synthesis (gluconeogenesis). The occurrence of both impaired glucose tolerance and diabetes is more common in individuals with CFLD with cirrhosis. CFLD is also an independent risk factor for the development of CF related diabetes (CFRD) in people with CF [25,62–64].

CFLD is a cause of hepatogenic diabetes, which refers to impaired glucose metabolism in patients with underlying cirrhosis and liver disease, where decreased insulin sensitivity and increased insulin resistance have been described [65]. The pathogenesis of CFRD is multifactorial and thought to be primarily due to progressive beta cell fibrosis and destruction resulting in a relative insulin deficiency [66]. Insulin resistance secondary to chronic inflammation, infection, and glucocorticoid usage may contribute to CFRD progression. In those with CFLD, there may be additional mechanisms by which glucose metabolism is altered resulting in hyperglycemia and increased risk of CFRD (Fig. 2).

Insulin resistance: With liver disease, altered insulin metabolism is secondary to a combination of portosystemic shunting and decreased hepatocyte mass, which can lead to decreased hepatic first-pass metabolism [67]. Liver disease can result in several perturbations in hormone secretion including elevated levels of the counter regulatory hormone glucagon as well as GH resistance [68,69]. Furthermore, insulin resistance is associated with elevated levels of free fatty acids which can cause peripheral insulin resistance by inhibiting insulin-stimulated glucose uptake and glycogen synthesis, further contributing to impaired glucose utilization [70].

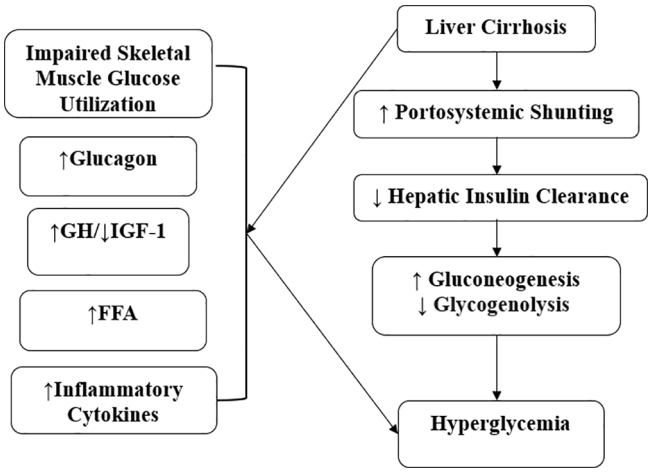

Fig. 2. Mechanisms of Impaired Glucose Metabolism in Liver Disease Fig. 2: Mechanisms of impaired glucose metabolism seen in liver disease. As described in the text, liver disease results in portosystemic shunting and decreased hepatic insulin clearance leading to an insulin resistant state. Impaired peripheral glucose uptake and metabolism, elevated glucagon, growth hormone (GH) resistance and elevated free fatty acids (FFA) and inflammatory cytokines in liver disease further contribute to increased hepatic glucose production and decreased glycogenolysis leading to hyperglycemia.

GH/IGF-1: In chronic liver disease, GH resistance can be seen with alteration in the GH-IGF-1 axis. IGF-1 is produced by the liver in response to GH. In the setting of cirrhosis and progressive hepatocyte dysfunction, there is impaired IGF-1 secretion leading to elevated levels of circulating GH. GH signaling in the liver is reduced in patients with liver disease and is associated with decreased hepatic insulin sensitivity [71]. Additionally, impaired hepatic FFA metabolism in liver disease resulting from a combination of impaired GH action as well as increased oxidative stress and lipotoxicity promotes further hepatocellular injury [72]. FFA can in turn increase hepatic glucose production and decrease peripheral glucose metabolism [73].

Inflammatory cytokines: Liver disease is associated with elevated levels of circulating inflammatory cytokines including IL-6, IL-1 and TNF-α. Pro-inflammatory cytokines can also lead to altered glucose metabolism through impaired insulin signaling, increased lipolysis and decreased lipogenesis and glucose oxidation [74,75].

CFLD and CFRD: Overall, a combination of the above factors may explain impaired glucose metabolism in the setting of liver disease. Although the association between the increase of CFRD in those with CFLD has been described, there has been little research into the exact mechanisms involved. Reduced insulin sensitivity along with impaired insulin secretion have recently been described in patients with CFLD with portal hypertension and suggest that this mechanism may help explain their increased risk of CFRD [76]. CFRD with CFLD is also independently associated with poor clinical outcomes including a decline in pulmonary function, increased risk of hospitalization, impaired nutritional status and increased risk of mortality [32,77]. Currently, CF guidelines suggest screening for CFRD starting at age 10 years. The development of CFLD is most common in the pediatric age range and given the association of CFLD with CFRD (with poor clinical outcomes), some have suggested earlier screening for CFRD in setting of known CFLD.

Transplantation and CFLD: Liver transplantation may be required for decompensated liver failure. In general, referral for consideration of liver transplantation is indicated for patients with CFLD and cirrhosis with hyperammonemia, encephalopathy, coagulopathy, significant ascites, or uncontrolled variceal bleeding. Transplantation is associated with improved survival, lung-function, as well as nutritional status in those with CFLD [78,79]. In those with CF undergoing lung transplantation, 33% had pre-existing CFRD compared to 57% of patients undergoing combined lung-liver transplant [80]. Additionally, approximately one quarter of patients develop CFRD post-liver transplantation, mainly due to immunosuppressive therapy with high dose glucocorticoid and calcineurin+ mTOR inhibitors [80]. Since most people with CF are pancreatic insufficient and there is a high co-occurrence of CFRD, pancreatic transplantation can be considered in conjunction with another solid organ transplant that requires chronic immunosuppression (liver + pancreas or lung + pancreas). Pancreatic transplant can reverse both exocrine and endocrine pancreatic dysfunction thereby treating pancreatic insufficiency and potentially reversing diabetes. Despite the high prevalence of CFRD with CFLD, combined liver and pancreatic transplants are infrequently performed in those with CF. Several case series and reports examined short-term outcomes following pancreatic transplant in those with CF and reported high rates of reversal of exocrine and endocrine pancreatic function post-transplantation [81–83]. Limiting factors of combined liver and pancreatic transplantation may include the increased surgical complexity of combined transplantation, surgeon experience level by center, as well as potential increased risk for complications [84].

Conclusion and future directions

Diagnosis of CFLD and prediction of disease progression remains a

clinical challenge. Identification of novel CFLD biomarkers as well as the role of newer imaging techniques to predict progression are needed. The development of effective treatments for CFLD remains limited and current interventions focus on optimization of nutritional status and identification and treatment of comorbid conditions. Understanding the extent to which highly effective modulator therapies may prevent the development or modify the progression of CFLD and associated endocrinopathies remains an active area of research.

CRediT authorship contribution statement

Jordan S. Sherwood: Conceptualization, Writing – original draft, Writing – review & editing. **Jagdeesh Ullal:** Conceptualization, Writing – review & editing. **Katherine Kutney:** Conceptualization, Writing – review & editing. **Kara S. Hughan:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

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