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ALTERATIONS IN LIPIDS AFTER INITIATION OF HIGHLY EFFECTIVE MODULATORS IN PEOPLE WITH CYSTIC FIBROSIS

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Abstract

Risk of cardiovascular disease (CVD) may be changing in people with cystic fibrosis (pwCF) with widespread use of highly effective modulator therapy (HEMT). We performed a retrospective analysis of patients who had lipids checked before and after initiation of ivacaftor or elexacaftor/tezacaftor/ivacaftor. We hypothesized that HEMT negatively impacts lipids (total cholesterol [TC], low-density lipoprotein [LDL], high-density lipoprotein [HDL], TC/HDL ratio). 41 adult patients were included. Paired t-tests showed statistically significant increases in TC (mean difference 16.3 mg/dL, p=0.007, n=40), LDL (mean difference 17.1 mg/dL, p<0.001, n=35), and TC/HDL ratio (mean difference 0.40, p=0.014, n=39) after HEMT initiation. HDL was unchanged (mean difference −1.5 mg/dL, p=0.69, n=39). Linear mixed models showed CF liver disease was associated with significantly blunted changes in TC and LDL. Family history of CVD risk factors was associated with significantly accentuated increases in TC and LDL. These data suggest a role for more lipid screening in pwCF.

Keywords

Cystic fibrosis; CFTR modulators; Cholesterol; Cardiovascular disease

1. Background

Historically, cardiovascular disease (CVD) has been rare in people with cystic fibrosis (pwCF) [1–3]. However, with advances in CF treatments, pwCF are living longer, experiencing increased rates of being overweight or obese, and facing a higher lifetime

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risk of cystic fibrosis related diabetes (CFRD) related to aging [4, 5]. Recent case reports of myocardial infarction, combined with prior evidence of pre-clinical atherosclerosis, suggest that the risk of CVD in pwCF may be changing. [6–8].

Hyperlipidemia is an important risk factor for CVD. Prior to widespread HEMT use, lipid studies in pwCF often demonstrated low total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL), whereas triglycerides were typically elevated compared to age-matched controls [9–14]. It is unknown, however, whether HEMT like ivacaftor (IVA) or elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) influences serum lipids in pwCF due to altered absorption or metabolism.

2. Methods

We conducted a retrospective observational study to test the hypothesis that initiation of HEMT would significantly alter lipid profiles in pwCF. The study was approved by the University of North Carolina Institutional Review Board (IRB). Included pwCF were ≥18 years of age at time of chart review and had lipids checked within 5 years of starting HEMT and at any timepoint thereafter. Lipids were not consistently collected in fasting state. Testing at UNC was performed by the Atellica CH Cholesterol_2 (Chol_2) assay via enzymatic testing with the Atellica CH Analyzer (by Siemens). Calculated LDL was determined by the Friedewald equation [15]. Testing performed at outside lab facilities (27/82 samples, or 32.9%) may have used other methods, which were not documented. Exclusion criteria included solid organ transplantation and type 1 diabetes. Primary endpoints were absolute values and changes in TC, LDL, HDL, and TC/HDL ratio from baseline after HEMT initiation. Demographic and clinical characteristics were assessed at HEMT initiation and at the time of the post-HEMT lipid panel. The presence of pancreatic insufficiency, CFRD, and CF liver disease (CFLD) were determined by careful chart review of history, imaging, lab, and prescription data. Other CVD risk factors were similarly ascertained, including hypertension (by diagnosis code), any recorded family history of CVD or CVD risk factors (including hypertension, hyperlipidemia, heart disease, stroke), tobacco use, and body mass index (BMI).

Pre/Post-HEMT TC, HDL, LDL, and TC/HDL values were compared via paired t-tests. The significance of findings did not change when potential outliers were excluded; therefore, all data were used. Secondary analyses using linear mixed effect models were performed to assess the effect of selected individual covariates (age, sex, pancreatic status, CFRD, CFLD, statin therapy, prior modulator therapy, duration on HEMT, BMI, family history) on the size and significance of lipid parameter changes using GraphPad Prism version 9.5.0.

3. Results

41 patients met inclusion criteria (Table 1). An average of 37 months (range 5-91 months) separated lipid panel measurements. Patients were on HEMT an average of 18 months when the post-HEMT lipid panel was performed. 23 patients were on lumacaftor/ivacaftor (LUM/IVA) or tezacaftor/ivacaftor (TEZ/IVA) prior to HEMT. HEMT consisted of IVA (n=3), or ELX/TEZ/IVA (n=38).

Baseline CVD risk factors were assessed in the study cohort. Tobacco use was low (3 patients). Nine patients (22%) had hypertension. Five patients had TC >200 mg/dL and seven patients were prescribed statins. Fifteen patients (37%) were overweight (BMI≥25 kg/m^2), four additional patients (10%) were obese (BMI≥30 kg/m^2). Twenty patients (49%) had a documented family history of CVD or CVD risk factors.

After initiation of HEMT, significant changes in lipid profiles were observed. TC, LDL, and the TC/HDL ratio significantly increased, while HDL did not change significantly (Table 2). BMI also significantly rose from 25.0 kg/m^2 to 26.0 kg/m^2 and 3 additional patients were diagnosed with hypertension. Five additional patients had TC >200 mg/dL post-HEMT initiation, and 16 had an increase in TC of ≥20 mg/dL. Three patients were newly prescribed a statin medication.

Linear models evaluated potential factors associated with changes in TC and LDL. The presence of CFLD was associated with a significantly blunted change in TC after HEMT initiation (p=0.034; TC mean difference pre/post HEMT −3.0 mg/dL in those with CFLD vs. 23.6 mg/dL in those without CFLD). Patients with CFLD also had a significantly blunted change in LDL after HEMT initiation (p=0.009; LDL mean difference −2.7 mg/dL in those with CFLD vs. 23.5 mg/dL in those without CFLD). In contrast, family history of CVD risk factors was associated with a significantly larger increase in TC after HEMT initiation (p=0.002; TC mean difference 33.8 mg/dL in those with family history vs. 0.3 mg/dL in those without documented family history). Family history was also associated with a significantly larger increase in LDL after HEMT initiation (p=0.023; LDL mean difference 25.9 mg/dL in those with family history vs. 6.6 mg/dL in those without family history) (Figure 1). Neither baseline nor change in BMI was correlated with magnitude of change in TC or LDL, nor was pancreatic status, CFRD, age, sex, statin use, prior modulator therapy, or duration on HEMT.

4. Discussion and Conclusions

This study provides valuable insights into the changes in lipid profiles and CVD risk factors in pwCF after initiating HEMT. Statistically significant increases in TC and LDL occurred in pwCF started on HEMT over a relatively short period of time, whereas cardioprotective HDL did not change.

In a study by Petersen et al., lipid changes were assessed in patients with CFRD after initiation of ELX/TEZ/IVA. They noted similar increases in TC and LDL as observed in our study, though HDL also significantly increased [16]. In our study, CFRD was not associated with the magnitude of change in TC or LDL, indicating that CFRD may not be the only criteria that should be used for lipid screening in pwCF. However, a family history of CVD risk factors was associated with larger increases in TC and LDL, highlighting the importance of assessing family history in pwCF. Although our cohort had few pancreatic sufficient patients (n=6), prior studies pre-HEMT have demonstrated that TC, LDL, and triglycerides are higher in these patients [13, 14]. Three PS patients were on statin therapy, potentially blunting significant increases in TC and LDL.

These results have potential implications for future screening and treatment practices. Current Cystic Fibrosis Foundation guidelines recommend annual lipid screening for patients with CFRD plus other CVD risk factors [17]. However, our data suggest that a broader population of pwCF may require lipid screening, particularly considering ~90% of patients are eligible for HEMT. Our data also support previous reports of increasing hypertension in pwCF, especially after ELX/TEZ/IVA initiation [4, 18]. When combined with other CVD risk factors, lipid lowering therapy for hyperlipidemia should be considered in more pwCF on HEMT.

Our study's limitations include its retrospective nature and small sample size. Samples for lipid measurement were not consistently collected in the fasting state, preventing meaningful triglyceride evaluation. Testing methods may have varied at outside lab facilities. Our study population was also older, with higher rates of hypertension, CFRD, and obesity than reported in the US Registry, indicating a selection bias in this sample related to perceived need of measuring a lipid profile [5]. Family history of CVD was assessed inconsistently, however while details were limited (such as which relatives were affected), broadly inclusive use of family history appears to be a risk factor for changes in lipids at least in this higher risk group. These limitations reduce our ability to understand the effects of HEMT on a lower-risk population. Further data is needed, therefore, to refine risks in the general CF population and in subpopulations of interest. Prospective collection of samples at timed intervals related to HEMT initiation would also be useful.

Future investigations include understanding how HEMT affects lipid absorption and synthesis. In our population, CFLD was associated with minimal change in TC and LDL, and lower cholesterol levels have also been noted in patients with cirrhosis from other causes [19, 20]. This raises the question whether HEMT increases lipid levels via increased hepatic synthesis. However, untangling potential effects of HEMT on serum cholesterol levels, absorption, and synthesis requires additional study. We must also determine whether HEMT-induced changes in lipid profiles and other risk factors will translate into clinically apparent CVD. Our preliminary conclusions include emphasizing lipid screening in pwCF with family history of CVD and other CVD risk factors.

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Abbreviations

CVD	cardiovascular disease
pwCF	people with cystic fibrosis
HEMT	highly effective modulator therapy

CFRD	cystic fibrosis related diabetes
TC	total cholesterol
LDL	low-density lipoprotein
HDL	high-density lipoprotein
IVA	ivacaftor
ELX/TEZ/IVA	elexacaftor-tezacaftor-ivacaftor
IRB	Institutional Review Board
CFLD	cystic fibrosis liver disease
BMI	body mass index
LUM/IVA	lumacaftor-ivacaftor
TEZ/IVA	tezacaftor-ivacaftor
FEV1pp	forced expiratory volume in 1 second, percent predicted

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Highlights:

- Risk of cardiovascular disease may be changing in people with cystic fibrosis
- Total cholesterol and low-density lipoprotein increased after starting modulators
- High-density lipoprotein did not change after modulator initiation
- Family history was associated with greater increases in total cholesterol
- Increased cholesterol screening may be warranted in cystic fibrosis

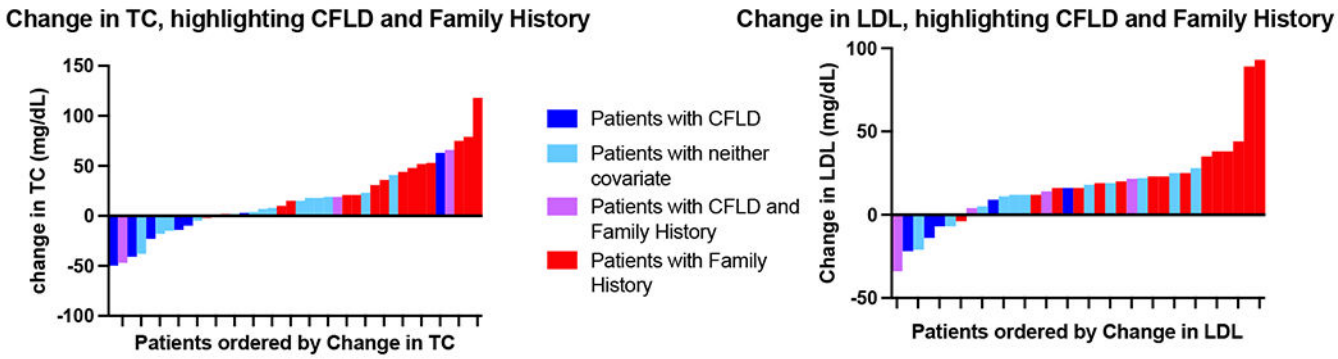

Figure 1.

Waterfall plots of change in TC and change in LDL. TC = total cholesterol; CFLD = CF liver disease; LDL = low-density lipoprotein.

Table 1.

Study population characteristics (n=41)

Mean Age at HEMT start, years (range)	40 (16 – 73)
Mean Duration HEMT, months (range)	18 (3 – 49)
Mean Baseline FEV1pp, % (range)	66% (19 - 125%)
Mean Baseline BMI (kg/m^2) (range)	25.0 (17.4 – 33.6)
Female (%)	27 (66%)
Pancreatic Insufficient (%)	35 (85%)
CFRD (%)	23 (56%)
CF liver disease (%)	12 (29%)
Chronic pseudomonas infection (%)	27 (66%)
Prior modulator therapy (%)	23 (56%)

HEMT = highly effective modulator therapy; FEV1pp = forced expiratory volume in 1 second, percent predicted; BMI = body mass index; CFRD = cystic fibrosis related diabetes; CF = cystic fibrosis.

Table 2.

Lipid measurements before and after modulator initiation

	Pre-HEMT mean	Post-HEMT mean	Difference mean (95%CI)	p value
TC (mg/dL) n = 40 *(ref < 200 mg/dL)*	152.5	168.8	16.3 (4.8, 27.7)	0.007
HDL (mg/dL) n = 39 *(ref: 40 - 60 mg/dL)*	53.2	52.2	−1.5 (−6.4, 4.3)	0.69
LDL (mg/dL) n = 35 *(ref: 40 - 99 mg/dL)*	73.5	90.6	17.1 (8.4, 25.8)	<0.001
TC/HDL n = 39 *(ref: 1.0 – 4.5)*	3.07	3.49	0.40 (0.09, 0.74)	0.014

Results from paired t-tests are shown. Reference normal ranges are italicized for context, though elevations beyond this range do incorporate additional stratification of risk not shown here. HEMT = highly effective modulator therapy; TC = total cholesterol; HDL = high-density lipoprotein; LDL = low density lipoprotein. CI = confidence interval.