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Original Article

Physical activity levels in cystic fibrosis patients before and after triple modulator therapy: A single-center retrospective pilot study

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Abstract
Background Regular physical activity (PA) and an active lifestyle are associated with health benefits and increased life expectancy in patients with cystic fibrosis (CF). The introduction of new modulator therapy may influence PA levels by improving patient's functional health status. This study aimed to investigate whether Elexacaftor/Tezacaftor/Ivacaftor (ETI), had an impact on daily PA levels in patients with CF. Methods 18 patients (7 males, 11 females) participated in the study. PA level and lung function data were measured objectively, with accelerometry (for 7 consecutive days) and spirometry respectively at: baseline (T0), 1 month after starting ETI (T1) and between 3 and 6 months post-ETI administration (T3+). Results The mean relative forced expiratory volume in 1 second ($FEV_{1\%pred}$) significantly increased from T0 (68.4±18.1) to T1 (78.2±21.2, $p<0.05$). The mean relative forced vital capacity ($FVC_{\%pred}$) significantly increased from T0 (88.2±14.9) to T1 (94.0±13.9, $p<0.05$). PA parameters at T0 were: 6460.2± 2068.8 steps/day and 46.8±35.0 min/day for moderate to vigorous PA (MVPA) time. None of the parameters presented statistical differences throughout all the measurements compared to T0. The mean steps/day were 6253.8±2253.5 at T1 and 7036.0±3177.0 at T3+. The mean MVPA time (min) were 36.2±15.6 at T1 and 48.9±24.4 at T3+. Conclusions Despite the observed improvement in lung function, daily PA levels in patients with CF do not show a significant enhancement after ETI treatment. This underscores the importance of ongoing support and encouragement for physical activity in patients with CF, even when undergoing modulator treatment. Implementing PA promotional programs remains crucial to fostering an active lifestyle in individuals with CF.
Keywords: health, mucoviscidosis, well-being, lifestyle, Elexacaftor/Tezacaftor/Ivacaftor

Introduction

Cystic fibrosis (CF) is a disease affecting at least 100 000 people around the world (Shteinberg et al., 2021). This monogenic disease is a multisystem autosomal recessive disorder caused by variants in the gene for cystic fibrosis transmembrane conductance regulator (CFTR) protein, a cell-surface localized chloride channel that regulates absorption and secretion of salt and water across epithelia (Bell et al., 2020). It is the most prevalent life-threatening autosomal recessive disorder among Caucasian populations (Gallati, 2013). CF primarily affects the respiratory, gastrointestinal, glandular, and reproductive systems (Lopes-Pacheco, 2020).
The treatment for CF patients has traditionally focused on managing and preventing symptoms associated with CFTR dysfunction, notably recurrent respiratory infections and pancreatic exocrine insufficiency (Elborn, 2016). Physical activity (PA) has been shown to enhance exercise capacity, slow the decline in lung function, and improve both quality of life and life expectancy in CF patients (Hulzebos et al., 2013). Consequently, regular PA is recommended in clinical practice and is often incorporated into treatment regimens (Dwyer et al., 2011). Despite the recognized benefits of PA, research suggests that CF patients encounter challenges in adopting physically active lifestyles (Cox & Holland, 2019). Current guidelines specific to CF patients recommend a minimum of 150 minutes per week, ideally 300 minutes per week, of moderate to vigorous PA (MVPA) (Swisher et al., 2015). The World Health Organization (WHO) similarly advises meeting the target of 150 minutes of MVPA distributed throughout the week, such as 30 minutes of MVPA, five times per week (World Health Organization, 2010).

While some studies, including those by Ward et al. (Ward et al., 2013) and Dillenhoefer et al. (Dillenhoefer et al., 2022), have reported that CF patients meet minimal PA recommendations, others indicate lower PA levels within the CF population (Cox & Holland, 2019). This variation in reported PA levels in the literature could be attributed to the methodology employed for assessing PA levels. Some studies have utilized questionnaires, which often subjectively measure the levels of PA in patients with CF, while accelerometers provide a more objective evaluation (Savi et al., 2013). Previous studies measuring PA with accelerometers in

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CF population reported values of 15 min/day of MVPA time (Troosters et al., 2009), 27 min/day of MPVA (Savi et al., 2013), 43 min/day of MVPA (Ward et al., 2013) and 103 min/day of MVPA (Dillenhoefer et al., 2022). Additionally, PA levels may be influenced by various facilitators or barriers, spanning individual, clinical, social, and environmental domains, as highlighted in recent literature (Cox & Holland, 2019; Denford et al., 2020). Changes in these factors over time could potentially impact the PA levels of CF patients. Changes in these factors over time could potentially impact the PA levels of CF patients.

In recent years, a novel class of therapies aimed at restoring CFTR protein function has emerged (Elborn, 2020; Paterson et al., 2020). This new therapy – the CFTR modulators – has led to significant improvements in pulmonary function, reduced respiratory infections, and enhanced nutrition (Edmondson et al., 2021). Such leap in the therapies have paved the way for the development of Elexacaftor-Tezacaftor-Ivacaftor (ETI), a new highly effective triple modulator treatment approved by the end of 2020. This treatment is addressed to patients who have at least one F508del mutation in the CFTR gene, which represents approximatively 90% of the CF population (FDA Approves New Breakthrough Therapy for Cystic Fibrosis, 2020). It has been proved to have beneficial effects not only in individuals with mild to moderate CF, but also in individuals with advanced pulmonary disease, including candidates for lung transplantation (Shteinberg & Taylor-Cousar, 2020).

However, while ETI has shown remarkable efficacy in improving pulmonary function and overall health outcomes, its impact on exercise capacity in CF patients remains debated. Burns et al. (Burns et al., 2022) found no significant improvement in exercise capacity among most CF patients following ETI treatment (VO_{2peak}: 37.7 $ml.min^{-1}.kg^{-1}$ pre-treatment and 34.5 $ml.min^{-1}.kg^{-1}$ post-treatment, P =0.07;. The authors state that the performance gains can only occur if matched by training and hypothesize that the lack of improvement may be due to a reduced PA level over the study period as a result of feeling better on ETI and also the SARSCoV2 pandemic. Nevertheless, this study did not assess the PA levels of the patients and could only hypothesize about the reasons without objective measurements. Conversely, a study by Causer et al., (Causer et al., 2022) observed for the first time improvements in lung function ($FEV_{1\%pred}$) and exercise capacity (VO_{2peak}) in 3 adolescents, following 6 weeks of treatment with ETI. The improvements in exercise capacity were greater in more severe CF lung disease and lower aerobic fitness baseline. However, it has to be considered that the sample size was small (n=3) and only 2 of them had their device-based PA data analyzed with one case increasing (+17%) and one case decreasing (-32%) the PA time. To date, there is no additional data available concerning the potential impact of ETI on PA levels. Furthermore, while other studies have demonstrated improvements in lung function post-ETI treatment (Hillen et al., 2022; Krivec et al., 2022; McGrath et al., 2022), they have not specifically examined the impact on daily PA levels.

Therefore, the objective of this study is to investigate the effects of ETI on PA levels in patients with CF. It is hypothesized that patients undergoing ETI treatment may experience a substantial increase in PA over time, potentially attributable to improvements in lung function and exercise capacity.

Material and Methods

Participants

This retrospective cohort study included patients diagnosed with CF who were regularly followed up at the CF center of the University Hospital Center of Limoges. Local ethical approval was obtained for this study, and all subjects provided informed consent.

Inclusion criteria were defined as follows: a diagnosis of CF confirmed by identification of genetic mutations and/or a positive sweat test, initiation of ETI treatment, age over 6 years old, a stable health status with at least a 6-week period away from exacerbation or antibiotic therapy and affiliation with a social security plan.

Non-inclusion criteria were defined as follows: being part of an interventional research protocol whose intervention could have influenced daily PA level or fitness level, being transplanted or awaiting a transplant and being under judicial protection, guardianship, or curatorship.

Study design

In order to determine the effects of new modulator therapy initiation in patients with CF, PA level and lung function data were obtained from routine clinical assessments at three time points: baseline (prior to treatment initiation, T0), one month after starting ETI (T1), and between three to six months post-ETI administration (T3+).

Physical activity level

PA level was objectively quantified using accelerometers (ActiGraph GT3X, Actigraph Corporation, Pensacola, FL). Patients were instructed to wear the accelerometer on their waist, positioned on their dominant side, for 7 consecutive days at T0, T1, and T3+. Devices were programmed to record at a frequency of 30 Hz, meaning that the accelerometer recorded data at every 1/30th of a second. Tri-axial data collected from accelerometers were analyzed using the software Actilife V6.11.9 which converted the data into the number of minutes per day spent in various PA intensity categories. The aim was to measure minutes per day of MVPA, light (PA) time, and sedentary time. Step counts were derived solely from accelerometer data collected on the vertical axis. Steps per day were calculated by averaging the steps taken per day across valid wear days.

Lung function

According to international guidelines, lung function parameters were assessed using spirometry (NDD Medical Technologies, Inc., Switzerland). Relative forced expiratory volume in 1 second ($FEV_{1\%pred}$) and relative forced vital capacity ($FVC_{\%pred}$) were measured in patients in a seated position and wearing a nose clip. Data were computed according to sex, age, height, and ethnicity, based on reference regression equations developed by the Global Lung Function Initiative (Quanjer et al., 2012).

Data analysis

Data is presented as mean ± standard deviation. All analyses were performed using SPSS v.29 for Windows. Kolmogorov-Smirnov test, was used to examine data's normality.

Paired sample t-test was used to show differences, in the lung function and PA data, between T0 (defined as baseline pre-treatment value) and the different measurements (T1 and T3+) when data was normally distributed, and Wilcoxon signed-rank test was used to compare non-normally distributed data.

To further explore PA level over the 7-day period of measurement, data was grouped in 3 periods: data from Monday to Friday (week), data from Saturday and Sunday (weekend) and data from Monday to Sunday (7 days). Significance level was set for $p<0.05$.

Results

The study population was composed by 18 patients with CF (7 males and 11 females). Since there were no statistically significant differences in the mean values of any clinical parameters between the adult (n=16) and adolescent (n=2) groups, we did not separate the data by age group. Data of the patient's characteristics at T0 are summarized in Table I.

Table I. Characteristics of the subjects at T0.

N=18	Age (years)	27.9±10.2
Anthropometric data	Weight (kg)	57.1±13.7
	Height (m)	164.9±9.7
	BMI ($kg.m^{-2}$)	21.0±3.2
Pulmonary data	Forced expiratory volume in 1s (%)	68.4±18.1
	Forced vital capacity (%)	88.2±14.9
GFTR gene mutation	Delta F508 homozygotic (n (%))	12 (66.7)
	Delta F508 heterozygotic (n (%))	6 (33.3)
Comorbidities	Nasal polyposis (n (%))	9 (50)
	Gastroesophageal reflux (n (%))	3 (16.7)
	Distal intestinal obstruction syndrome (n (%))	5 (27.8)
	Hemoptysis (n (%))	5 (27.8)
	Exocrine pancreatic insufficiency (n (%))	15 (83.3)
	Diabetes (n (%))	2 (11.1)
	Osteoporosis (n (%))	1 (5.6)

Lung function evolution

In order to see the lung function evolution of the patients before and after the ETI treatment, $FEV_{1\%pred}$ and $FVC_{\%pred}$ values for each measurement time are resumed in **Figure I**.

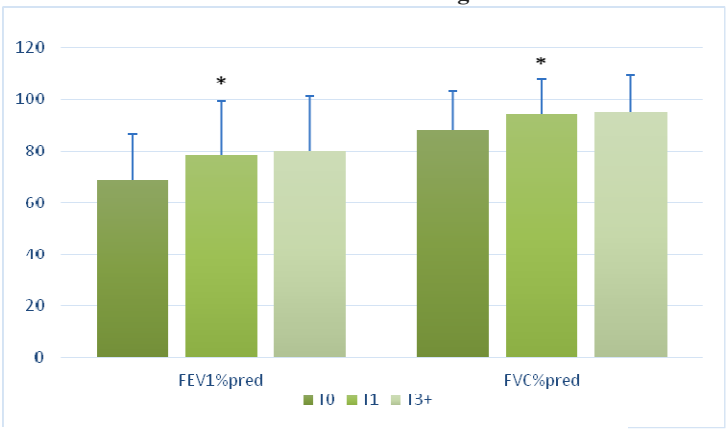

Figure I. Evolution of pulmonary parameters along the measurements (n=18).

Data are presented as mean group values and standard deviation. Difference from previous measurement: * ($P < 0.05$).

FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, T0: baseline, T1: 1 month after receiving ETI, T3+: between 3 and 6 months after receiving ETI, %pred: percentage of predicted normal values.

Physical activity evolution

In order to see the evolution of PA level of the patients along the ETI treatment, **Table II** presents the mean daily steps, the mean daily sedentary time, the mean daily light PA time and the mean MVPA time.

Table II. Evolution of the physical activity parameters along the measurements.

Parameter	T0 (n=18)	T1 (n=11)	T3+ (n=10)
Daily steps	6460.2±2068.8	6253.8±2253.5	7036.1±3177.0
Daily sedentary time (min)	570.2±80.2	531.9±133.3	552.0±143.8
Daily light PA time (min)	159.3±50.7	166.9±46.1	169.4±54.6
Daily moderate PA time (min)	42.2±30.2	32.7±12.7	44.1±21.8
Daily vigorous PA time (min)	4.4±5.5	3.4±6.6	4.1±5.4
Daily MVPA time (min)	46.8±35.0	36.2±15.6	48.9±24.4

Data are presented as mean±SD. T0: baseline, T1: 1 month after receiving ETI, T3+: between 3 and 6 months after receiving ETI.

All parameters changes did not reach statistical significance between any period (week, weekend, 7 days) nor any measurement (T1, T3+) compared to T0.

For further comprehension of the individual differences and evolution in MVPA time, data is presented with boxplots and dotplots to see the individual differences between each measurement compared to T0 **(Figures 2 and 3).** A line at 30 minutes has been plotted in each figure for easily identifying which measurements were above and below the international PA guidelines (30 minutes/day).

In **Figure II,** individual MVPA values at T0 and T1 are plotted. Four out of 11 patients did not meet the 30min/day recommended PA before ETI treatment initiation. One month after the treatment, only 3 patients out of 11 remain under the minimum recommended daily PA level, one patient having increased his PA level above the 30min/day threshold.

Overall, among the 11 patients, 6 of them decreased the MVPA time, while 5 increased it after the treatment.

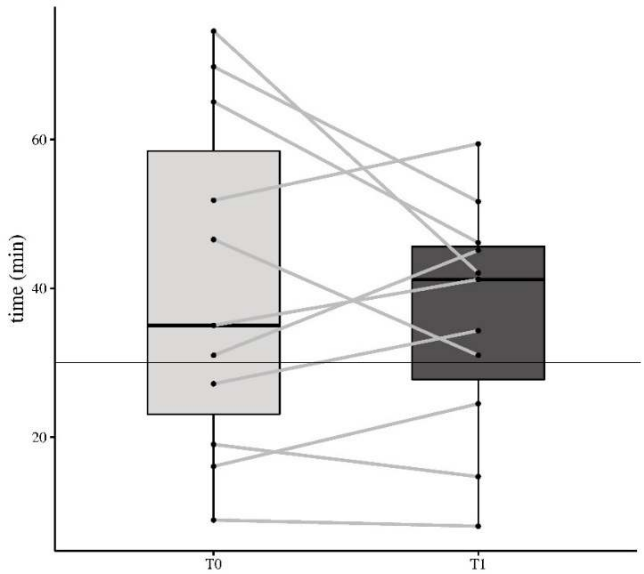

Figure II. Individual evolution of the daily moderate to vigorous physical activity time between T0 and T1 (n=11). Data are presented as mean group values (boxplots) and individual values (dotplots). T0: baseline, T1: 1 month after receiving ETI.

Figure III reports the individual MVPA values at T0 and T3+. Five out of 10 patients did not meet the 30min/day recommended PA before ETI initiation and while 7 of them increased their MVPA time at T3+, 3 of them decreased it.

At T0, one of the patient's values stood out as MVPA time was above 160min/day, and despite a reduction of two thirds at T3+, values were still above 30 min.

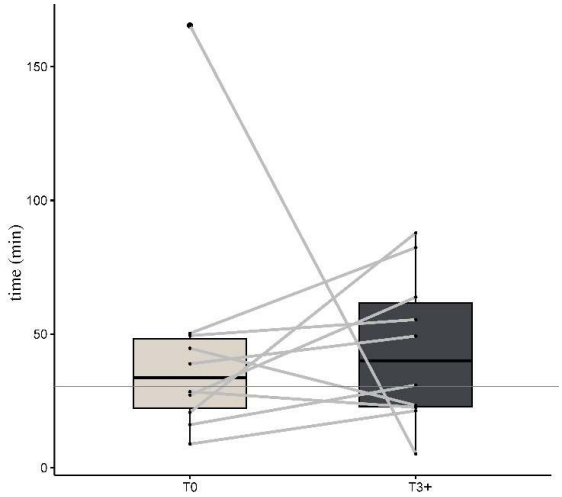

Figure III. Individual evolution of the daily moderate to vigorous physical activity time between T0 and T3+ (n=10). Data are presented as mean group values (boxplots) and individual values (dotplots). T0: baseline, T3+: between 3 and 6 months after receiving ETI.

Discussion

To the best of our knowledge, this study is the first to investigate the effect of ETI on daily PA level in patients with CF. Our results highlight that despite an improvement on lung function parameters after starting the treatment, PA parameters presented no difference between measurements. These results reject our hypothesis in which we stated that patients would benefit from a clinical improvement and incur a substantial PA increase.

PA is not only advocated for patients with CF but also for the general population due to its multifaceted benefits, such as reduced risk of chronic diseases, enhanced pulmonary function, increased muscle endurance, alleviation of anxiety and depression, and improved social interaction. For patients with CF, PA is considered as an important part of treatment and disease management (Dwyer et al., 2011; Swisher et al., 2015) and is arguably even more important than for the general population.

In our study, PA was assessed at 3 different time points: T0, T1 and T3+. At T0 (prior to treatment initiation), mean MVPA time of our patients was 46.8±35.0 min.day^{-1}. It has to be emphasized that, at a group level, our patients already met the current minimum international PA recommended guidelines of 30 minutes of MVPA per day (World Health Organization, 2010) before the treatment (**Table II**). This result is really interesting as it may provide some potential health benefits for the patients.

This could be explained by the fact that the staff of the CF center where the patients composing the study population are monitored, has a PA professional. This professional is tasked with overseeing the patients and assisting them in adopting a more active lifestyle through guidance, behavioral modifications, educational initiatives, and physical exercise sessions. The high mean MVPA level observed at T0 could be indicative of the effectiveness of the interventions implemented by this professional.

The lack of statistically significant differences in any PA parameters following the introduction of treatment is likely due to the already relatively high baseline levels of PA across all parameters. However, it is important to acknowledge that the data exhibited heterogeneity among patients. For example, prior to treatment (T0), 6 patients had MVPA values below 30 minutes per day, while 12 had values above 30 minutes per day. Additional differences and disparities among patients and measurements could be attributed to varying personal preferences and individual perceptions of PA following treatment.

Mean daily steps of patients ranged between 6000 and 8000 steps/day both before and after treatment, as shown in **Table II**. Since the sedentary lifestyle index is defined as having a value of ≤5,000 steps per day (Tudor-Locke et al., 2008), our patients could be classified as active. However, they consistently fell within a range of 500-600 minutes per day of sedentary time in all measurements (**Table II**), which is a relatively high value, approaching the recommended cut-off of 9 hours per day sedentary behavior (Ku et al., 2018). Mean light PA time ranged from 150 to 200 minutes per day (**Table II**). It may be beneficial to decrease sedentary time by encouraging patients to engage in less sedentary behaviors, while simultaneously increasing their light PA time or MVPA levels (Bianchim et al., 2022).

In regard to our other findings, it is noteworthy that we observed a short-term enhancement in lung function globally upon initiating the treatment (**Figure I**). While Burns et al., did not observe improvements in lung function following ETI and stated that performance gains can only occur if matched by training (Burns et al., 2022), our patients did experience improved lung function after the first month of treatment. Indeed,

$FEV_{1\%pred}$ significantly increased from T0 (68.4%) to T1 (78.2%), and $FVC_{\%pred}$ also showed a significant increase from T0 (88.2%) to T1 (94.0%). Subsequently, values reached a plateau at T3+. These results align with prior studies demonstrating improvements in lung function following treatment (Causer et al., 2022; Hillen et al., 2022; Krivec et al., 2022; McGrath et al., 2022) and highlight the profound gains in the health of patients with CF since the introduction of ETI. These improvements could be attributed to the mechanism by which ETI reverses the CF pathophysiological process, enhancing the function of the F508del mutant CFTR protein at the cell surface and thereby improving chloride ion transport (Ridley & Condren, 2020).

According to the literature, only one study has assessed PA level in two patients with CF before and after ETI treatment (Causer et al., 2022). This study reported an increase in PA level in one case (+17%), but also a decrease in the other case (-32%). In our study, we observed only a slight trend toward improvement in mean MVPA time.

This main finding underscores the notion that the engagement of patients with CF in an active lifestyle may be influenced by individual and environmental factors (Cox & Holland, 2019; Denford et al., 2020), rather than solely relying on clinical factors. In fact, the PA professional recounted various viewpoints expressed by patients during their PA sessions regarding the treatment's impact on their PA levels. While some patients increased their daily MVPA time due to improved physical health and motivation, others reported a decrease in PA. Those reporting a reduction claimed that since they were already feeling better and PA was integrated into their treatment, they no longer felt the need for it. The diverse opinions and individual perceptions in this study post-ETI are consistent with prior research (Almulhem et al., 2022). Indeed, PA assessment is not standard or consistent in clinical practice (Shelley et al., 2019), leading to a limited understanding of PA in the CF population. Dillenhoefer et al., demonstrated that supervision facilitated motivating CF patients to enhance daily PA and highlighted the necessity for precise action plans and concrete coping strategies to foster an active lifestyle (Dillenhoefer et al., 2022). It is consequently of medical interest to quantify actual PA levels in patients with CF to help prescribe individual PA programs designed to improve their health.

Strengths and limitations

A major strength of this study lies in the careful and objective assessment of PA in patients with CF before and after ETI. This is particularly valuable given the scarcity of information in this area, owing to the novelty of the treatment and the dearth of PA data in CF patients. Another strength is the individual comparison between periods to better comprehend the inter-individual differences between patients.

However, we should also acknowledge some limitations and caveats in this study. Primarily, the retrospective design resulted in incomplete datasets for some PA measurements and a relatively small sample size, which can compromise the robustness of the findings. Moreover, the absence of data on exercise capacity and individuals' social and environmental characteristics hinders a comprehensive exploration of the lack of PA improvement despite observed enhancements in pulmonary function. A multicentric study examining variations based on geographical location would also be of considerable interest.

Conclusions and perspectives

Our findings highlight the fact that ETI has no positive effect on the daily PA levels of patients with CF. However, it is noteworthy that our patients have already met the recommended daily PA threshold of 30 minutes of moderate to vigorous physical activity (MVPA). This achievement can be attributed to the presence of a PA professional accompanying them. Thus, our findings show the importance of PA and sedentary time assessment across the spectrum of age and disease severity for patients with CF and that despite being under ETI treatment and improving lung function parameters, patients with CF may still require assistance and encouragement to engage in PA. Therefore, PA promotion programs, carried out by PA professionals, are crucial to help patients with CF to either achieve or sustain an active and healthy lifestyle. We believe that the future of CF care, particularly concerning PA recommendations, will require a paradigm shift away from general recommendations and a move towards an individualized, holistic approach by a PA specialist.

Conflicts of Interest

The authors declare no conflict of interest.

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