1-5-2024

# Impact of Elexacaftor/Tezacaftor/Ivacaftor on Lipid and Fat-Soluble Vitamin Levels and Association with Body Mass Index

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## Recommended Citation

Patel T, McBennett K, SankararamanS, et al. Impact of elexacaftor/tezacaftor/ivacaftor on lipidand fat-soluble vitamin levels and association with body massindex. Pediatr Pulmonol. 2024;59:734-742.doi:10.1002/ppul.26823

Received: 12 August 2023 | Accepted: 4 December 2023

DOI: 10.1002/ppul.26823

ORIGINAL ARTICLE

PEDIATRIC PULMONOLOGY WILEY

# Impact of elexacaftor/tezacaftor/ivacaftor on lipid and fat-soluble vitamin levels and association with body mass index

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**Funding information**
Cystic Fibrosis Foundation

## Abstract

**Introduction:** Cystic fibrosis transmembrane conductance regulator (CFTR) modulators improve gastrointestinal absorption of nutrients and may result in changes in body mass index (BMI), serum lipids, and fat-soluble vitamin levels. We hypothesized that serum lipids and vitamin levels would increase with CFTR modulator therapy and that greater increase in lipids and vitamin levels would be related to greater increase in BMI.

**Methods:** A retrospective study was performed to evaluate the impact of elexacaftor/tezacaftor/ivacaftor (ETI) on nutritional parameters, serum lipids, and fat-soluble vitamin levels. Pre-ETI values (<2 years prior) and post-ETI values (>1 month after) were compared. Linear regression was used to evaluate whether change in BMI is associated with the change in lipid and/or vitamin levels and whether modulator duration is associated with the degree of rise in lipid and/or vitamin levels.

**Results:** Adults and adolescents with CF ($n = 137$) were evaluated before and 31–300 days after starting ETI. Median BMI (adults 21.9 vs. 23.5 kg/m$^2$; adolescents 48 vs. 63 percentile) increased after initiation of ETI. Total cholesterol (126 vs. 154 mg/dL), low-density lipoprotein cholesterol (63 vs. 78 mg/dL), non-high-density lipoprotein cholesterol (84 vs. 102 mg/dL), and high density lipoprotein cholesterol (43 vs. 49 mg/dL) increased after ETI, while triglycerides and very low density lipoprotein did not change. Median values for vitamin D (34.5 vs. 38.0 ng/mL) and vitamin A (40.1 vs. 47.9 µg/dL) increased, while vitamin E did not change significantly. There was no significant correlation between BMI change or duration of modulator therapy with vitamin levels or lipid changes.

**Conclusion:** After initiation of ETI therapy, serum lipids increased in our population, but most values remained within the normal range. Vitamins A and D levels increased post-ETI and no changes were noted in vitamin E. No significant

correlation between the degree of BMI change and the magnitude of increase in lipids or vitamin levels was found.

KEYWORDS

elexacaftor/tezacaftor/ivacaftor, lipid, metabolic, modulator, vitamin

## 1 | INTRODUCTION

Cystic fibrosis (CF) is a multisystem disorder caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1] CFTR dysfunction results in pulmonary disease, exocrine pancreatic insufficiency, infertility, and diabetes.[2] Historically, people with CF (PwCF) often had malnutrition, as well as deficiencies in fat-soluble vitamin levels (A, D, E, and K), and low cholesterol levels.[3,4]

The life expectancy for PwCF in the United States is now 56 years, a significant improvement from previous predicted life expectancies.[1] This success can be attributed to multiple factors such as early identification of CF through newborn screening, aggressive nutritional strategies, improved pulmonary management, and, most recently, the modulator therapies targeting the CFTR protein defect itself.[1] Elexacaftor–tezacaftor–ivacaftor (ETI) therapy, a highly effective modulator, resulted in 10% increase in percent predicted forced expiratory volume in 1 s (ppFEV1) after just 4 weeks and 1.04 kg/m$^2$ body mass index (BMI) gain over 24 weeks compared to placebo.[5,6] Despite these extraordinary changes, it remains unclear whether CFTR modulators fully correct the malabsorptive phenotype of CF and whether modulator-treated pwCF will be at risk for dyslipidemia and cardiovascular disease.[7]

Existing literature suggests several mechanisms of weight gain with highly effective modulator therapy and mixed results regarding changes in vitamin and lipid values. A 2019 study of 23 children with gating-mutations treated with the highly-effective modulator ivacaftor found that reduced intestinal inflammation, improved fat malabsorption, and reduced resting-energy expenditure all contributed to weight gain with CFTR modulators.[7] Fat mass increases with ETI as measured by DXA and bioelectrical impedance, with conflicting results regarding lean mass improvement.[8-10] Importantly, 40% of adults with CF are now overweight or obese and may be at risk for cardiometabolic complications.[11] Four studies found improvement in total cholesterol and low-density lipoprotein (LDL) cholesterol after ETI, though the change was only significant in patients with CF-related diabetes (CFRD) in one study.[12-15] In contrast, earlier studies of lumacaftor/ivacaftor found reduction in total and LDL cholesterol.[16,17] Most existing studies find either no change or higher vitamins A and D levels after ETI, while changes in vitamin E are variable.[13,18-23] Case reports of vitamin A toxicity with ETI suggest that changes in absorption vary between individuals.[24] Elevation of liver enzymes occurs with ETI therapy in many cases, though improvement in CF-associated liver disease, particularly hepatic steatosis, has been reported with ivacaftor and lumacaftor/ivacaftor, possibly due to improvement in essential fatty acid deficiency.[6,25-27]

Given the importance of understanding how highly effective modulators impact extrapulmonary manifestations of CF, we undertook a retrospective study of adolescents and adults treated with ETI at our center. Our first aim was to quantify the change in lipids (total cholesterol [TC], LDL, high-density lipoprotein [HDL], non-HDL, and triglycerides), vitamin levels (vitamins A, E, and D), and other nutritional markers before and after taking ETI. The secondary aims were to assess whether the change in BMI relates to change in lipids and fat-soluble vitamin levels and whether the duration of ETI therapy relates to the change in nutritional parameters. We hypothesized that lipid levels and vitamin levels would increase after ETI therapy and that an increase in BMI would correlate with an increase in lipids but not with fat-soluble vitamin levels.

## 2 | METHODS

We performed retrospective chart review of all ETI eligible PwCF at the LeRoy W. Matthews Cystic Fibrosis Center to evaluate the impact of ETI on metabolic and nutritional parameters. All study procedures were approved by the University Hospital Institutional Review Board before study initiation. Eligible subjects were identified through the local CF Center Registry based on a diagnosis of CF and a prescription for ETI. Demographic and patient characteristics such as age, sex, BMI, ppFEV1, and pancreatic exocrine status were obtained from the local CF center registry. Additional patient characteristics such as the presence of advanced CF liver disease (CFLD), presence of CFRD, and transplant (lung and/or liver) status were obtained through chart review. All pancreatic insufficient subjects remained on their CF-specific vitamin products and vitamin doses were adjusted only if there were deficiencies or elevated levels.

We evaluated the impact of ETI treatment on multiple clinical and laboratory outcomes, including BMI, serum lipids, and vitamins A, D, and E. Pulmonary function testing, serum albumin, total protein, and liver enzymes were also assessed. All demographics, clinical characteristics, and laboratory parameters were collected from the local CF registry and confirmed by chart review. BMI and laboratory assessments did not always occur at the same time point. Subjects without any biochemical data were excluded from the study, as were subjects whose pre-ETI data was more than 2 years before the start of ETI or whose post-ETI data was obtained within 1 month of starting ETI. One subject who started a cholesterol-lowering medication during the study period was excluded from lipid analyses.

Baseline characteristics are described separately for adults ≥18 years of age and adolescents <18 years of age and were tested for

between-group differences in sex distribution and ppFEV1 using a Wilcoxon rank-sum test for continuous data or chi-squared test for categorical data. BMI was evaluated separately for pediatric and adult subjects because in the pediatric population, BMI is expressed as a percentile (specific for age and sex) and in adults as a numerical (kg/m$^2$). Pre- and post-ETI data were evaluated using a Wilcoxon signed-rank test. Next, we evaluated the relationship between change in BMI and change in lipid and fat-soluble vitamin levels by linear regression. There were not sufficient lipid panels performed in the pediatric age group, so lipid analyses were only performed in adults. Duration of ETI therapy and degree of change in total cholesterol, LDL, HDL, non-HDL, vitamin D, and vitamin A were assessed with linear regression. Statistical analysis was performed using SAS.

## 3 | RESULTS

One hundred and thirty-six subjects met the criteria for study inclusion, including 110 adults and 26 adolescents (Table 1). Adult subjects were of a higher proportion of male (63%) compared to pediatric subjects (46%), but the difference was not statistically significant. As expected, pre-ETI pulmonary function (ppFEV1) was significantly higher in adolescents than adults, consistent with the age-related decline in pulmonary function seen in the CF population.

BMI, ppFEV1, lipid levels, vitamin levels, and liver enzymes before and after ETI are summarized in Table 2. BMI was significantly higher post-ETI in both the adult (median 21.9 vs. 23.5 kg/m$^2$, $p < .0001$) and pediatric (median 48%–63%, $p = .0116$) groups, consistent with established literature. The median duration of ETI therapy at the time of BMI measurement was 181 days (range 31–300 days). Pulmonary function (ppFEV1) similarly increased from a median of 66.1%–77.3% after ETI therapy, $p < 0.0001$.

Total cholesterol, LDL cholesterol, non-HDL cholesterol, and HDL cholesterol all increased significantly after ETI therapy, while very low-density lipoprotein (VLDL) cholesterol and triglyceride (TG) levels did not (Table 2). The median vitamin D level increased from 34.5 to 38 ng/mL and vitamin A level increased from 40.1 to 47.9 µg/dL, but the vitamin E level did not increase significantly. Median serum albumin (4.1 to 4.4 mg/dL) and total bilirubin (0.4 to 0.7 mg/dL) both increased significantly post-ETI; however, there was no significant change in aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl-transferase (GGT), alkaline phosphatase (ALP), or total protein with ETI in this cohort.

The degree of change in BMI did not correlate significantly with the change in lipid or vitamin levels in adults, nor did the degree of change in BMI correlate significantly with the change in vitamin levels in the pediatric population with CF. (data not shown) Modulator

**TABLE 1** Demographics and baseline characteristics of people with CF before initiating elexacaftor/tezacaftor/ivacaftor (ETI).

| Characteristics | Overall *n* = 136 | Pediatric group *n* = 26 | Adult group *n* = 110 | *p* Value |
|---|---|---|---|---|
| Age (years) | 27 (20–37) | 15 (12–16) | 30 (24–9) | <.001[a] |
| Sex | | | | .121[b] |
| Female | 55 (40%) | 14 (54%) | 41 (37%) | |
| Male | 81 (60%) | 12 (46%) | 69 (63%) | |
| Body mass index (%, kg/m$^2$) | | 48 (29–74)[1] | 21.9 (19.8–24.7)[2] | |
| FEV1%pred (before ETI) | 66 (46–87) | 90 (79–99)[1] | 60 (42–72)[3] | <.001[a] |
| Genotype | | | | |
| F508del/f508del | 82 (60%) | 15 (58%) | 67 (61%) | |
| F508del/other | 54 (40%) | 11 (42%) | 43 (39%) | |
| Other/other | 0 | 0 | 0 | |
| Pancreatic insufficiency | 129 (95%) | 26 (100%) | 103 (94%) | |
| CF-liver disease | 7 (5%) | 1 (4%) | 6 (5%) | |
| Liver transplant | 1 (1%) | 0 | 1 (1%) | |
| CF-related diabetes | 34 (25%) | 3 (12%) | 31 (28%) | |

*Note*: Values are expressed as median (interquartile range) or number (%).

Abbreviation: CF, cystic fibrosis.

[a]Wilcoxon rank-sum test.

[b]Pearson's chi-squared test.

[1]$n = 25$.

[2]$n = 93$.

[3]$n = 88$.

**TABLE 2** Variables of interest before and after elexcaftor/tezacaftor/ivacaftor (ETI) therapy.

| | *n* | Pre-ETI | Post-ETI | *p* Value |
|---|---|---|---|---|
| BMI (adult) | 82 | 21.9 (19.6–24.8) | 23.5 (20.6–25.8) | <.0001 |
| BMI percentile (adolescents) | 25 | 48.0 (29.0–73.8) | 63.0 (43.8–79.9) | .0116 |
| FEV1 (% predicted) | 98 | 66.1 (47.2–87.4) | 77.3 (57.4–97.3) | <.0001 |
| Total cholesterol (mg/dL) | 35 | 126 (110–148) | 154 (137–179) | <.0001 |
| LDL (mg/dL) | 31 | 63 (50–81) | 78 (66–97) | .0025 |
| HDL (mg/dL) | 33 | 43 (35–51) | 49 (42–59) | .0013 |
| Non-HDL (mg/dL) | 33 | 84 (66–101) | 102 (82–123) | .0018 |
| VLDL (mg/dL) | 31 | 19 (15–26) | 18 (14–25) | .3965 |
| Triglycerides (mg/dL) | 36 | 96 (72–128) | 100 (74–134) | .8663 |
| Vitamin D (ng/mL) | 68 | 34.5 (24.5–41.0) | 38.0 (32.0–48.5) | <.0001 |
| Vitamin A (ug/dL) | 56 | 40.1 (32.5–55.5) | 47.9 (40.6–56.7) | .005 |
| Vitamin E (mcg/mL) | 59 | 9.2 (6.5–11.5) | 9.6 (6.9–13.2) | .2928 |
| GGT (IU/L) | 66 | 15.5 (12–26) | 16 (12–24) | .9751 |
| Albumin (g/dL) | 98 | 4.1 (3.8–4.5) | 4.4 (4.1–4.6) | <.0001 |
| Total protein (g/dL) | 98 | 7.2 (6.6–7.6) | 7.1 (6.8–7.4) | .6542 |
| Alkaline phosphatase (U/L) | 78 | 103 (75–138) | 96 (70–116) | .6542 |
| AST (U/L) | 98 | 22.5 (18–31) | 22 (18–32) | .4350 |
| ALT (U/L) | 98 | 26 (16–38) | 25 (18–37) | .4218 |
| Bilirubin total (mg/dL) | 98 | 0.4 (0.3–0.6) | 0.7 (0.4–0.9) | <.0001 |

*Note*: Values are expressed as median (interquartile range).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

duration was not significantly associated with a greater rise in total cholesterol, LDL, non-HDL, HDL, vitamin A, D, or E levels (Figure 1).

## 4 | DISCUSSION

Adolescent and adult PwCF in our center demonstrated significantly higher serum total cholesterol, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol after initiation of ETI, though most cholesterol levels remained within the healthy population reference range. Levels of fat-soluble vitamins A and D increased after treatment with ETI, while vitamin E did not. Like prior studies, BMI, pulmonary function, and serum albumin levels improved with ETI. Interestingly, liver serologies did not change significantly in our study. There was not a significant association between the degree of weight gain and change in nutritional markers, as we had hypothesized. These results add to the existing literature suggesting highly effective CFTR modulator therapy is associated with changes in lipid and fat-soluble vitamin levels. Our results differ from prior studies in that the cholesterol increase was found in all subjects, not just those with CF-related diabetes, and both vitamins A and D increased in our population.

An increase in BMI in both children and adults has been noted in many studies after the initiation of modulator therapies, with greater weight gain after highly effective modulator therapies such as Iva (for PwCF with gating mutations) and ETI.[21,22,28-36] Petersen and colleagues found that the mean rate of change in BMI was 1.47 kg/$m^2$/yr (95% confidence interval, 1.08–1.87) greater after initiation of ETI. A decrease in resting energy expenditure and/or better intestinal absorption due to reduced intestinal inflammation and, rarely partial improvement in pancreatic function have been reported as possible reasons for the increase in BMI.[7,36-39] Gelfond et al. noted an improvement of intestinal pH post ivacaftor which may improve absorption, through improved dissolution of enteric-coated enzymes and less precipitation of bile acids.[40] Several studies have also suggested a positive effect on glucose tolerance, which could lead to increase in BMI.[41,42] Gur et al. examined the effect of ETI on weight and body composition, finding a 2.5 kg average weight gain and a 0.9 kg/$m^2$ average BMI increase. The body composition analysis demonstrated a significant increase in lean body mass and percent fat *z*-score, though other studies found no change in lean mass.[9,10] Although higher BMI has historically been associated with improved survival in PwCF, the possibility of adverse consequences from obesity in CF is a growing concern.[43,44]

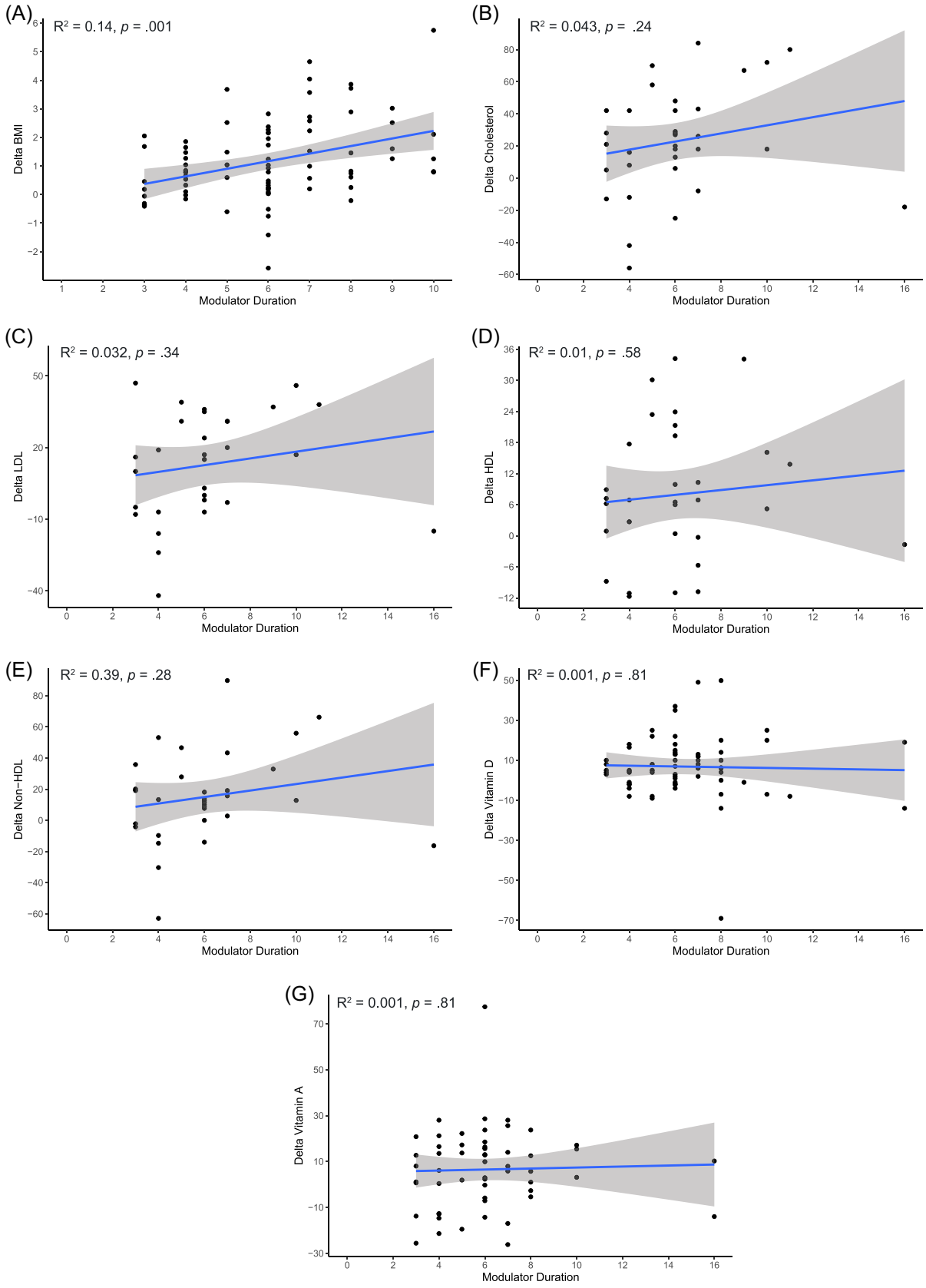


**FIGURE 1** Correlation between the duration of elexacaftor/tezacaftor/ivacftor CFTR modulator therapy and the change in body mass index (BMI) (A), total cholesterol (B), LDL cholesterol (C), HDL cholesterol (D), non-HDL cholesterol (E), vitamin D (F), and vitamin A (G). Modulator duration is expressed in months. Units are mg/dL for cholesterol, ng/mL for vitamin D, and μg/dL for vitamin A. CFTR, cystic fibrosis transmembrane conductance regulator; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Cystic fibrosis is classically associated with reduced serum lipid levels due to fat malabsorption, except for occasional hypertriglyceridemia.[3] As expected, cardiovascular disease has been rarely reported in PwCF and autopsy studies demonstrated minimal coronary plaque.[45] This notwithstanding, an association between obesity, insulin resistance, and higher lipid levels has been demonstrated in PwCF, even before the broad use of highly effective modulator therapies.[44,46] Several authors have investigated the association between CFTR modulators and serum lipids (Table 3). Two groups studied adults and children before and after Lum/Iva therapy and found a decrease in total cholesterol and no increase in other lipids.[16,17] Petersen found an increase in total cholesterol, HDL cholesterol, and LDL cholesterol with ETI only in the subset of adults with CFRD.[12] In contrast, we found a significant increase in HDL and LDL cholesterol in the population overall despite a low proportion of subjects with CFRD. Despotes et al. found an increase in total cholesterol and LDL only.[15] Yuzyuk compared modulator and non-modulator-treated children with CF and noted higher HDL and lower VLDL in children treated with modulators.[48] Carnovale found an increase in non-HDL cholesterol in adolescents and adults with CF after ETI and proposed that an increase in hepatic synthesis and secretion of lipoproteins was responsible. Similar to our study, an increase in albumin was noted by Carnovale, which could result from increased hepatic synthesis and secretion of albumin due to reduced inflammation.[13] Interestingly, hepatic transaminases did not increase significantly in our cohort after ETI therapy, conflicting with other studies.[49] Hepatic steatosis has been associated with both malnutrition and high BMI in pwCF and could confound assessments of liver enzymes.[50]

Changes in fat-soluble vitamins have been documented in studies of Iva, Lum/Iva, and ETI though not all studies find a difference. The most consistent finding across studies is an increase in vitamin A levels.[16,22,23] The changes in vitamin D and vitamin E were variable between modulators and between the studied cohorts (Table 4). Sommerburg and colleagues noted an increase in vitamin A and a decrease in vitamin E following Lum/Iva therapy for a follow-up duration of up to 2 years after its initiation.[16] The increase in vitamin A was believed to be secondary to increased intestinal absorption and decreased utilization related to reduced inflammatory status. In this cohort, plasma vitamin E levels and vitamin/cholesterol ratio were reduced during the same time frame and multiple reasons were postulated, such as decreased intestinal absorption by competitive inhibition, altered lipid digestion, increased distribution of vitamin E in the adipose tissue, and increased vitamin E degradation.[16] Using animal models, investigators have also demonstrated that vitamin A can inhibit the absorption of other fat-soluble vitamins.[53,54]

Francalanci noted a significant increase in vitamins A, D, and E levels post-ETI, whereas the current study found only increased vitamins A and D. This discrepant result could be due to age differences, differences in vitamin dosage and formulations, seasonal trends (for vitamin D), duration of follow up, and correction for vitamin E based on lipid levels.[22] Generally, an increase in vitamin levels is believed to be related to increased absorption.[18] Symptomatic hypervitaminosis A has been reported in few cases[23,24,55,56] and, in most studies, the increase in vitamin A is not extremely high. Apart from increased intestinal absorption, an improvement in systemic inflammation could also contribute to higher vitamins A

**TABLE 3** Summary of studies evaluating the impact of elexcaftor/tezacaftor/ivacaftor (ETI) on serum lipids.

| References | Population | Modulator | BMI change | Change in cholesterol |
|---|---|---|---|---|
| Ronan et al.[47] | 24 adults in the USA | Iva | Not presented | Increase in total cholesterol 0.2 mmol/L and HDL 0.16 mmol/L |
| Sommerburg et al.[16] | 41 children in Germany | Lum/Iva | *z*-score +0.2 SD | Decrease total cholesterol 0.09 mmol/L |
| Gelzo et al.[17] | 20 adults in Italy | Lum/Iva | Not presented | Decrease total cholesterol 3 mg/dL |
| Petersen et al.[12] | 134 adults in the USA | ETI | 1.47 kg/m2/yr | Increase total cholesterol 0.67 mmol/L/yr, LDL-C 0.47 mmol/L/yr, HDL 0.23 mmol/L/yr in CFRD group |
| Talish et al.[14] | 21 adults in the USA | ETI | 0.61 kg/m$^2$ | Increase total cholesterol 11 mg/dL, LDL-C 18 mg/dL |
| Carnovale et al.[13] | 20 children >12 years or adults in Italy | ETI | 3.1 kg/m$^2$ | Increase total cholesterol 23 mg/dL, LDL 44 mg/dL, and nonsignificant decrease in HDL |
| Yuzyuk et al.[9] | 153 children and adolescents in the USA | ETI | Not applicable | Higher HDL and lower VLDL in subjects on CFTR modulator compared to not on modulator |
| Despotes et al.[15] | 41 adults in the USA | ETI | Not presented | Increase total cholesterol 16 mg/dL and LDL 17 mg/dL. |

*Note*: To convert total cholesterol, LDL, HDL, VLDL, non HDL from mmol/L to mg/dL, multiply by 38.67.

Abbreviations: BMI, body mass index; ETI, elexacaftor/tezacaftor/ivacaftor; Iva, ivacaftor; Lum/Iva, lumacaftor/ivacaftor.

**TABLE 4** Summary of published studies evaluating vitamin levels before and after modulator treatment.

| References | Number of participants | Modulator used | Significant changes in vitamin levels |
|---|---|---|---|
| Burgel 2020[51] | 845 | Lum/Iva | No significant changes in vitamin levels |
| Gelzo et al.[17] | 20 | Lum/Iva | Vitamin E increased |
| Sommerburg et al.[16] | 41 | Lum/Iva | Vitamin A increased<br>Vitamin E decreased |
| Wright et al.[18] | 76 | ETI | Vitamin D increased |
| Baumberger et al.[19] | 366 | ETI | Comparative statistics not provided |
| Kuffel et al.[20] | 15 | ETI | Vitamins A and D increased |
| | 9 | Iva | No significant changes in vitamin levels |
| Carnovale et al.[13] | 20 | ETI | Vitamin A increased |
| Proud et al.[21] | 155 | ETI | Vitamin A increased |
| Hergenroeder et al.[52] | 54 | ETI | Vitamin E decreased |
| Gaschignard et al.[35] | 34 | Lum/Iva | Vitamin E increased |
| Francalanci et al.[22] | 9 | Iva | Vitamin E increased |
| | 42 | Lum/Iva | Vitamin A increased |
| | 29 | ETI | Vitamins A, D, and E increased |
| Schembri et al.[23] | 54 | ETI | Vitamin A increased |
| Present study | 56 | ETI | Vitamin A increased |
| | 68 | | Vitamin D increased |

Abbreviations: ETI, elexacaftor/tezacaftor/ivacaftor; Iva, ivacaftor; Lum/Iva, lumacaftor/ivacaftor.

and D levels.[57,58] Importantly, pancreatic insufficient subjects in our study were treated with CF-specific vitamin products and doses were only adjusted for deficiencies or elevated levels per clinical routines.

Our study has several limitations, most notably that not all data was available for every subject and there was a variable duration of modulator therapy. We chose to exclude data taken within 1 month of ETI initiation to allow time for physiologic adjustment to the drug. In addition, the COVID-19 pandemic interrupted care for many people living with CF, complicating annual lab acquisition. Due to limited subjects with pancreatic exocrine sufficiency, we did not separately analyze pancreatic sufficient subjects. We did not report inflammatory markers such as C reactive protein to evaluate inflammatory status which are associated with low fat-soluble vitamin levels. Vitamin dose changes were not recorded as part of this study but would usually have occurred after the laboratory evaluation in response to abnormally high or low values. Given the retrospective nature, we could not evaluate various pertinent factors such as body composition, pubertal status in adolescents, and adherence to therapies which provide valuable insights into this topic.

Despite these limitations, our study has the following strengths. We included both adult and pediatric pwCF with the assessment of lipids and vitamin levels before and after starting ETI. The study population is well characterized, with important co-morbidities identified. We chose to include both pediatric (over 12 years of age) and adults with CF not only to increase the sample size, but also to evaluate the differences in response to ETI in adolescents and adults.

In conclusion, we evaluated 136 adult and adolescent PwCF before and >1 month after initiation of the highly effective CFTR modulator ETI and found increase in ppFEV1, BMI, serum HDL, non-HDL, and LDL cholesterol, as well as increase in fat-soluble vitamins A and D. Vitamin E levels did not increase in our study population. This data adds to the existing literature supporting changes in nutritional status in individuals with cystic fibrosis. Further prospective research is needed to understand the impact of highly effective modulator therapy on risks associated with obesity, including cardiovascular risk.

## AUTHOR CONTRIBUTIONS

**Tanvi Patel**: Data curation; writing—review and editing; investigation; project administration; writing—original draft. **Kimberly McBennett**: Conceptualization; formal analysis; project administration; writing—review and editing; supervision; methodology; data curation. **Senthilkumar Sankararaman**: Writing—review and editing; supervision; validation; methodology; writing—original draft. **Teresa Schindler**: Writing—review and editing; methodology; validation. **Krithika Sundaram**: Investigation; writing—review and editing. **Nori Mercuri Minich**: Formal analysis; writing—review and editing. **Sindhoosha Malay**: Formal analysis; writing—review and editing. **Katherine**

**Kutney**: Writing—original draft; writing—review and editing; formal analysis; investigation; data curation; validation.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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## REFERENCES

1. McBennett KA, Davis PB, Konstan MW. Increasing life expectancy in cystic fibrosis: advances and challenges. *Pediatr Pulmonol*. 2022;57(S1):S5-S12.
2. Gibson-Corley KN, Meyerholz DK, Engelhardt JF. Pancreatic pathophysiology in cystic fibrosis. *J Pathol*. 2016;238(2):311-320.
3. Figueroa V, Milla C, Parks EJ, Schwarzenberg SJ, Moran A. Abnormal lipid concentrations in cystic fibrosis. *Am J Clin Nutr*. 2002;75(6):1005-1011.
4. Bailey J, Krick S, Fontaine KR. The changing landscape of nutrition in cystic fibrosis: the emergence of overweight and obesity. *Nutrients*. 2022;14(6):1216.
5. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet*. 2019;6736(19):6-14.
6. Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor–Tezacaftor–Ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med*. 2019;381(19):1809-1819.
7. Stallings VA, Sainath N, Oberle M, Bertolaso C, Schall JI. Energy balance and mechanisms of weight gain with ivacaftor treatment of cystic fibrosis gating mutations. *J Pediatr*. 2018;201:229-237.
8. Proud D, Duckers J. Weight a minute: exploring the effect on weight and body composition after the initiation of elexacaftor/tezacaftor/ivacaftor in adults with CF. *J Cyst Fibros*. 2023;22:847-850.
9. Gur M, Bar-Yoseph R, Hanna M, et al. Effect of Trikafta on bone density, body composition and exercise capacity in CF: a pilot study. *Pediatr Pulmonol*. 2023;58(2):577-584.
10. Granados A, Chan CL, Moheet A, Vigers T, Arbeláez AM, Larson Ode K. The impact of elexacaftor/tezacaftor/ivacaftor on body composition in a small cohort of youth with cystic fibrosis. *Pediatr Pulmonol*. 2023;58(6):1805-1811.
11. Cystic Fibrosis Foundation Patient Registry. Bethesda, Maryland; 2021.
12. Petersen MC, Begnel L, Wallendorf M, Litvin M. Effect of elexacaftor-tezacaftor-ivacaftor on body weight and metabolic parameters in adults with cystic fibrosis. *J Cyst Fibros*. 2022;21(2):265-271.
13. Carnovale V, Scialò F, Gelzo M, et al. Cystic fibrosis patients with F508del/minimal function genotype: laboratory and nutritional evaluations after one year of Elexacaftor/Tezacaftor/Ivacaftor treatment. *J Clin Med*. 2022;11(23):6900.
14. Talish M, Fukushima L, Wang J, Lee C, Rao A. 228 Hold the mayo on the elexacaftor/tezacaftor/ivacaftor special! A single-center experience. *J Cyst Fibros*. 2022;21(S2):S136.
15. Despotes KA, Ceppe AS, Donaldson SH. Alterations in lipids after initiation of highly effective modulators in people with cystic fibrosis. *J Cyst Fibros*. 2023;22:1024-1026.
16. Sommerburg O, Hämmerling S, Schneider SP, et al. CFTR modulator therapy with lumacaftor/ivacaftor alters plasma concentrations of lipid-soluble vitamins a and e in patients with cystic fibrosis. *Antioxidants*. 2021;10(3):483.
17. Gelzo M, Iacotucci P, Caputo M, et al. Lumacaftor/ivacaftor improves liver cholesterol metabolism but does not influence hypocholesterolemia in patients with cystic fibrosis. *J Cyst Fibros*. 2021;20(1):e1-e6.
18. Wright BA, Ketchen NK, Rasmussen LN, Bartels AR, Singh SB. Impact of elexacaftor/tezacaftor/ivacaftor on vitamin D absorption in cystic fibrosis patients. *Pediatr Pulmonol*. 2022;57(3):655-657.
19. Baumberger K, Busby C, Mascarella A, McKinzie C, Stephenson K, Kam C. 208 Fat-soluble vitamin level trends after elexacaftor/tezacaftor/ivacaftor therapy. *J Cyst Fibros*. 2022;21:S123.
20. Kuffel H, Hoppe J, Meier M, et al. 214: Improvement in fat-soluble vitamin levels following highly effective CFTR modulator use in children with CF. *J Cyst Fibros*. 2021;20:S105.
21. Proud D, Datta D, Ketchell I, et al. P160 "Seeing a trend"—increasing vitamin A levels on elexacaftor/tezacaftor/ivacaftor therapy. *J Cyst Fibros*. 2022;21:S110.
22. Francalanci M, Terlizzi V, Fevola C, et al. Nutritional status and circulating levels of fat-soluble vitamins in cystic fibrosis patients: a cohort study and evaluation of the effect of CFTR modulators. *Children*. 2023;10(2):252.
23. Schembri L, Warraich S, Bentley S, Carr S, Balfour-Lynn I. Impact of elexacaftor/tezacaftor/ivacaftor on fat-soluble vitamin levels in children with cystic fibrosis. *J Cyst Fibros*. 2023;22:843-846.
24. Southern KW, Barben J, Goldring S, et al. Raised intracranial pressure in three children with cystic fibrosis receiving Elexacaftor-Tezacaftor-Ivacaftor modulator therapy. *Am J Respir Crit Care Med*. 2023;208(1):103-105.
25. Hayes Jr, D, Warren PS, McCoy KS, Sheikh SI. Improvement of hepatic steatosis in cystic fibrosis with ivacaftor therapy. *J Pediatr Gastroenterol Nutr*. 2015;60(5):578-579.
26. Kutney K, Donnola SB, Flask CA, et al. Lumacaftor/ivacaftor therapy is associated with reduced hepatic steatosis in cystic fibrosis patients. *World J Hepatol*. 2019;11(12):761-772.
27. Tewkesbury DH, Athwal V, Bright-Thomas RJ, Jones AM, Barry PJ. Longitudinal effects of elexacaftor/tezacaftor/ivacaftor on liver tests at a large single adult cystic fibrosis centre. *Journal of Cystic Fibrosis*. 2023;22(2):256-262.
28. Nichols DP, Paynter AC, Heltshe SL, et al. Clinical effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in people with cystic fibrosis a clinical trial. *Am J Respir Crit Care Med*. 2022;205(5):529-539.
29. Schwarzenberg SJ, Vu PT, Skalland M, et al. Elexacaftor/tezacaftor/ivacaftor and gastrointestinal outcomes in cystic fibrosis: report of promise-GI. *Journal of Cystic Fibrosis*. 2023;22:282-289.
30. Davies J, Robertson S, Cooke J, Higgins M, Rosenfeld M. S112 Long-term safety and efficacy of ivacaftor in paediatric patients aged 2–5 years with cystic fibrosis and a CFTR gating mutation. *Thorax*. 2016;71(Suppl 3):A67.
31. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med*. 2015;373:1-12.
32. Graeber SY, Vitzthum C, Pallenberg ST, et al. Effects of Elexacaftor/Tezacaftor/Ivacaftor therapy on CFTR function in patients with cystic fibrosis and one or two F508del alleles. *Am J Respir Crit Care Med*. 2022;205(5):540-549.
33. Bartels A, Singh S, Pena T. Weight changes after initiating Elexacaftor/Tezacaftor/Ivacaftor in Patients with Cystic Fibrosis. 2022.

34. Ramsey BW, Davies J, Gerard McElvaney N, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365:1663-1672.
35. Gaschignard M, Beaufils F, Lussac-Sorton F, et al. Nutritional impact of CFTR modulators in children with cystic fibrosis. *Front Pediatr*. 2023;11:11.
36. Konstan MW, Mckone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med*. 2017;5(2):107-118.
37. Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). *Cochrane Database Syst Rev*. 2020;12:CD010966.
38. Tétard C, Mittaine M, Bui S, et al. Reduced intestinal inflammation with Lumacaftor/Ivacaftor in adolescents with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2020;71(6):778-781.
39. Crowley J, Croinin K, Mullane D, Chroinin MN. Partial restoration of pancreatic function in a child with cystic fibrosis. *J Cyst Fibros*. 2022;21:264. doi:10.1016/j.jcf.2021.08.032
40. Gelfond D, Heltshe S, Ma C, et al. Impact of CFTR modulation on intestinal pH, motility, and clinical outcomes in patients with cystic fibrosis and the G551D mutation. *Clin Transl Gastroenterol*. 2017;8(3):e81.
41. Hasan S, Khan MS, Lansang MC. The effect of cystic fibrosis transmembrane conductance regulator modulators on impaired glucose tolerance and cystic fibrosis related diabetes. *J Clin Transl Endocrinol*. 2022;29:100301.
42. Korten I, Kieninger E, Krueger L, et al. Short-term effects of Elexacaftor/Tezacaftor/Ivacaftor combination on glucose tolerance in young people with cystic fibrosis—an observational pilot study. *Front Pediatr*. 2022;10:10.
43. Kutney KA, Sandouk Z, Desimone M, Moheet A. Obesity in cystic fibrosis. *J Clin Transl Endocrinol*. 2021;26:100276.
44. Harindhanavudhi T, Wang Q, Dunitz J, Moran A, Moheet A. Prevalence and factors associated with overweight and obesity in adults with cystic fibrosis: a single-center analysis. *J Cyst Fibros*. 2020;19(1):139-145.
45. Holman RL, Blanc WA, Andersen D. Decreased aortic atherosclerosis in cystic fibrosis of the pancreas. *Pediatrics*. 1959;24:34-39.
46. Bonhoure A, Boudreau V, Litvin M, et al. Overweight, obesity and significant weight gain in adult patients with cystic fibrosis association with lung function and cardiometabolic risk factors. *Clin Nutr*. 2020;39(9):2910-2916.
47. Ronan G, Ronan NJ, Shortt C, et al. 128 The metabolic consequences of CFTR modulation with ivacaftor in a single adult cystic fibrosis centre cohort. *J Cyst Fibros*. 2015;14:S90.
48. Yuzyuk T, McDonald CM, Zuromski LM, et al. Improvement of lipid and lipoprotein profiles in children and adolescents with cystic fibrosis on CFTR modulator therapy. *J Cyst Fibros*. 2023;22:1027-1035.
49. Griese M, Costa S, Linnemann RW, et al. Safety and efficacy of elexacaftor/tezacaftor/ivacaftor for 24 weeks or longer in people with cystic fibrosis and one or more F508del alleles: interim results of an open-label phase 3 clinical trial. *Am J Respir Crit Care Med*. 2021;203(3):381-385.
50. Ayoub F, Trillo-Alvarez C, Morelli G, Lascano J. Risk factors for hepatic steatosis in adults with cystic fibrosis: similarities to non-alcoholic fatty liver disease. *World J Hepatol*. 2018;10(1):34-40.
51. Burgel P-R, Munck A, Durieu I, et al. Real-life safety and effectiveness of lumacaftor-ivacaftor in patients with cystic fibrosis. *Am J Respir Crit Care Med*. 2020;201(2):188-197. doi:10.1164/rccm.201906-1227oc
52. Hergenroeder G, Faino A, Bridges G, et al. 195 Impact of elexacaftor/tezacaftor/ivacaftor on serum markers of fat-soluble vitamin levels in people with cystic fibrosis. *J Cyst Fibros*. 2022;21:S114-S115.
53. Goncalves A, Roi S, Nowicki M, et al. Fat-soluble vitamin intestinal absorption: absorption sites in the intestine and interactions for absorption. *Food Chem*. 2015;172:155-160.
54. Sklan D, Donoghue S. Vitamin E response to high dietary vitamin A in the chick. *J Nutr*. 1982;112(4):759-765.
55. Miller MJ, Foroozan R. Papilledema and hypervitaminosis A after elexacaftor/tezacaftor/ivacaftor for cystic fibrosis. *Can J Ophthalmol*. 2022;57(1):e6-e10.
56. Wisniewski BL, Aylward SC, Jordan CO, Kopp BT, Paul GR. Hypervitaminosis A with fulminant secondary intracranial hypertension following personalized medicine-based Elexacaftor/Tezacaftor/Ivacaftor initiation in a preadolescent with cystic fibrosis. *J Cyst Fibros*. 2022;21(3):e217-e220.
57. Greer RM, Buntain HM, Lewindon PJ, et al. Vitamin A levels in patients with CF are influenced by the inflammatory response. *J Cyst Fibros*. 2004;3(3):143-149.
58. Woestenenk JW, Schulkes DA, Schipper HS, van der Ent CK, Houwen RHJ. Dietary intake and lipid profile in children and adolescents with cystic fibrosis. *J Cyst Fibros*. 2017;16(3):410-417.


**How to cite this article:** Patel T, McBennett K, Sankararaman S, et al. Impact of elexacaftor/tezacaftor/ivacaftor on lipid and fat-soluble vitamin levels and association with body mass index. *Pediatr Pulmonol*. 2024;59:734-742. doi:10.1002/ppul.26823