



## Applied nutritional investigation

## Impact of CFTR modulator therapy on body composition as assessed by thoracic computed tomography: A follow-up study



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## ABSTRACT

**Objective:** Treatment with cystic fibrosis transmembrane conductance regulator (CFTR) modulators in individuals with cystic fibrosis (CF) has brought a significant change in forced expiratory volume in 1 second (FEV<sub>1</sub>) and clinical parameters. However, it also results in weight gain. The aim of our study is to evaluate the effect of CFTR modulator treatment on body composition, measured by computed tomography (CT).

**Methods:** Adult subjects with CF under follow-up at La Princesa University Hospital were recruited. All of them were on elxacaftor–tezacaftor–ivacaftor (ELX/TEZ/IVA) treatment. Body composition analysis was conducted using CT scans and an open-source software. The results were then compared with bioimpedance estimations, as well as other clinical and spirometry data.

**Results:** Our sample consisted of 26 adult subjects. The fat mass compartments on CT scans correlated with similar compartments on bioimpedance, and normal-density muscle mass exhibited a strong correlation with phase angle. Higher levels of very low-density muscle prior to treatment were associated with lower final FEV<sub>1</sub> and less improvement in FEV<sub>1</sub> after therapy. We observed an increase in total body area ( $P < 0.001$ ), driven by increases in total fat mass ( $P < 0.001$ ), subcutaneous fat ( $P < 0.001$ ), visceral fat ( $P = 0.002$ ), and intermuscular fat ( $P = 0.022$ ). The only muscle compartment that showed an increase after treatment was very low-density muscle ( $P = 0.032$ ).

**Conclusions:** CT scans represent an opportunity to assess body composition on CF. Combination treatment with CFTR modulators, leads to an improvement in FEV<sub>1</sub> and to an increase in body mass in all compartments primarily at the expense of fat mass.

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## Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes the CFTR protein, resulting in alterations at the level of epithelial surfaces especially in the gastrointestinal and respiratory tracts. Malnutrition in CF is related to exocrine pancreatic insufficiency, leading to

malabsorption of carbohydrates, fats, and fat-soluble vitamins. It is also secondary to increased energy expenditure due to heightened respiratory effort, chronic inflammation, and intercurrent respiratory infections; this energy expenditure is primarily an issue in patients with severely depressed forced expiratory volume in 1 second (FEV<sub>1</sub>) and less so in those with higher levels of FEV<sub>1</sub> [1,2].

It is well known that adult patients with CF can exhibit lower body mass index (BMI), lower fat-free mass, and reduced musculo-skeletal mass compared to the general population [2]. Additionally, there are studies demonstrating that relying solely on BMI as a parameter for malnutrition in CF patients results in underdiagnosis of patients with decreased fat-free mass and sarcopenia [2–4]. Hence, clinical guidelines recommend that body composition measurement techniques such as bioimpedance (BIA) and dual-energy X-ray absorptiometry (DXA) should be included in the routine

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assessment of this population. Some measurements of body composition such as excess fat and a decrease in musculoskeletal mass and in bone mineral density measured by BIA and DXA have all been associated with poorer lung function and a higher risk of exacerbation [2–7].

Over the past decade, targeted therapy with CFTR modulators in CF has shown to cause significant improvement in clinical parameters, such as an increase in FEV<sub>1</sub> and a reduction in exacerbations in patients with at least one Phe508del CFTR mutation, with an acceptable safety profile [8,9]. Currently, several drugs with different mechanisms of action that modulate CFTR protein defects are available, some of which are used in combination, such as elexacaftor–tezacaftor–ivacaftor (ELX/TEZ/IVA) [8]. They have demonstrated a capacity to increase BMI and fat mass as measured by BIA [10].

The use of abdominal computed tomography (CT) for the assessment of body composition in various medical conditions is gaining prominence, especially in oncology, given its correlation with clinical and prognostic variables [11,12]. The advantage of CT over BIA lies in its greater sensitivity and in its ability to assess various compartments of muscle mass types [13,14]. Furthermore, the use of CT scans in follow-up represents an opportunity to recover body composition in rare disease cohorts as previously published [15]. While the measurement of these parameters in abdominal imaging studies is validated and readily available with open-source programs like ImageJ [16,17], the assessment of body composition in thoracic CT has been validated more recently in advanced chronic lung disease, lung cancer, and COVID-19 [18–20]. To our knowledge, the only study evaluating body composition by thoracic CT in CF was conducted in lung transplant patients [21], but there are still no available studies assessing CFTR modulator treatment.

In this context, the aim of this study is to assess the response to CFTR modulator treatment in terms of body composition as measured by thoracic CT, and with anthropometric measurements, as well as determining its correlation with clinical outcomes and body composition by BIA.

## Methods

### Population

CF patients were recruited from La Princesa University Hospital, where they were under the care of the Adult Cystic Fibrosis Unit (Respiratory Medicine Department) and the Endocrinology and Nutrition Department. All patients were deemed eligible to initiate treatment with ELX/TEZ/IVA and were subsequently followed prospectively from the initiation of the treatment. The subjects were selected from a prospective cohort already reported by our group in which body composition was measured by BIA [22].

The inclusion criteria for this study were as follows: 1) men and women >18 y of age, 2) diagnosis of CF with at least one copy of the F508del CFTR gene, 3) patients who were scheduled to receive ELX/TEZ/IVA treatment, 4) patients capable of providing informed consent to participate in the study, 5) a negative pregnancy test was required for women of childbearing age, along with the use of contraceptive methods, and 6) the availability of CT images clearly depicting the T12 level before commencing ELX/TEZ/IVA treatment and after a minimum of 6 mo of treatment.

The exclusion criteria were: 1) patients on treatment with other combination regimens, 2) patients who had undergone lung transplantation, 3) pregnancy and lactation, 4) inability to provide informed consent or comply with study conditions, and 5) patients

with acute pulmonary exacerbations and no IV glucocorticoids or IV antibiotics for 6 wk preceding.

Ethics approval was granted by the Internal Ethics Committee of our institution, La Princesa University Hospital, and the study was conducted in accordance with the Declaration of Helsinki. The internal ethics committee's code was 5282.

### BIA and clinical data

Biochemical and fundamental anthropometric data were extracted from electronic health records. Body composition was assessed using BIA before the initiation of ELX/TEZ/IVA combination treatment, at 3 mo and at 6 mo into the treatment. For precise BIA measurements, subjects fasted for a minimum of 4 h, hydrated with a standardized amount of water 30 min before, rested for 10 min, wore minimal clothing, emptied their bladder, maintained consistent measurement timing, and ensured clean electrode contact. Accurate height and weight measurements were taken before placing conductive electrodes on the right hand and foot. BIA measurements were then collected using an InBody 770 (InBody, Inc.) following the manufacturer's guidelines. In addition, a spirometry was conducted to assess the respiratory function (FEV<sub>1</sub>) before the initiation of ELX/TEZ/IVA combination treatment, at 3 mo and at 6 mo into the treatment.

In the context of routine clinical practice, a 75-g oral glucose tolerance test was conducted following an overnight fast. Blood samples were obtained through an indwelling catheter at 0, 30, 60, 90, and 120 min to analyze glucose and insulin levels. An integrated analysis of oral glucose tolerance test plasma insulin levels was performed using the trapezoidal rule to assess the area under the curve, following a methodology employed in previous studies [23,24]. Plasma insulin levels were assayed at the UM Fairview Laboratory using a double-antibody method with radioimmunoassay (Immulite 2000, Siemens, Erlangen, Germany). Plasma glucose levels were measured using the glucose oxidase method (Vitros, Ortho-Clinical Diagnostics, Raritan, NJ).

### CT image analysis

Body composition was evaluated by analyzing CT images acquired as part of routine clinical practice before commencing the ELX/TEZ/IVA combination regimen and subsequently following a minimum of 6 mo of treatment. An experienced radiologist selected high-quality CT images of patients at the T12 level. Images with high contrast, absence of artifacts, and visible surgical interventions were excluded. It was confirmed that there were no medications that could interfere with the CT scan image prior to the procedure. CT image processing was performed using NIH ImageJ version 2.3.0 [16], following the protocol available in [Supplementary Material S1](#). Subsequently, area subtraction was executed using R version 4.0.3 [25].

The following body composition measurements were obtained: total body area, visceral fat tissue (VFA; HU = −190, −30), subcutaneous fat area (SFA; HU = −190, −30), intermuscular fat area (IMFA; HU = −190, −30), total fat area (TFA; HU = −190, −30), very low-density muscle area (VLDMA; HU = −29, −1), low-density muscle area (LDMA; HU = 0, 34), normal-density muscle area (NDMA; HU = 35, 100), high-density muscle area (HDMA; HU = 101, 150), very high-density muscle area (VHDMA; HU = 151, 199), and total muscle area (TMA; HU = −29, 199) [26]. After the measurement step, correlation between both analyses was tested using the Spearman's rho test. Subsequently, the data were normalized by dividing them by the square of patients' height in meters. Finally, the mean of both measurements was obtained.

## Statistical analysis

Quantitative variables were expressed as median and range or mean and standard deviation (SD), depending on Gaussian distribution, while qualitative variables were presented as counts and percentages. Normality of variables was assessed using the Shapiro–Wilk test. Student's paired *t* test was applied to analyze two related samples, while its nonparametric counterpart (Wilcoxon test) was used if the sample distribution was non-normal. A correlation matrix was constructed to identify associations between clinical parameters, BIA estimations, and body composition markers over time (positive rho values indicated variation in the same direction, while negative rho values indicated variation in opposite directions).

Subsequently, the best predictive multiple linear regression model for the variable FEV<sub>1</sub> after ELX/TEZ/IVA treatment was selected from all possible equations between clinical variables (gender, BMI, diabetes mellitus, prior treatment with CFTR modulators and body composition variables at T12), based on Mallows' Cp. Once the best model was chosen, it was adjusted for potential interactions between variables. Statistically significant interactions were assessed to construct the final model.

Lastly, two-way ANOVA models were used to assess the change in FEV<sub>1</sub> before and after ELX/TEZ/IVA treatment, while controlling for age, gender, prior treatment with CFTR modulators, and body composition variables at T12, as well as their interaction terms.

For all statistical analyses, STATA 17.0 BE-Basic Edition (Lakeway Drive, College Station, TX), Graphpad Prism version 9 (Boston, MA), and R version 4.0.3 were employed. A *P*-value <0.05 was considered statistically significant.

## Results

### Sample characteristics

The final sample consisted of 26 CF patients (Table 1). The median age was 28.8 y (±11.2 y), 34.6% of the patients were female. All patients carried the F508del gene mutation, with 34.6% being homozygous and the remaining heterozygous. All patients were receiving enzyme replacement therapy for exocrine

**Table 1**  
Sample characteristics

| Variable                                     | Median pre-ELX/TEZ/IVA                                       |
|--|--|
| n  | 26   |
| Sex: men                                     | 17 (65.4%)   |
| Age (y)                                      | 28.8 (24.1–35.3)   |
| Previous treatment CFTR                      | 10 (38.5%)   |
|  | tezacaftor/ivacaftor 100/150 mg 1 (3.9%)                     |
|  | ivacaftor 150 mg 1 (3.9%)                                    |
|  | tezacaftor/ivacaftor 100/150 mg + ivacaftor 150 mg 8 (30.8%) |
| Homozygous F508                              | 9 (34.6%)  |
| FEV <sub>1</sub>                             | 72.6 ± 17.2  |
| BMI (kg/m <sup>2</sup> )                     | 22.3 ± 2.9   |
| Time between first and last CT scan (y)      | 2.0 (1.5–2.5)  |
| Time from first CT to start of treatment (y) | 1.0 (0.5–1.5)  |
| Time from start of treatment to last CT (y)  | 1.0 (0.9–1.0)  |

BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; CT, computed tomography; FEV<sub>1</sub>, forced expiratory volume in 1 second.

Data are expressed as number and percentage, median and p25–75 interquartile range or mean ± standard deviation.

pancreatic insufficiency. Additionally, 38.5% of the patients had previously received treatment with a different CFTR modulator. Specifically, 3.9% had received tezacaftor/ivacaftor 100/150 mg, 3.9% had received ivacaftor 150 mg, and 30.8% were on a regimen of tezacaftor/ivacaftor 100/150 mg + ivacaftor 150 mg/d.

The mean FEV<sub>1</sub> before initiating treatment was 71.9% ± 17.2%. BMI prior to treatment initiation was 22.5 (p25–75 20.9–23.8 kg/m<sup>2</sup>).

*Body composition measured by CT correlates with parameters measured by BIA and clinical variables in CF.*

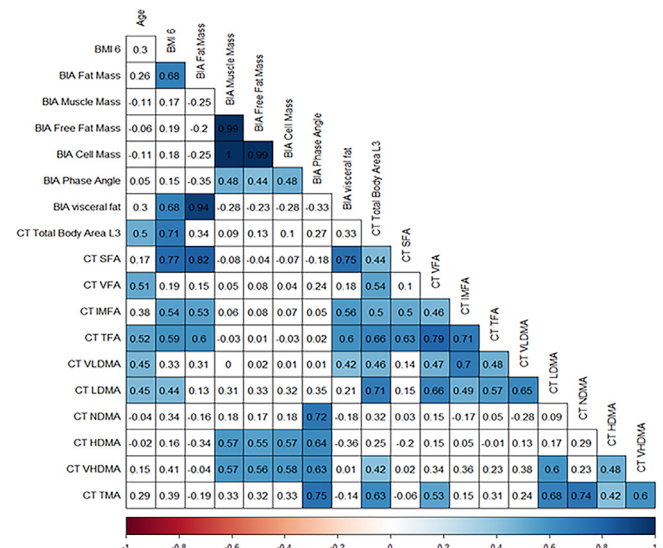
A Spearman correlation matrix was performed to assess associations between clinical variables, BIA and CT body composition (Fig. 1A, *P* < 0.05).

Age positively correlated with IMFA, VLDMA, and LDMA in CT scans. These CT findings aligned with BIA estimations. Notably, there were strong positive correlations between TFM in CT and BIA, as well as between VFA in BIA and SFA on CT. However, no significant correlations were found between FMA in BIA and VFA on CT.

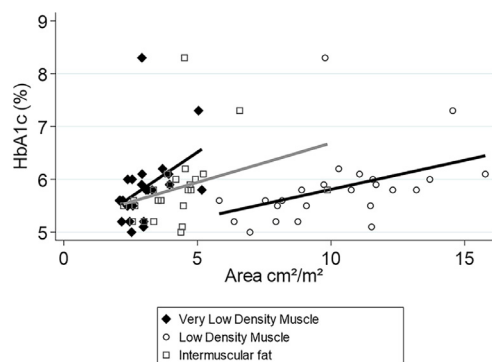
MM measured in BIA correlated with VHDMA on CT, but not with TMA, NMDA, LDMA, and VLDMA.

There was a positive correlation between the phase angle measured by BIA and muscle compartments on CT: TMA, VHDMA, HDMA, and NDMA. However, there was no correlation with lower density muscle compartments (LDMA and VLDMA).

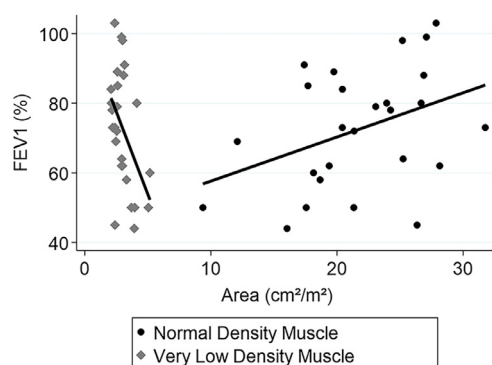
Interestingly, glycated hemoglobin (HbA1c) was positively associated with IMFA (Spearman's rho = 0.571, *P* = 0.004), VLDMA (Spearman's rho = 0.469, *P* = 0.021), and LDMA (Spearman's rho = 0.605, *P* = 0.002; Fig. 1B). Pretreatment FEV<sub>1</sub> was inversely associated with VLMA (Spearman's rho = −0.5081, *P* = 0.02) and positively associated with NMDA (Spearman's rho = 0.523, *P* = 0.045; Fig. 1C).



**Fig. 1A.** Correlation matrix of body composition measured by CT and parameters measured by BIA. Values represent the Spearman's rank correlation coefficient, rho ( $\rho$ ) between body composition measured by CT and parameters measured by BIA both assessed within a period lower than 3 mo. Significant negative correlations are shown in orange and significant positive correlations in blue. Color intensity increases with the magnitude of correlation. White colored cells indicate a nonsignificant correlation. BMI, body mass index; HDMA, high-density muscle area; IMFA, intermuscular fat area; LDMA, low-density muscle area; NMDA, normal-density muscle area; SFA, subcutaneous fat area; TBA, total body area; TFA, total fat area; TMA, total muscle area; VFA, visceral fat area; VHDMA, very high-density muscle area; VLDMA, very low-density muscle area.



**Fig. 1B.** Association between HbA1c and very low-density muscle area, low-density muscle area and intermuscular fat. HbA1c was positively correlated with VLMDA ( $\rho = 0.469$ ,  $P = 0.021$ ). HbA1c, glycated hemoglobin.



**Fig. 1C.** Association between pre-ELX/TEZ/IVA FEV1 and very low-density muscle and normal-density muscle. Very low-density muscle exhibits a negative association with FEV1 ( $\rho = -0.5081$ ,  $P = 0.02$ ), whereas normal-density muscle shows a positive association with FEV1 ( $\rho = 0.523$ ,  $P = 0.045$ ). FEV1, forced expiratory volume in 1 second.

The remaining compartments studied did not exhibit statistically significant associations with clinical variables. The nonsignificant  $\rho$  values are displayed in white background in [Figure 1A](#). VHDMA results were notably low, making precise interpretation challenging.

The area under the curve of insulin levels demonstrated a moderate association with Subcutaneous fat  $\text{cm}^2/\text{m}^2$  (Spearman's  $\rho$ : 0.474,  $P = 0.047$ ). The remaining body composition variables did not exhibit any significant association with insulin levels. Additionally, fasting triglyceride levels were correlated with subcutaneous fat  $\text{cm}^2/\text{m}^2$  (Spearman's  $\rho$ : 0.5845,  $P = 0.046$ ) and total fat  $\text{cm}^2/\text{m}^2$  (Spearman's  $\rho$ : 0.6479,  $P = 0.023$ ). No association was observed between other body composition compartments and triglyceride levels. There was no association between baseline cholesterol and body composition compartments. All these lipid panel and insulinemia results are presented in the [Supplementary Material](#).

#### ELX/TEZ/IVA treatment exerts an impact on body composition measured by CT

A comparative statistical analysis was performed using data acquired from T12 vertebral segmentation a median of 1 y (0.5–1.5) before the commencement of treatment and after a median of 1 y (0.9–1.0) from the initiation of treatment to compare with baseline data. In general, an increase in body mass was observed, particularly in the adipose tissue compartment, when comparing the time periods before and after ELX/TEZ/IVA

treatment. [Figure 2](#) illustrates an example of a T12 image analysis for the same patient before and after treatment using the Image J program.

A significant increase was observed in TBA from 207.9 (195.7–218.9) to 217.7 (203.1–235.7) ( $P < 0.001$ ), TFA from 27.9  $\text{cm}^2/\text{m}^2$  (19.8–39.3) to 35.7  $\text{cm}^2/\text{m}^2$  (26.6–52.8) ( $P < 0.001$ ), SFA from 13.6  $\text{cm}^2/\text{m}^2$  (6.5–17.5) to 18.5  $\text{cm}^2/\text{m}^2$  (11.3–20.9) ( $P < 0.001$ ), VFA from 13.6  $\text{cm}^2/\text{m}^2$  (6.8–18.2) to 19.6  $\text{cm}^2/\text{m}^2$  (7.9–27.5) ( $P = 0.002$ ), and IMFA from 4.3  $\text{cm}^2/\text{m}^2$  (3.4–4.7) to 5.0  $\text{cm}^2/\text{m}^2$  (3.7–5.6) ( $P = 0.022$ ). In contrast, the only muscle compartment that showed an increase was VLMDA from 2.9  $\text{cm}^2/\text{m}^2$  (2.4–3.3) to 3.0  $\text{cm}^2/\text{m}^2$  (2.7–3.8) ( $P = 0.032$ ). All other muscle compartments remained unchanged despite ELX/TEZ/IVA treatment and are presented in [Table 2](#). The impact of ELX/TEZ/IVA treatment on the fat and muscle compartments is graphically depicted in [Figure 3](#).

#### Impact of baseline body composition measured by CT on FEV<sub>1</sub> after ELX/TEZ/IVA treatment

The effect of baseline body composition, as measured by CT, on FEV<sub>1</sub> after ELX/TEZ/IVA treatment was evaluated through an exhaustive analysis employing all possible multiple linear regression methods [\[27\]](#). The independent variables considered included gender, age, BMI, prior treatment with CFTR modulators, as well as TFA, SFA, IMFA, TMA, LDMA, VLMDA, HDMA, and VHMDA data obtained from the CT scan performed before the initiation of ELX/TEZ/IVA treatment.

A total of 32 767 hierarchical submodels were generated. The optimal model, which included BMI, prior CFTR modulator treatment, SFA, and VLMDA, produced a Mallows' Cp of 3.39 and an adjusted R-squared of 0.457. Within this model, prior CFTR modulator treatment revealed a  $\beta$  of  $-12.83$ , 95% CI ( $-25.60$  to  $-0.063$ ),  $P = 0.049$ ; subcutaneous fat fraction showed a  $\beta$  of  $-1.00$ , 95% CI ( $-1.79$  to  $-0.21$ ),  $P = 0.016$ , and very low-density muscle fraction displayed a  $\beta$  of  $-10.58$ , 95% CI ( $-17.76$  to  $-3.40$ ),  $P = 0.006$  ([Fig. 4](#)), all identified as risk factors associated with reduced FEV<sub>1</sub> after 6 mo of ELX/TEZ/IVA treatment. Notably, BMI exhibited a trend toward a protective effect on final FEV<sub>1</sub>, but it did not reach statistical significance ( $\beta = 3.73$ ,  $P = 0.058$ , [Fig. 4](#)). No statistically significant interactions between variables were observed in the final model.

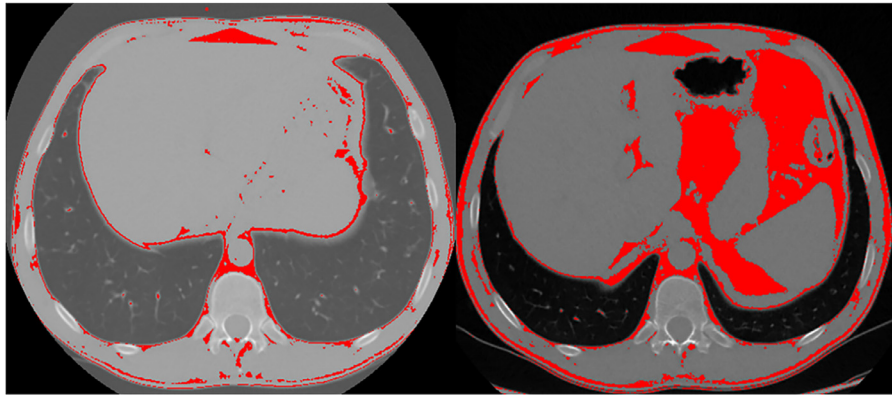
Finally, to examine the differences between FEV<sub>1</sub> before and after ELX/TEZ/IVA treatment, a two-way ANOVA model was used, controlled for age, gender, prior CFTR modulator therapy, VLMDA, and their interactions with other first-order variables. The results revealed that the differences in FEV<sub>1</sub> before and after treatment were statistically significant (Roy's largest root 1.17,  $F = 2.85$ ,  $P = 0.0370$ ), independently of the control variables. Furthermore, patients with VLMDA had lower initial and final FEV<sub>1</sub> following pharmacological treatment ( $P = 0.022$ ). However, it is noteworthy that ELX/TEZ/IVA treatment improved FEV<sub>1</sub> in CF patients, irrespective of alterations in VLMDA (interaction  $P$ -value  $> 0.05$ ).

#### Discussion

Scientific evidence suggests that CFTR modulator therapy yields favorable outcomes in CF patients, including increased FEV<sub>1</sub> and reduced exacerbations [\[8,9\]](#). However, these benefits are often associated with an increase in BMI and other changes in body composition that could potentially give rise to future cardiovascular events [\[1,28\]](#).

In our study, in line with previous research, we observed an increase in FEV<sub>1</sub> in patients treated with ELX/TEZ/IVA, along with a





**Fig. 2.** Image analysis of CT T12 before and after ELX/TEZ/IVA treatment. An increase in attenuation is observed in visceral and subcutaneous adipose tissue (red color) following ELX/TEZ/IVA treatment.

median increase in BMI of 1 kg/m<sup>2</sup> over the course of 6 mo. Traditional nutritional management of CF has focused on encouraging a higher intake of high-calorie foods rich in fats and carbohydrates [29,30]. This classical approach has led to increased rates of overweight, obesity, and fat mass gain in CF patients treated with ELX/TEZ/IVA leading to a new set of recommendations centered around reducing energy requirements [10,29,31,32].

Moreover, modern nutritional assessment, in accordance with these new guidelines, extends beyond classical anthropometrics [33]. It emphasizes monitoring the muscle and body fat compartments, making it essential for CF patients. Techniques like BIA have gained popularity in assessing body composition. Studies that measure body composition and bone mineral density through DXA in patients treated with ELX/TEZ/IVA have reported weight gain, particularly in terms of fat-free mass and fat mass, alongside an increase in bone mineral density [34]. This weight gain, primarily in fat, has been confirmed in long-term 24-mo follow-ups, highlighting the importance of evaluating body composition in the medium and long term [35]. However, to our knowledge, this is the first study that has used thoracic CT to evaluate body composition in CF patients with the F508del mutation before and after ELX/TEZ/IVA.

CT has been found to be superior to other body composition techniques such as BIA in detecting lean body mass and fat mass [36,37]. The use of thoracic CT for assessing body composition is comparable to abdominal CT and has been validated for this purpose [18–21]. Our data suggest a correlation between body composition as measured by CT and BIA, in line with findings from

other authors. However, there is generally less correlation in the muscular compartment [38–41]. Notably, there is a strong correlation in our cohort between the phase angle in BIA, a well-known prognostic factor in various pathologies including CF [42–45], and TMA as measured by CT, which is consistent with the study by Viertel, et al. [46].

However, the advantage of CT over BIA lies not only in its greater sensitivity but also in its ability to assess various compartments of muscle mass types (VLDMA, LMDA, NMDA, and VDMA), which is significant for prognosis [13,14]. Specifically, we observed in this study an increase in SFA, VFA, IMFA, and TFA. The increase in fat mass aligns with findings in other studies using BIA [4,47]. Significantly, the only muscle compartment that demonstrated changes was VLDMA, which, along with IMFA, has been proposed as a surrogate for myosteatosis [48]. Myosteatosis significantly impacts metabolism and is associated with impaired insulin sensitivity, thereby contributing to metabolic dysfunction [49]. Similarly, our data showed that VLDMA was associated with age, poorer pretreatment FEV<sub>1</sub>, and higher HbA1c levels, while NMDA appeared to be associated with better pretreatment respiratory function. Multivariate analyses unveiled that pretreatment VLDMA was an independent risk factor for diminished FEV<sub>1</sub>, although the medication's impact remained beneficial across all cases, regardless of body composition.

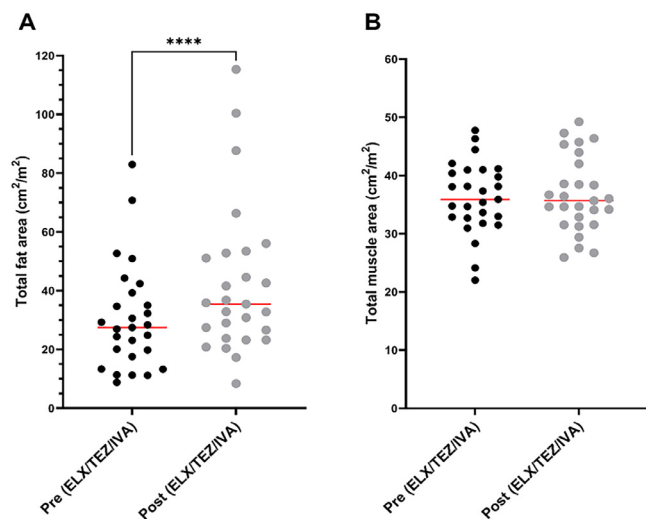
Negative impact of VLDM has been observed in other settings, including an increased risk of osteoporosis in community-dwelling elderly population [50], poorer physical condition in rheumatoid arthritis [51], and even a higher risk of mortality in patients with

**Table 2**  
Body composition before and after ELX/TEZ/IVA treatment

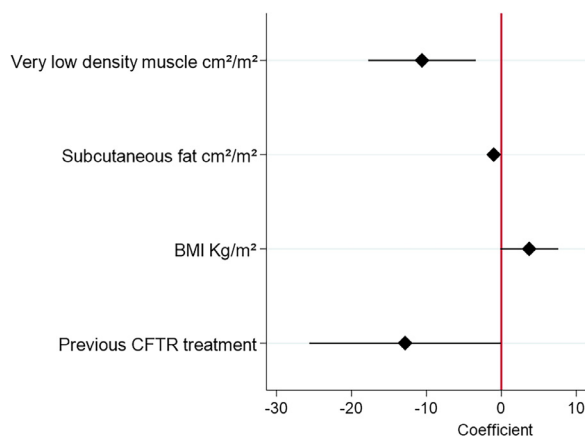
| Variable  | pre-ELX/TEZ/IVA     | post-ELX/TEZ/IVA    | P-value |
|---|---------------------|---------------------|---------|
| BMI (kg/m <sup>2</sup> )                                    | 22.5 (20.9–23.8)    | 23.3 (21.8–24.3)    | 0.002   |
| Total area (cm <sup>2</sup> /m <sup>2</sup> )               | 207.9 (195.7–218.9) | 217.7 (203.1–235.7) | <0.001  |
| Subcutaneous fat (cm <sup>2</sup> /m <sup>2</sup> )         | 13.6 (6.5–17.5)     | 18.5 (11.3–20.9)    | <0.001  |
| Visceral fat (cm <sup>2</sup> /m <sup>2</sup> )             | 13.6 (6.8–18.2)     | 19.9 (7.9–27.5)     | 0.002   |
| Intermuscular fat (cm <sup>2</sup> /m <sup>2</sup> )        | 4.3 (3.4–4.7)       | 5.0 (3.7–5.6)       | 0.022   |
| Total fat (cm <sup>2</sup> /m <sup>2</sup> )                | 27.9 (19.8–39.3)    | 35.7 (26.6–52.8)    | <0.001  |
| Very low-density muscle (cm <sup>2</sup> /m <sup>2</sup> )  | 2.9 (2.4–3.3)       | 3.0 (2.7–3.8)       | 0.032   |
| Low-density muscle (cm <sup>2</sup> /m <sup>2</sup> )       | 10.0 (8.0–11.7)     | 10.7 (8.9–12.4)     | 0.064   |
| Normal-density muscle (cm <sup>2</sup> /m <sup>2</sup> )    | 21.3 (18.1–26.3)    | 20.2 (16.5–23.9)    | 0.430   |
| High-density muscle (cm <sup>2</sup> /m <sup>2</sup> )      | 1.2 (0.9–1.6)       | 1.3 (1.0–2.0)       | 0.194   |
| Very high-density muscle (cm <sup>2</sup> /m <sup>2</sup> ) | 0.4 (0.3–0.5)       | 0.4 (0.3–0.5)       | 0.831   |
| Total muscle (cm <sup>2</sup> /m <sup>2</sup> )             | 36.6 (32.9–40.9)    | 35.9 (32.9–42.0)    | 0.539   |

BMI, body mass index; HDMA, high-density muscle area; IMFA, intermuscular fat area; LDMA, low-density muscle area; NMDA, normal-density muscle area; SFA, subcutaneous fat area; TBA, total body area; TFA, total fat area; TMA, total muscle area; VFA, visceral fat area; VHDMA, very high-density muscle area; VLDMA, very low-density muscle area

Values represent median (p25–p75). P-value from Wilcoxon paired test



**Fig. 3.** Change in total fat mass (A) and total muscle mass (B) after ELX/TEZ/IVA treatment. After ELX/TEZ/IVA treatment, an increase in total fat mass (A) was observed, from 27.9 (19.8–39.3) cm<sup>2</sup>/m<sup>2</sup> to 35.7 (26.6–52.8) cm<sup>2</sup>/m<sup>2</sup> ( $P < 0.001$ ), while total muscle mass (B) showed no significant changes ( $P = 0.539$ ).  $P$ -value from Wilcoxon paired test. Median is plotted with a red line in both graphics.



**Fig. 4.** Forest plot representing the coefficients of the selected optimal model. Prisms represent beta coefficients, and lines represent 95% confidence intervals. BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator.

Chronic Obstructive Pulmonary Disease [52]. These findings remark the significance of muscle quality, in addition to quantity, in CF patients. Considering the improvement in exercise capacity observed in patients treated with CFTR modulators and the benefits of physical activity on anthropometric parameters, implementing physical exercise programs tailored to the individual needs of patients under ELX/TEZ/IVA treatment may be a valuable approach to increase muscle quality on these patients [53]. Notably, current clinical guidelines may not sufficiently address this aspect, emphasizing the need for expert nutritional and rehabilitation care, including the use of body composition measurement techniques, for patients receiving CFTR modulator therapy. Considering our results, we believe that the approach should focus on promoting physical activity and individualized macro and micronutrient intake for patients under ELX/TEZ/IVA treatment, considering the potential benefits of enhanced exercise capacity and body composition on lung function [54]. CFTR modulator therapy has the potential to extend the life expectancy of CF patients, and our patients experienced benefits despite alterations in body

composition. Nonetheless, it is imperative to recognize that the presence of concurrent chronic conditions, such as hypertension, diabetes, or obesity-related ailments, may introduce complexities and influence the long-term prognosis of these patients, particularly if body weight gain remains uncontrolled.

This study has several limitations. First, the small sample size may hinder the detection of potential differences that were not observed. Additionally, most of the patients in the study had normal weight and were not undernourished before therapy, so the results obtained may not be generalizable to CF populations with malnutrition. Moreover, dietary surveys and physical activity assessments were not conducted, which would have allowed for the direct examination of treatment effects when adjusted for these covariates. Finally, the timing of CT scans in women was not normalized according to the menstrual cycle, which could introduce biases, as measurements derived from thoracic CT scans may be influenced by the female menstrual cycle [55]. Future multicenter studies will be indispensable to assess the implementation of hygienic-dietary interventions aimed at enhancing the nutritional quality of the diet and the incorporation of physical activity programs to improve these variables. These measures aim to reduce excessive fat and monitor cardiovascular complications in individuals with CF undergoing CFTR modulator treatment.

In summary, the triple combination ELX/TEZ/IVA in patients with CF with the F508del mutation leads to weight and BMI increase, primarily driven by changes in the fat compartment as observed in thoracic CT scans, without producing improvements in the muscle compartment. We recommend not only using BIA measurements but also thoracic CT scan as an easy technique, readily available that can provide additional useful information in these patients. Multidisciplinary treatment is pivotal in managing CF, and strategic approaches that include dietary counseling and exercise prescription are essential for improving body composition and nutritional status to prevent long-term complications.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRedit authorship contribution statement

**Víctor Navas-Moreno:** Writing – review & editing, Writing – original draft, Resources, Project administration. **Fernando Sebastian-Valles:** Writing – review & editing, Visualization, Methodology, Formal analysis, Conceptualization. **Víctor Rodríguez-Laval:** Software, Resources, Conceptualization. **Carolina Knott-Torcal:** Writing – review & editing, Investigation. **Mónica Marazuela:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Nuria Sánchez de la Blanca:** Validation, Software. **Jose Alfonso Arranz Martín:** Project administration, Conceptualization. **Rosa María Girón:** Resources, Investigation, Conceptualization. **Miguel Antonio Sampedro-Núñez:** Writing – review & editing, Visualization, Validation, Supervision, Data curation.

## Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

All patients gave written informed consent and ethics approval was granted by the Hospital de La Princesa committee's (code was 5282).

## Consent for publication

Not applicable.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.nut.2024.112425](https://doi.org/10.1016/j.nut.2024.112425).

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