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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk factors for hepatic steatosis in adults with cystic fibrosis: Similarities to non-alcoholic fatty liver disease

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Abstract

AIM

To investigate the clinical, biochemical and imaging characteristics of adult cystic fibrosis (CF) patients with hepatic steatosis as compared to normal CF controls.

METHODS

We performed a retrospective review of adult CF patients in an academic outpatient setting during 2016. Baseline characteristics, genetic mutation analysis as well as laboratory values were collected. Abdominal imaging (ultrasound, computed tomography, magnetic resonance) was used to determine presence of hepatic steatosis. We compare patients with hepatic steatosis to normal controls.

RESULTS
Data was collected on 114 patients meeting inclusion criteria. Seventeen patients (14.9%) were found to have hepatic steatosis on imaging. Being overweight (BMI > 25) (P = 0.019) and having a higher ppFEV1 (75 *vs* 53, P = 0.037) were significantly associated with hepatic steatosis. Patients with hepatic steatosis had a significantly higher median alanine aminotransferase level (27 *vs* 19, P = 0.048). None of the hepatic steatosis patients had frank CF liver disease, cirrhosis or portal hypertension. We found no significant association with pancreatic insufficiency or CF related diabetes.

CONCLUSION
Hepatic steatosis appears to be a clinically and phenotypically distinct entity from CF liver disease. The lack of association with malnourishment and the significant association with higher BMI and higher ppFEV1 demonstrate similarities with non-alcoholic fatty liver disease. Long term prospective studies are needed to ascertain whether CF hepatic steatosis progresses to fibrosis and cirrhosis.

Key words: Cystic fibrosis liver disease; Hepatic steatosis; Non-alcoholic fatty liver disease

Core tip: Our retrospective cohort study of cystic fibrosis (CF) patients with hepatic steatosis demonstrates that hepatic steatosis in CF is associated with a higher body mass index as well as a higher percent predicted forced expiratory volume in 1 s, as compared to normal CF controls. None of our patients with hepatic steatosis exhibited evidence for advanced liver disease. Our findings are novel and demonstrate similarities between hepatic steatosis in CF and adult non-alcoholic fatty liver disease and future prospective studies are required to determine whether this steatosis may evolve into cirrhosis.

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INTRODUCTION

Cystic fibrosis (CF) is the most common fatal autosomal recessive disease in Caucasians. The majority of clinical manifestations of CF are due to a mutation of the CF transmembrane receptor (CFTR) resulting in defective chloride transport[1]. Outside of the classic pulmonary manifestations of CF, involvement of other organ systems such as the hepatobiliary and gastrointestinal system is common[2]. With improving care and increasing life expectancy, CF liver disease (CFLD) has arisen as a major cause of morbidity and mortality for CF patients. CFLD is now considered the third leading cause of death in CF patients after lung disease and transplantation complications[3]. Due to varying definitions of CFLD, its prevalence in adults has been reported to be between 3%-37%[4-6].

Biliary cirrhosis is the classic phenotypical manifestation of CFLD and is directly attributed to the underlying CFTR defect. However, the spectrum of hepatobiliary disease in CF patients is wide and ranges from asymptomatic elevations in aminotransferases, to end-stage cirrhosis and portal hypertension. Hepatic steatosis detected on imaging or biopsy is the most common hepatic manifestation, with a prevalence rate of 20%-60%[7,8]. While steatosis has classically been considered a benign condition in CF patients, the relationship between hepatic steatosis and the ultimate development of fibrosis and cirrhosis remains unclear[8,9]. In light of the increasing awareness of non-alcoholic steatohepatitis (NASH) as a major cause for cirrhosis there have been calls for the reconsideration of the importance of this clinical entity in CF patients[10].

Due to the fact that steatosis has classically been considered a benign lesion, patients with isolated steatosis are often excluded from studies on CFLD[11-13]. There has been little dedicated study of the risk factors for steatosis and the clinical characteristics of CF patients that exhibit this lesion. To better characterize patients with hepatic steatosis and ascertain the clinical characteristics and risk factors associated with this finding, we conducted a cross-sectional study of adult CF patients in an academic outpatient setting.

MATERIALS AND METHODS

Patients

Patients enrolled at the University of Florida Adult Cystic Fibrosis Center during the year 2016 with a confirmed diagnosis of CF who were at least 18 years of age and had at least 1 year of complete follow up were eligible for inclusion in this cross-sectional analysis. Demographic, clinical, radiographic and laboratory data on patients eligible for inclusion were retrospectively collected. Patients with incomplete clinical, laboratory and/or radiological data were excluded. All patients with laboratory or imaging findings to suggest hepatic abnormalities underwent testing for chronic liver diseases including viral hepatitis, Wilson disease, autoimmune hepatitis, primary sclerosing cholangitis and alpha-1-antitrypsin deficiency. Patients found to have any of the previous diseases were excluded from the analysis. Patients with known CF liver disease based on well-accepted criteria by Debray were also excluded[8].

Definitions

Diagnosis of CF was confirmed by the combination of clinical symptoms and an elevated sweat chloride

⩾ 60 mmol/L or the presence of two disease-causing mutations in CF transmembrane conductance regulator gene (*CFTR*). *CFTR* mutation testing was performed by amplification of selected regions of the *CFTR* gene, followed by detection of wild-type and mutant sequences. Chronic pseudomonas colonization was defined as detection within a period of 6 mo of a minimum of three positive *P. aeruginosa* cultures, with at least 1 mo between the positive cultures[14]. Patients were considered pancreatic insufficient if they demonstrated clinical symptoms and fecal elastase values less than 200 μg/g[15]. All patients at our clinic undergo annual 2 h oral glucose tolerance testing (OGTT) and a diagnosis of CF related diabetes (CFRD) was established if the patient met standard diagnostic criteria outlined by the American Diabetes Association[16]. History of alcohol consumption was patient reported and documented in the medical chart. Patients were considered to have "any alcohol use" if they reported any amount of alcohol intake in the past 2 years. Significant alcohol intake was defined as > 21 drinks per week in men and > 14 drinks per week in women over a 2-year period[17]. Hyperlipidemia was based on documentation in the medical chart and/or elevations of total cholesterol, LDL or fasting triglyceride levels above standard laboratory cut-offs.

Imaging criteria for determination of hepatic steatosis

Patients were considered to have hepatic steatosis on ultrasound if their liver demonstrated increased echogenicity as compared to the right kidney and impaired visualization of diaphragm and intrahepatic vessels[18,19]. Low hepatic attenuation on CT as compared to the spleen, or decreased T2 signal intensity on MRI were also considered to represent steatosis[20]. All previously mentioned imaging studies, have been independently validated with good sensitivity and specificity for the detection of hepatic steatosis in comparison to biopsy[21-23].

Testing for other forms of liver disease

Non-invasive markers of liver disease: We calculated the scores of three non-invasive biomarkers of hepatic fibrosis including AST-to-platelet ratio index (APRI), fibrosis-4 index (FIB-4) and the AST-to-alanine aminotransferase (ALT) ratio (AAR) (see supplementary files for formulas). These scoring systems have been heavily evaluated for use in chronic hepatitis C, hepatitis B and NASH[24-26]. Recently, criteria for the evaluation of CFLD that include the use of these non-invasive markers have been developed[27], thus we have included these scores in our analysis.

Statistical analysis

Normally distributed data are presented as proportions (mean ± SD) and for variables not conforming to a normal distribution as median and interquartile range (IQR). Two-sample comparisons were by Fisher's exact and χ^2 tests as appropriate. For proportions, student's *t* test was used for normally distributed variables and Mann-Whitney *U* test for other variables. Shapiro-Wilk test was used to determine normality of continuous variables. A two-sided *P*-value of < 0.05 was used to indicate statistical significance in all analyses. STATA version 13.0 (Statacorp, College Station, TX, United States) was used for statistical analysis.

RESULTS

Basic demographics

Of the 143 adult CF patients evaluated for inclusion, 114 met inclusion criteria. Of the 112 patients with known mutations, 57 had a homozygous *ΔF508* mutation, 47 had a heterozygous *ΔF508* mutation and 11 had other mutations. Median age at time of study was 29 years (IQR 24-35), median BMI was 20.9 kg/m^2 (19.3-24.9) and median percent predicted FEV_1 ($ppFEV_1$) was 57 (36-76). Ninety-two patients were pancreatic insufficient, 80 patients were chronically colonized with Pseudomonas aeruginosa, 47 had CF related diabetes mellitus (CFRD) and 26 had a history of childhood meconium ileus.

Imaging findings

Three imaging modalities (abdominal ultrasound, CT imaging, MR imaging) were used to evaluate and establish the presence of hepatic steatosis as described in the methods section. Ten patients were found to have steatosis based on ultrasound, 6 patients based on CT and 1 patient through MR imaging. Two patients demonstrated borderline splenomegaly with a spleen span of 13 cm[8]. None were found to have hepatomegaly or signs of portal hypertension.

Clinical features of patients with and without hepatic steatosis

Seventeen patients (14.9%) were found to have hepatic steatosis on imaging. The clinical characteristics of patients with hepatic steatosis as compared to those without are illustrated in Table 1. Eight of the 17 patients (47%) with hepatic steatosis were overweight with a BMI > 25 kg/m^2. Only being overweight (*P* = 0.019) and having a higher $ppFEV_1$ (75 *vs* 53, *P* = 0.037) were significantly associated with hepatic steatosis. When BMI was analyzed as a continuous variable, the significant association between higher BMI and hepatic steatosis persisted (22.3 *vs* 20.7, *P* = 0.010).

There was no significant association of hepatic steatosis with gender, age at time of study, homozygous or heterozygous ΔF508 genotype or a childhood history of meconium ileus. There was also no association with hypertension, hyperlipidemia, CFRD or any alcohol use. None of our patients had a history of significant alcohol use. None of the patients with hepatic steatosis had CF liver disease based on criteria proposed by Debray *et al*[8]. There was no association between pancreatic

Table 1 Demographics of our patient sample

Feature	All subjects	Data by hepatic steatosis		
		Hepatic steatosis	No steatosis	*P* value
No. of patients	114	17	97	
Male/female	58/56	9/8	49/48	0.854
Median age at time of study (IQR)	29 (24-35)	27	29	0.981
Median BMI (IQR)	20.9 (19.3-24.9)	22.3	20.7	0.010[a]
Underweight (BMI < 18.5)	19	2	17	0.557
Overweight (BMI > 25)	28	8	20	0.019[a]
Genotype				
ΔF508/ΔF508	57	11	46	0.216
ΔF508/other	44	6	38	0.714
Other	11	0	11	0.140
Unknown	2	0	2	
ppFEV$_1$	57 (36-76)	75	53	0.037[a]
Chronic pseudomonas colonization	80	14	66	0.234
Pancreatic insufficiency	92	15	77	0.394
Replacement dose	2011 (1334-2405)	1897	2012	0.610
Meconium ileus	26	4	22	0.939
CFRD	47	4	43	0.108
Hypertension	5	1	4	0.561
Hyperlipidemia	12	1	11	0.665
Any alcohol use	42	8	34	0.344
On CFTR modulator therapy	29	6	23	0.312

[a]*P* < 0.05. IQR: Interquartile range; BMI: Body mass index; ppFEV1: Percent predicted forced expiratory volume in 1 s; CFRD: Cystic fibrosis related diabetes mellitus; CFTR: Cystic fibrosis transmembrane conductance regulator.

Table 2 Comparison of biomarkers between patients found to have hepatic steatosis and those without steatosis on imaging

Biomarker	Data by hepatic steatosis		*P* value
	Hepatic steatosis (*n* = 17, 15%)	No hepatic steatosis (*n* = 97, 85%)	
AST	23 (20-29)	21 (16-26)	0.284
ALT	27 (19-36)	19 (13-32)	0.048[a]
ALP	103 (75-120)	99 (73-150)	0.793
Platelets	279 (244-311)	270 (207-342)	0.764
Total bilirubin	0.3 (0.3-0.4)	0.4 (0.2-0.5)	0.022[a]
INR	1 (1-1.1)	1 (1-1.1)	0.350
Albumin	3.7 (3.5-4.2)	4.2 (3.8-4.4)	0.034[a]
LDL	78.5 (44-89)	63.5 (45-81)	0.424
HDL	36.5 (31-42)	45 (36-56.5)	0.091
Triglycerides	78.5 (65-96)	80.5 (62-114.5)	0.756
Total cholesterol	124.5 (93-152)	133 (103-162.5)	0.819
HbA1c	6.5 (5.8-7.1)	6.1 (5.5-6.7)	0.097

[a]*P* < 0.05. AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; INR: International normalized ratio; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; HbA$_{1c}$: Hemoglobin A$_{1c}$.

insufficiency and the presence of hepatic steatosis and there was no statistically significant difference in daily pancreatic enzyme replacement dosing between the two groups. There was also no significant association between being on CFTR modulator therapy and hepatic steatosis.

Laboratory values and non-invasive biomarkers of liver disease in patients with and without hepatic steatosis

The laboratory values and non-invasive biomarkers of liver disease of patients with hepatic steatosis as compared to those without are illustrated Tables 2 and 3, respectively. Patients with steatosis had a significantly higher median ALT level (27 *vs* 19, *P* = 0.048), lower total bilirubin (0.3 *vs* 0.4, *P* = 0.022) and lower albumin (3.7 *vs* 4.2, *P* = 0.034). There was no significant difference between total cholesterol, LDL, HDL or triglyceride in the two groups. There was a trend towards a higher HbA1c level in hepatic steatosis patients (6.5 *vs* 6.1, *P* = 0.097). In terms of non-invasive biomarkers of liver disease, only the AAR was significantly lower in patients with hepatic steatosis (0.79 *vs* 1, *P* = 0.017). There were no significant differences in APRI or FIB-4 scores.

Table 3 Comparison of non-invasive biomarkers of hepatic fibrosis between patients found to have hepatic steatosis and those without steatosis on imaging

Biomarker	Data by hepatic steatosis		*P* value
	Hepatic steatosis (*n* = 17, 15%)	No hepatic steatosis (*n* = 97, 85%)	
APRI	0.28 (0.14-0.27)	0.19 (0.12-0.32)	0.579
FIB-4	0.49 (0.35-0.67)	0.57 (0.36-0.82)	0.629
AAR	0.79 (0.65-1.08)	1.00 (0.82-1.33)	0.017[a]

[a]*P* < 0.05. APRI: Aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis 4 score; AAR: Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio.

DISCUSSION

In this cross-sectional study of 114 adult CF patients, 14.9% of patients were found to have hepatic steatosis. None met widely accepted criteria for CF liver disease[8]. Hepatic steatosis was found to be significantly asso-

ciated with a higher BMI as well as higher ppFEV$_1$. Patients with steatosis had a significantly higher ALT level and a significantly lower AAR value. There was no association of hepatic steatosis with hypertension, hyperlipidemia, alcohol use or CFRD.

While CFLD manifestations such as focal and multilobular cirrhosis have been well described, hepatic steatosis in CF adults has not been well characterized in the literature. In our cohort, a higher BMI was significantly associated with hepatic steatosis and a significant proportion (47%) of our patients with hepatic steatosis were overweight with a BMI > 25 kg/m^2. While the association between obesity and steatosis in non-alcoholic fatty liver disease (NAFLD) has been well-described[28], this has not been previously reported in patients with CF. Only one study in predominantly pediatric CF patients reported no association between overweight BMI and steatosis, however did not specifically include data to support that conclusion[29]. We believe that our findings may indicate a possible similarity between hepatic steatosis in CF adults and other forms of adult liver disease such as NAFLD. While it has been suggested that steatosis in CF patients may be related to alcohol use[7,9], none of our patients consumed significant amounts of alcohol. Even when considering any amount of alcohol use, we found no significant difference between patients with and without hepatic steatosis.

To further delineate possible similarities with NAFLD, we investigated the association between hepatic steatosis and classic risk factors for NAFLD including hypertension and hyperlipidemia[30]. We found no significant association with either. However, we note that our study cohort is relatively young with a low prevalence of both conditions. Another classic risk factor for NAFLD is insulin resistance and associated diabetes mellitus. We did not find a significant association between hepatic steatosis and CFRD in our cohort. While multiple authors have hypothesized that insulin resistance and CFRD are possible risk factors for hepatic steatosis in CF patients[7,31,32], our study is the first note a the lack of such an association in adult patients with hepatic steatosis.

Early studies of CFLD associated the finding of hepatic steatosis with severe malnutrition[33] while others have associated it with essential fatty acid deficiency[34]. However, it has been noted in later studies that many cases occur in patients with excellent nutritional status[7]. In our cohort, there was no significant association of steatosis with pancreatic insufficiency and the mean daily pancreatic enzyme replacement dose was similar between the two groups. This, in addition to our findings and regarding BMI above, do not support overt malnutrition as a risk factor for steatosis. Interestingly, we also found a significantly higher ppFEV$_1$ in our hepatic steatosis group. Multiple studies have demonstrated that better nutritional status has been linked to improved pulmonary function and ppFEV$_1$[35]. We believe that the higher BMI demonstrated in the steatosis group reflected better nutritional status and associated improved ppFEV$_1$. Another possibility, although less likely, is that patients with overall less severe pulmonary disease and better ppFEV$_1$ at baseline were able to maintain adequate nutrition and caloric intake leading to a higher BMI and ultimately associated hepatic steatosis.

Other risk factors for hepatic steatosis have been suggested in the literature, such as high levels of circulating cytokines in the setting of chronic infection as well as chronic antibiotic therapy[7,36]. We however found no association between chronic pseudomonas colonization (and indirectly the associated chronic antibiotic use) and hepatic steatosis. In addition, we also demonstrated a lack of association between gender or childhood meconium ileus and hepatic steatosis, both of which are classic risk factors for CFLD[37]. None of our hepatic steatosis patients met criteria for classic CFLD and none had imaging findings concerning for portal hypertension or cirrhosis. This supports the fact that hepatic steatosis in CF adults is likely phenotypically and pathophysiologically distinct from classic CFLD and possibly shares similarities with NAFLD.

Serum activities of ALT, AST and alkaline phosphatase have previously been shown to correlate with liver fibrosis in CFLD but not steatosis[29]. In one series 57% of those with steatosis detected on ultrasound had an associated elevation in aminotransferases[38]. In our cohort we found that those with hepatic steatosis only had a significantly higher ALT level as compared to those without. We found no difference in calculated non-invasive biomarkers of fibrosis including APRI and FIB-4 scores. The median AST-to-ALT ratio (AAR) in hepatic steatosis patients was < 1 and was significantly lower than patients without steatosis. This likely reflects the overall predominance of significant ALT elevation in comparison to AST elevation in our steatosis cohort. It is unclear whether this pattern is specific to CF patients with steatosis and would require validation in larger cohorts. An AAR value of $\geqslant$ 1 has been found to be predictive of cirrhosis in chronic viral hepatitis and NASH[39-41], thus routine monitoring of AAR for increasing values may be worthwhile during long term follow up of CF patients with hepatic steatosis to monitor for possible progression to fibrosis and cirrhosis.

Our study has several limitations. Our relatively small sample size and single center analysis may limit generalizability. However, we note that the University of Florida Health System is a major referral center in the southeastern United States, which increases the external validity or our results. The retrospective nature of our study only allows us to ascertain associations without determination of causality. Finally, the lack of histopathological analysis of our hepatic steatosis patients may be a relative limitation. However, it has been well-established that the clinical utility of liver biopsy is quite limited due to the patchy nature of liver

disease in CF patients and liver biopsy is not routinely recommended in patients with CFLD.

Future studies may incorporate liver biopsy into their design, as well as other means of detecting insulin resistance in patients with steatosis such as homeostatic model assessment (HOMA). There have also been studies indicating significant differences in the blood levels of fatty acids and serum phospholipids between patients with CFLD and controls[42]. It would be of interest for future studies to compare such levels between patients with steatosis and controls.

In summary, in this cross-sectional analysis of adult CF patients we demonstrate a significant association between higher BMI and hepatic steatosis as detected by abdominal imaging. A trend towards higher Hba1c was also noted in patients with hepatic steatosis. We hypothesize that hepatic steatosis in adult CF patients shares similarities with NAFLD. Future, long-term prospective studies are needed to ascertain whether adult hepatic steatosis progresses to fibrosis and cirrhosis.

ARTICLE HIGHLIGHTS

Research background

Hepatic steatosis is increasingly recognized in patients with cystic fibrosis (CF) on imaging. Patients often do not demonstrate associated laboratory abnormalities or abnormal physical findings. Whether hepatic steatosis represents a manifestation of classic CF liver disease is unknown. The risk factors for such a manifestation are also unknown.

Research motivation

To describe the clinical characteristics of CF patients with hepatic steatosis and to describe risk factors for the condition as compared to patients with hepatic steatosis.

Research methods

A retrospective cohort study compares cases with hepatic steatosis to controls.

Research results

Our study demonstrates that CF patients with hepatic steatosis demonstrate a higher body mass index (BMI) as well as improved pulmonary function reflected by higher forced expiratory volume as compared to normal controls. These findings indicate that patients with hepatic steatosis were relatively healthier and had an improved nutritional status as compared to controls.

Research conclusions

To our knowledge, this study is the first retrospective study dedicated to characterizing hepatic steatosis in adults with CF. The authors found patients with hepatic steatosis to have a higher body mass index as well as better pulmonary function. The authors did not find any patients with frank liver disease. The findings indicate similarities to non-alcoholic fatty liver disease. Whether this finding evolves into cirrhosis will need to be determined with longer prospective studies.

Research perspectives

CF patients with hepatic steatosis should be followed closely to determine the evolution of their disease. Caution should be exercised by providers since this lesion may exhibit similarity to non-alcoholic fatty liver disease which is now known to progress to cirrhosis in a sub-set of patients. Future, long-term prospective studies of CF patients with hepatic steatosis are needed to identify how frequently patients progress to cirrhosis.

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