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Original Article

Longer term follow-up of abdominal symptoms (CFAbd-Score) after initiation of Elexacaftor / Tezacaftor / Ivacaftor in adults with cystic fibrosis

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ABSTRACT

Background: Whether improvements in gastrointestinal (GI) symptoms observed with Elexacaftor/Tezacaftor/Ivacaftor (ETI) treatment are sustained in the longer-term requires exploration. This study investigated how GI-symptoms change with longer-term ETI use in pancreatic insufficient adults with cystic fibrosis (awCF).
Methods: Participants completed up to three abdominal symptom questionnaires, employing the validated CFAbd-Score. Changes in total CFAbd-Score and its five domains, pain, gastroesophageal reflux-disease (GERD), disorders of bowel movement (DBM), disorders of appetite (DA) and quality of life (QOL), were analysed pre-ETI (T0) and at ≤1.5 years (T1) and 2–4 years of ETI-therapy (T2).
Results: A total of 165 CFAbd-Scores from 68 participants were analysed (median age: 34 years; IQR: 28–39). Total CFAbd-Score significantly ($p < 0.05$) and clinically meaningfully decreased from 20.4 ± 1.6 pre-ETI (median:40 weeks pre-treatment) to 15.3 ± 1.9 and 16.8 ± 1.6 at T1 (median: 25 weeks of ETI) and T2 (median: 148 weeks of ETI), respectively. The CFAbd-Score's domains DA and QoL only significantly decreased between T0 and T1, whereas DBM only significantly decreased after 2–4 years of ETI therapy (T2). GERD scores were significantly lower at both T1 and T2.
Conclusion: While GI symptoms in awCF significantly improve within the first 1.5 years of ETI-therapy, they appear to somewhat wane with longer-term use, despite GI-symptom burden still being lower compared to pre-ETI. However, we cannot differentiate whether this results from reduced adherence, a decrease in ETI effects, or long-term changes in diet, gut microbiota or symptom perception. The longer-term impact of ETI and other potential modulator therapies on GI symptoms requires ongoing monitoring.

1. Introduction

Cystic fibrosis (CF) is a life-limiting autosomal recessive disease caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene [1]. The gene encodes an apical membrane anion channel (CFTR) which conducts chloride and bicarbonate and regulates sodium and calcium ionic transport. Defective CFTR expression has a profound influence on the gastrointestinal (GI) tract, including exocrine and endocrine pancreatic function, hepatobiliary effects, altered GI transit, abnormal tenacious mucus, CF-related gut dysbiosis and inflammation [1,2]. These GI manifestations give rise to a plethora of troublesome GI symptoms, a key research priority for pwCF [3].

The introduction of the triple modulator therapy, elexacaftor/ tezacaftor / ivacaftor (ETI) for over 90 % of pwCF in Europe has resulted in improved lung function, weight, and reduced pulmonary exacerbations [4,5]. As a result of improvement in clinical outcomes, a greater emphasis can now be placed on better understanding the aetiology and treatment of extra-pulmonary conditions such as CF-related GI

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manifestations [3]. Early results using the CFAbd-Score, the first CF-specific validated GI patient-reported outcome measure (PROM) revealed significant and clinically meaningful improvements in GI symptoms post ETI therapy [6,7]. However, differences between cohorts have suggested that age and pancreatic status may differentially impact on the level of symptomatic relief [6]. Differences in GI symptomology is likely to reflect a complex milieu of medications, extent of CF-related gut dysbiosis (CFRGD), degree of inflammation, structure tissue damage as well as duration and extent of CFTR correction [6]. The initial, and often partial, symptomatic improvement associated with ETI may be further accentuated by a longer duration of therapy through improved gut physiology, reduced inflammation and subtle improvements in gut dysbiosis [7–9]. However, during use of the highly effective CFTR-modulator therapy, ETI effects may wane over time, and/or adherence could analogously decline. In this study, we investigate the relationship between duration of ETI treatment and abdominal symptoms in adult with CF (awCF).

2. Methods

2.1. Study design and data collection

Adults attending the Leeds Adult CF Unit were prospectively recruited. Eligibility criteria comprised pancreatic insufficiency, ability to give informed consent and absence of other significant GI pathologies (such as short bowel syndrome, Crohn's disease or ulcerative colitis), lung transplantation, prognosis less than six months and pregnancy.

All participants completed at least two abdominal symptom questionnaires, one before and one after commencing ETI therapy, as part of the Igloo-CF study [10,11]. Participants completed paper copies of the CFAbd-Score questionnaire at a routine outpatient appointment after informed voluntary written consent had been obtained. A favourable ethical opinion was received from London Bromley Research Ethics Committee (Reference 18/LO/2241).

Clinical and sociodemographic data collected included percentage predicted forced expiratory volume in one second ($ppFEV_1$), anthropometric data including, height (m), weight (kg) in order to calculate BMI (kg/m^2). All values for $ppFEV_1$ were calculated using the Global Lung Function Initiative reference system (GLI) [12].

2.1.1. Assessment of abdominal symptoms

Abdominal symptoms were assessed with the CFAbd-Score which, together with its scoring algorithm that weights different items and domains differently, was developed in line with FDA recommendations and has been identified as a meaningful and practical tool for monitoring abdominal symptoms in pwCF [6,10,13–16]. Participants were asked to complete 28 questions grouped into the 5 domains within the scoring system: pain, gastroesophageal reflux disease (GERD), disorders of bowel movement (DBM), disorders of appetite (DA) and quality of life (QOL) impairment owing to GI symptoms, over the previous 2 weeks. Participants had not received intravenous (IV) antibiotics in the two weeks prior to completing the questionnaire.

2.2. Data analysis

Up to three abdominal symptom questionnaires per patient were included in analysis. All participants completed a questionnaire at time point 0 (T0, baseline), a median (IQR) of −40 [−49, −29] weeks (min:−91 weeks, max:−4 weeks) prior to commencing ETI therapy. A further 1–2 CFAbd-Scores were completed after commencing ETI therapy. For analysis, the abdominal symptom questionnaires after commencing ETI were grouped into two main time frames based on their distribution: ≤ 1.5 years on ETI therapy (T1) and 2–4 years taking ETI therapy (T2). Specifically, $n = 38$ were included in T1, where questionnaires were completed between 3 and 71 weeks (median (IQR) time: 25 [17,33] weeks) after commencing ETI and $n = 59$ at T2, where CFAbd-Scores were completed within a timeframe of 95–199 weeks (median (IQR) time: 148 [128,159] weeks) after commencing ETI therapy.

Statistical analysis was performed as previously described in Mainz et al. [6]. In brief, linear-mixed effects models were employed, with time point, previous modulator, sex and age (as a continuous variable) as fixed factors. Data for the DA and QoL domains were log-transformed previous to analysis in order to satisfy assumptions on residuals. Results for these domains are reported as back-transformed estimated marginal means.

3. Results

3.1. Demographic and clinical characteristics

A total of 68 awCF (median age: 34 years [IQR: 28–39]; 22 female [32.4 %]) were included in the study, with 165 CFAbd-Scores included in analysis. Table 1 details the demographic and clinical characteristics of participants analysed. All participants completed a CFAbd-Score at T0 (baseline), 29 subjects had scores at both T1 and T2 while 9 and 30 subjects completed T0 and then either T1 or T2 respectively.

CFRLD- cystic fibrosis related liver disease; CFRD: cystic fibrosis-related diabetes, CFTRm: cystic fibrosis transmembrane conductance regular modulator, EN: Enteral Nutrition; IQR: Interquartile range; Single therapy: ivacaftor alone; Double therapy: lumacaftor/ivacaftor or tezacaftor/ivacaftor

3.2. Changes in BMI and $ppFEV_1$ with ETI therapy

Compared to T0 (pre-ETI), both BMI and $ppFEV_1$ significantly increased following ≤ 1.5 (T1) and 2–4 years (T2) of ETI (Table 2). There was an increase in $ppFEV_1$ from 54.4 ± 2.8 pre-ETI, to 66.4 ± 2.9 at both T1 and T2 ($p < 0.001$ for both). Body mass index increased from 24.3 ± 0.5 kg/m^2 at T0 (pre-ETI), to 26.0 ± 0.6 kg/m2 and 25.1 ± 0.6 kg/m^2 at T1 and T2 respectively ($p < 0.0001$ and $p = 0.002$,Table 1).

3.3. Changes in abdominal symptoms with ETI therapy

Total CFAbd-Score significantly decreased after commencing ETI therapy, from 20.4 ± 1.6 pre-ETI (T0) to 15.3 ± 1.9 and 16.8 ± 1.6 at T1 and T2 respectively, ($p = 0.005$, $p = 0.014$, Table 2, Fig. 1). Compared to pre-ETI, symptoms of GERD significantly decreased at both T1 and T2 (p

Table 1
Demographic and clinical characteristics.

	T0 (baseline) N = 68
Age (years) median (IQR)	34 (28, 39)
Sex N (%)	
Male	46 (68 %)
Female	22 (32 %)
Genotype N (%)	
F508del homozygous	47 (69 %)
F508del heterozygous	21 (31 %)
Chronic lung colonization N (%)	
Pseudomonas aeruginonsa	42 (62 %)
Staphylococcus aureus	23 (34 %)
Burkholderia cepacia	7 (10 %)
Aspergilus fumigatus	31 (46 %)
EN nutrition N (%)	8 (12 %)
Previous CFTRm therapy	
None	18 (27 %)
Single therapy	5 (7 %)
Double therapy	45 (66 %)
CFRLD	28 (41 %)
CFRD	22 (32 %)
Azithromycin	26 (38 %)
Movicol / Polyethylene glycol	9 (13 %)

Table 2
Estimated marginal means and standard errors resulting from the mixed-effects models for the CFAbd-Score, ppFEV1 and BMI.

		Time point 0: Pre-ETI $n = 68$	Time point 1: ≤1.5 years on ETI therapy $n = 38$	Time point 2: >1.5 years on ETI therapy $n = 59$
CFAbd-Score completed:				
T0, T1 and T2		N = 29	N = 29	N = 29
T0 and T1		N = 9	N = 9	——
T0 and T2		N = 30	——	N = 30
Total CFAbd-Score		20.4 ± 1.6	15.3 ± 1.9 $p = 0.005$	16.8 ± 1.6 $p = 0.014$
Domains of the CFAbd-Score	**Pain**	18.8 ± 2.2	13.5 ± 2.8 n.s	17.6 ± 2.4 n.s.
	GERD	24.8 ± 2.8	16.6 ± 2.9 $p = 0.005$	15.3 ± 2.0 $p = 0.0001$
	DBM	27.9 ± 2.0	24.9 ± 2.3 n.s	24.0 ± 2.0 $p = 0.03$
	DA	3.9 ± 0.9	1.7 ± 0.5 $p = 0.004$	3.9 ± 0.9 n.s.
	QoL	6.3 ± 1.4	3.2 ± 1.0 $p = 0.013$	5.0 ± 1.2 n.s
ppFEV1		54.4 ± 2.8	66.4 ± 2.9 $p < 0.0001$	66.4 ± 2.9 $p < 0.001$
BMI (kg/m2)		24.3 ± 0.5	26.0 ± 0.6 $p < 0.0001$	25.1 ± 0.6 $p = 0.002$

*p-values represent statistical significance with respect to the baseline value.
BMI –body mass index DA- Disorders of appetite; DSM - Disorders of bowel movement (DBM); ETI - elexacaftor/ tezacaftor / ivacaftor; QL - GI-related quality of life impairment, pwCF – people with cystic fibrosis.

= 0.005 and $p = 0.0001$ respectively, Table 2, Fig. 1). In contrast, the domains DA and QoL only significantly decreased between T0 and T1, when on ETI ≤ 1.5 years, $p = 0.004$ and $p = 0.013$ respectively (Table 2). After 2–4 years of ETI therapy (T2), both DA and QoL domains were not significantly different to pre-treatment (T0), Table 2, Fig. 1. Mean pain domain score non-significantly decreased from 18.8 ± 2.2 at T0 to 13.5 ± 2.8 at T1 and then 17.6 ± 2.4 at T2, Table 2, Fig. 1. Compared to baseline, DBM only significantly decreased after 2–4 years of ETI therapy (T2, $p = 0.03$), not reaching statistical significance between T0 and T1 (Table 2, Fig. 1).

4. Discussion

An absence, reduction or dysfunction of CFTR has a profound effect on pancreas, gut and hepatobiliary physiology and function which leads to a high prevalence of GI symptoms in pwCF. Symptoms are further accentuated by exposure to drugs such as antibiotics, as well as additional pathologies such as CF-related diabetes, pancreatic malabsorption and CF-related gut dysbiosis [10,17]. These troublesome symptoms to some extent can be improved by ETI therapy through partial correction of CFTR function as well as indirectly by improved clinical stability, reduced antibiotic use, downregulating of inflammation and changes in GI physiology. While studies to date have reported significant improvements in GI symptoms, differences between ages and cohorts are evident [6,7]. Potentially, by adulthood, the extent of structural and inflammatory-mediated damage may dampen or prolong the period of time needed for maximal improvement in GI symptoms. To this end, we investigate in adults with CF the longer-term changes in GI symptoms with ETI therapy. While ETI therapy significantly improved GI symptoms, they did not entirely resolve. This suggests further investigation and GI symptom management is required even in the presence of highly effective modulator therapy (HEMT).

The overall significant improvement in abdominal symptoms with

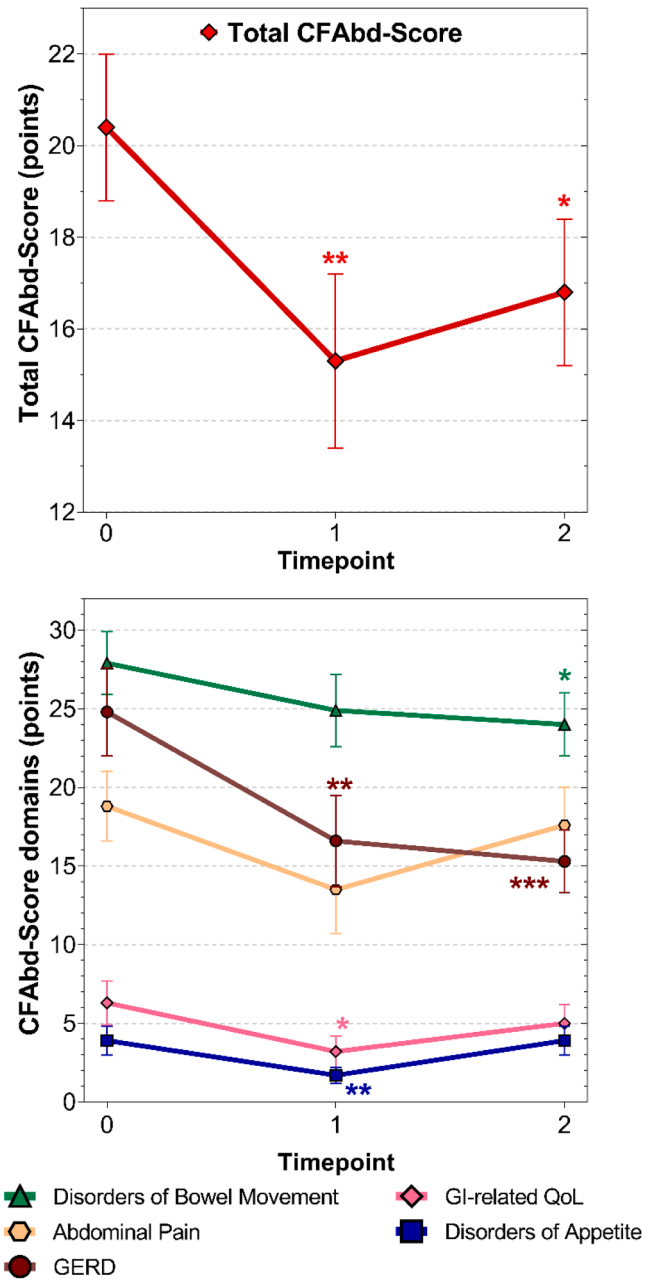

Fig. 1. Total CFAbd-Score and its five domains at the three time points. Time point 0 (median, IQR): −40[−49, −29] weeks, time point 1 (median, IQR): 25 [17,33] weeks, time point 2: 148[128,159] weeks).
*, **, and *** indicate p-values <0.05, 0.01 and 0.001, respectively. p-values represent statistical significance with respect to the baseline value.

ETI therapy is concordant with a number of studies which employed the CFAbd-Score [7,18]. For example, in a cohort of 45 German participants, there were cumulative significant decreases in CFAbd-Scores after 3–4 weeks of ETI [18], and in RECOVER, a UK and Irish cohort study, a more pronounced improvement after 12 months of therapy [7]. It is noteworthy that in this latter study, 66 % of participants were < 18 years old [7], compared to a median age of 34 years old (IQR 28, 39) in our study and 100 % of our participants aged ≥ 18 years. We hypothesize that age is an important variable affecting the degree of GI symptom improvement with ETI therapy. Perception of GI symptoms, adherence to treatments and diet may also differ between ages. Schwarzenberg et al. [19] found a statistically, but not clinically, significant improvement in GI symptoms with six months of ETI treatment in those aged >

12 years old. However, they did not employ CF-specific abdominal questionnaires, which along with other potential cohort differences, such as diet, could have influenced findings [19].

There is early evidence to suggest a direct physiological impact of ETI on the gut. Orocecal transit time and total colonic volumes, quantified in serial MRIs, reduced and small bowel water content increased after 18 months of ETI therapy [9]. However, despite these improvements, GI symptoms did not significantly change with ETI therapy in the 11 participants included, aged ≥12 years old [9]. This could be owing to the small sample size and, most likely, to the very low burden of symptoms in the pwCF who agreed to participate in the study. The mean CFAbd-Score in these 11 participants in CF was lower than in healthy controls assessed in our previous studies [6,14].

Mainz et al. [7] found that faecal calprotectin (FC), a marker of intestinal inflammation, significantly reduced with ETI therapy. Interestingly, the reduction in FC did not correlate with CFAbd-Score following ETI therapy [7], despite a previous study showing that the sub-domain of pain correlated to markers of intestinal inflammation [20]. It has been demonstrated in other conditions that multiple mechanisms can drive similar GI symptoms and they are often multifactorial in origin [21]. The complex, likely multiple mechanisms driving GI symptoms in pwCF requires further exploration.

While an overall improvement compared to pre-ETI treatment was observed, there were differences in the reported level of improvement by length of time on ETI therapy. Certain domains of the CFAbd-Score seemed to increase after a longer duration of ETI therapy. Potential explanations for this include sample size and that perceptions of GI symptoms may change with time, particularly with improved lung health, focus may further concentrate on GI health, including degree of abdominal pain. The often dramatic improvement in overall health after initiating ETI therapy may have influenced the overall perception of abdominal symptoms due to the stark contrast before and after treatment. In contrast, longer term treatment and clinical stability may have alter the degree to which changes in symptoms, such as appetite and abdominal pain are perceived and scored.

Moreover, to date, no significant ETI-related improvement has been observed in exocrine pancreatic function of pwCF carrying two severe CFTR mutations (Class I-III) above toddler age. Nevertheless, many patients may still be reducing their pancreatic enzyme replacement therapy (PERT) dose [22], and adherence to PERT and other therapies, including ETI therapy itself, may decline with time [23,24]. Postulated reasons for reduction in PERT dose could include a reduced perceived need for them owing to the initial reduction in symptoms and increased body weight, interpreted as improved intestinal absorption rather than effects of ETI on factors such as ETI potentially reducing mitochondrial metabolism or as a means to reduce body weight [25]. In the longer term, diet may also shift, modulating GI symptoms. For example, if fibre intake is increased, in line with healthy eating guidelines, some individuals' may experience pain if they are sensitive to fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs). Intertwined with this, there may be a shift in the gut microbiota, which could alter GI symptom profile [26].

Key strengths of this study include employing a CF-specific questionnaire, developed and validated in line with FDA recommendations, which has proved to be sensitive and validated to detect changes with time [6,7,13–16]. The improvement in BMI and lung function following ETI therapy is concordant with wider literature [4]. Limitations include the observation nature of the study, including uneven number of participants completing time points alongside long periods between time points, although this enabled assessment of longer-term changes with ETI therapy in the real world setting, it does introduce the risk of intervening events influencing findings and potential confounders, including diet, PERT dose (albeit the study was conducted prior to the national shortage), antibiotics and microbiota changes. Therefore, further research is essential. This should include the potential impact and interplay between GI symptoms, diet and the gut microbiota.

Improving CF-related gut dysbiosis and dietary modification may be new avenues to explore to reduce the burden of GI symptoms. This is being investigated in a number of non-CF conditions, including irritable bowel syndrome and inflammatory bowel disease [26,27]. An integrated approach to monitoring ETI effectiveness is required, including the impact of GI symptoms on quality of life. This is because adults with CF are navigating significant changes in expected lifespan, which may affect perception of GI symptoms, along with their overall health and wellbeing and health-related priorities. Perceptions of GI symptoms and further exploration of potential differences according to age and sex could be of value in tandem with assessing adherence to treatments.

In conclusion, we found that while GI symptoms improve with ETI therapy, in the presented cohort they do not continue to consistently improve with longer-term use, albeit scores across different domains display different dynamics. Therefore, GI symptoms remain a key clinical and research priority, even with HEMT. Further exploration of GI symptom profiles with continued longer-term use of ETI therapy and in the context of an ageing CF population is warranted. Alongside this, we need to better understand the mechanisms and develop effective treatment and lifestyle strategies to further improve abdominal symptoms.

CRediT authorship contribution statement

L.R. Caley: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft. **L. Gillgrass:** Methodology, Investigation, Writing – original draft. **C. Zagoya:** Methodology, Software, Formal analysis, Writing – review & editing, Visualization. **H. Saumtally:** Writing – original draft, Investigation. **F. Duckstein:** Writing – review & editing. **White H:** Writing – review & editing, Supervision, Funding acquisition. **J.G. Mainz:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition. **D.G. Peckham:** Conceptualization, Methodology, Resources, Writing – original draft, Supervision, Funding acquisition.

Declaration of competing interest

LRC has previously received a speaker fee from Vertex, DGP: speaker/board honoraria from Vertex, HW: Received previous funding from Gilead, which was not directly related to this research project and from Health Education England for simulated placement delivery funding., JGM reports independent grants and speaker/board honoraria from Vertex, Chiesi, Abbvie and Viatris outside the submitted work., CZ, FD HS and LG declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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References

[1] Elborn JS. Cystic fibrosis. Lancet 2016;388(10059):2519–31.
[2] De Lisle RC, Borowitz D. The cystic fibrosis intestine. Cold Spring Harb Perspect Med 2013;3(9):++.
[3] Rowbotham NJ, et al. A refresh of the top 10 research priorities in cystic fibrosis. Thorax 2023;78(8):840–3.
[4] Middleton PG, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med 2019;381(19):1809–19.
[5] Lopez A, et al. Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del. J Cyst Fibros 2023;22(4):607–14.
[6] Mainz JG, et al. Elexacaftor-tezacaftor-ivacaftor treatment reduces abdominal symptoms in cystic fibrosis-early results obtained with the CF-specific CFAbd-score. Front Pharmacol 2022;13:877118.
[7] Mainz JG, et al. Reduction in abdominal symptoms (CFAbd-Score), faecal M2-pyruvate-kinase and Calprotectin over one year of treatment with Elexacaftor-Tezacaftor-Ivacaftor in people with CF aged ≥12 years - the RECOVER study. J Cyst Fibros 2024;23(3):474–80.

[8] Caley LR, et al. EPS5.01 Change in gut microbiota following elexacaftor/tezacaftor/ivacaftor (ETI) therapy: preliminary analysis. Journal of Cystic Fibrosis 2023;22:S49.
[9] Yule A, et al. A longitudinal study assessing the impact of elexacaftor/tezacaftor/ivacaftor on gut transit and function in people with cystic fibrosis using magnetic resonance imaging (MRI). J Cyst Fibros 2024;23(5):984–90.
[10] Caley LR, et al. Diabetes is associated with increased burden of gastrointestinal symptoms in adults with cystic fibrosis. J Cyst Fibros 2023;22(2):275–81.
[11] Caley LR, et al. Body mass index and nutritional intake following Elexacaftor/Tezacaftor/Ivacaftor modulator therapy in adults with cystic fibrosis. J Cyst Fibros 2023;22(6):1002–9.
[12] Quanjer PH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324.
[13] Tabori H, et al. Relation of ultrasound findings and abdominal symptoms obtained with the CFAbd-score in cystic fibrosis patients. Sci Rep 2017;7(1):17465.
[14] Jaudszus A, et al. Validity and reliability of a novel multimodal questionnaire for the assessment of abdominal symptoms in people with cystic fibrosis (CFAbd-Score). Patient 2019;12(4):419–28.
[15] Administration USDoHaHSFaD, *GUIDANCE DOCUMENT: patient-reported outcome measures: use in medical product development to support labeling claims*. 2009.
[16] Mokkink LB, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol 2010;63(7):737–45.
[17] Caley LR, et al. Cystic fibrosis-related gut dysbiosis: a systematic review. Dig Dis Sci 2023;68(5):1797–814.
[18] Mainz, J.G., et al., *Dynamics of abdominal symptoms during the start of a new therapy with elexacaftor/tezacaftor/ivacaftor using the novel CFAbd-day2day questionnaire*. 2023. 14.
[19] Schwarzenberg SJ, et al. Elexacaftor/tezacaftor/ivacaftor and gastrointestinal outcomes in cystic fibrosis: report of promise-GI. J Cyst Fibros 2023;22(2):282–9.
[20] Jaudszus A, et al. Abdominal symptoms assessed with the CFAbd-score are associated with intestinal inflammation in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2022;74(3):355–60.
[21] Andreyev HJ, et al. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut 2012;61(2):179–92.
[22] Stastna N, et al. Improved nutritional outcomes and gastrointestinal symptoms in adult cystic fibrosis patients treated with elexacaftor/tezacaftor/ivacaftor. Dig Dis 2024;42(4):361–8.
[23] Hansen CME, et al. Medication adherence to CFTR modulators in patients with cystic fibrosis: a systematic review. Eur Respir Rev 2024;(173):33.
[24] Mehta Z, et al. Adherence to cystic fibrosis transmembrane conductance regulator (CFTR) modulators: analysis of a national specialty pharmacy database. J Drug Assess 2021;10(1):62–7.
[25] Jarosz-Griffiths HH, et al. Heightened mitochondrial respiration in CF cells is normalised by triple CFTR modulator therapy through mechanisms involving calcium. Heliyon 2024;(20):10.
[26] Vervier K, et al. Two microbiota subtypes identified in irritable bowel syndrome with distinct responses to the low FODMAP diet. Gut 2022;71(9):1821–30.
[27] He P, et al. Dietary Patterns and Gut Microbiota: the Crucial Actors in Inflammatory Bowel Disease. Adv Nutr 2022;13(5):1628–51.