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Original research

Combined CFTR modulator therapies are linked with anabolic benefits and insulin-sparing in cystic fibrosis-related diabetes

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ABSTRACT

Aims: Combined CFTR modulator therapies have dramatically altered pulmonary outcomes in patients with cystic fibrosis (CF). Their impact on glucose metabolism requires further investigations. This study aims to evaluate insulin requirements after initiation of combined CFTR modulator therapy in patients with CF-related diabetes (CFRD) and HOMA indices changes in CF patients without diabetes.

Methods: We retrospectively analyzed: 1) the effects of tezacaftor + ivacaftor and elexacaftor + tezacaftor + ivacaftor on FEV_1, weight, BMI, HbA1c, and daily insulin dose, in 17 CFRD patients and 2) the impact of tezacaftor + ivacaftor on HOMA indices in 15 CF patients without diabetes.

Results: Age was 37±12y in the CFRD group (70% men), 88% of whom were homozygous for F508del mutation. Diabetes duration was 15±10y. Median duration of combined CFTR modulator therapy was 16 months (IQR: 4) Thirteen patients received tezacaftor + ivacaftor, of whom 9 were switched to elexacaftor + tezacaftor + ivacaftor. Four patients received elexacaftor + tezacaftor + ivacaftor up front. A decrease in insulin needs was noticed in 88% of patients (0.85±0.3 *vs* 0.71±0.3U/kg/day; $p = 0001$). Total daily insulin dose decreased from 50±16 to 44±20U/day ($p = 0.017$). BMI improved (20.9 (IQR: 1.90) *vs* 22.1 kg/m^2 (IQR: 3.70); $p = 0.014$). HbA1c went from 7.3±1.1 to 7.7±1.6% ($p = 0.072$). Median age was 22y (IQR: 11) in the CF group without diabetes (67% men), 93% of whom were homozygous for F508del mutation. Duration of combined CFTR modulator therapy was 10±5 months. HOMA-B changes were not significant (129.2 (IQR: 84.8) *vs* 103.5% (IQR: 66.3) nor were HOMA-S changes (from 94±64 to 95±49%). HOMA-BxS decreased from 112±45 to 104±29% (NS). BMI rose from 21.9±3 to 23.1±3.5 kg/m^2 ($p = 0.047$). HbA1c was unchanged (5.0±0.5%). FEV_1 improved in both groups (+11% and + 7% of predicted value; $p < 0.001$; $p = 0.013$).

Conclusion: Combined CFTR modulator therapies are correlated with a decrease in insulin doses and positive effects on BMI and FEV_1. HOMA indices did not change on tezacaftor + ivacaftor among CF patients without diabetes.

Introduction

Cystic fibrosis (CF) is a worldwide and multi-ethnic autosomal recessive condition with the highest prevalence in Europe, North America, and Australia. CF results from mutations in both alleles of the CF transmembrane conductance regulator (CFTR) gene, which codes for the eponymous protein[1]. Lack or dysfunction of the CFTR channel gene disrupts the normal balance of fluids and electrolytes in various body secretions. This leads to mucus buildup in bronchial and gastrointestinal tracts, which promotes repeat infections, chronic inflammation, and ultimately, organ dysfunction[2].

Recent breakthroughs in CF care have changed the management paradigm of this condition, with CFTR modulators having brought about dramatic improvement in lung function, by addressing the root defect of CF. These drugs significantly improve the prognosis of many patients with CF. Their effect on glucose metabolism is being actively researched.

CF-related diabetes mellitus (CFRD), one of the commonest extra-pulmonary complications of CF, is a unique secondary type of

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFRD, cystic fibrosis-related diabetes; BCF, B-cell function; IS, insulin sensitivity; OGTT, oral glucose tolerance test; IVA, ivacaftor; LI, lumacaftor+ivacaftor; TI, tezacaftor+ivacaftor; ETI, elexacaftor+tezacaftor+ivacaftor; HOMA2, Homeostasis Model Assessment; CGM, continuous glucose monitoring; SMBG, self-monitoring blood glucose; TBR, time below range.

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diabetes, whose pathophysiological processes are present at an early age. There is a continuum of abnormalities in glucose tolerance, with patients going through various degrees of glucose intolerance to full-blown diabetes[3]. Thirty-five to 50% of adults with CF will develop CFRD[4]. CFRD is associated with an increased risk of respiratory exacerbation, decline of lung function, malnutrition, post-transplantation complications, and mortality[2]. The treatment of choice for CFRD is insulin[4].

CFRD's pathophysiology is multifaceted. Reduction of B-cell mass, local and systemic inflammation, as well as changes in incretins contribute to insulin deficiency and insulin resistance[2]. Moreover, the advent of CFTR channel modulators have raised suspicions that CFTR channel dysfunction may contribute to the genesis of CFRD, since these drugs brought about some positive impact on glycemic control[5–9]. Thus, some authors identified early glucose homeostasis disorders in young children without exocrine deficiency[10]. Others suggested that absence of, or abnormal CFTR channel function in B cells could impair insulin secretion[11,12], although this remains controversial and was not confirmed[13]. B-cell dysfunction in CFRD arises rather from infiltration of pancreatic islets by exocrine ductal cells expressing CFTR and by immune cells, leading to intra-insular inflammation and impaired insulin secretion[13]. The CFTR channel could also be involved in glucagon secretion, as negative glucose-sensing regulator in alpha cells. Defective or absent CFTR channels may counteract physiological glucagon suppression and contribute to glucose intolerance in patients with CF[14].

Most studies exploring the effect of CFTR channel modulators on glucose homeostasis analyzed clinical, biological, and epidemiological parameters to understand the beneficial effect of these therapies [6–9,15–23]. Various modulators were studied, with different methodologies, and the overall conclusions were mixed. To our knowledge, only four studies used mathematical modeling to account for the effect of CFTR channel modulators on glucose homeostasis, by simultaneously analyzing B-cell function (BCF), insulin sensitivity (IS), and insulin clearance from oral glucose tolerance test (OGTT) data. The first studied the effect of lumacaftor + ivacaftor (LI) in CF patients without diabetes [24], while the second studied both LI and elexacaftor + tezacaftor + ivacaftor (ETI) in a young CF population without diabetes[25]. Neither studies found a beneficial effect of CFTR modulators on glucose homeostasis. The third study, the first one exploring insulin secretion and sensitivity through OGTT derived measures before and after ETI, conducted by Chan et al., showed an improvement in insulin secretion but also an increase in insulin resistance in a 22-patients prospective study. BCF did not improve in this study[26]. The latest study showed no improvement of insulin secretion in a heterogeneous CF population (diabetic and nondiabetic) with at least one F508del, treated with ETI. However, glucose tolerance transitioned in almost 50% of cases over the study period[27]. No data is available concerning tezacaftor + ivacaftor (TI).

Homeostasis Model Assessment (HOMA2) is a widely-used non-invasive means to estimate both IS and BCF from fasting plasma glucose and insulin. Its use is validated in subjects with normal or impaired glucose tolerance (IGT) and in patients with type 2 diabetes (T2DM) [28]. The outline of the HOMA2 model is described in the Methods section. The primary outcomes of this research were insulin requirement of patients with CFRD following the introduction of combined CFTR modulators, and changes in HOMA indices of CF patients without diabetes. We hypothesized that insulin needs would decrease in the CFRD group and that HOMA indices would improve on treatment.

Subjects, materials and methods

We conducted a retrospective monocentric study to assess the impact of combined CFTR modulator therapies (TI and ETI) on insulin requirements in patients with CFRD and its effect on HOMA indices in CF patients without diabetes. We reviewed all adult (>18 years old) patients with CFRD and all CF patients without followed in a CF reference center of a tertiary level academic center. Diabetes was defined according to ADA and ISPAD guidelines, based on an HbA1c ≥6.5% and/or a pathological result from standard 75 g 2 h-OGTT. All patients had a diagnosis of CF based on a sweat chloride test with confirmatory genetic testing. To be included, patients with CFRD had to meet the 5 following criteria: being treated with insulin for at least 1 year; being regularly followed at the outpatient diabetes/CF centers; being modulator-naïve at initial evaluation; having received CFTR modulators for at least 1 month before final evaluation; and being on treatment at the final evaluation. To be included, CF patients without diabetes had to meet 4 criteria: being regularly followed at the outpatient CF center; having been tested with a standard 75 g 2 h-OGTT with insulinemia sampling (time points 0′ and 120′) before and on combined CFTR modulator therapy; and having received CFTR modulators for at least 1 month before final evaluation. Patients with cirrhosis or pregnant were excluded. Demographic, clinical, and biological characteristics were extracted from Medical Explorer® and EPIC® EMR softwares. Main variables collected were standard demographic features (age, gender), type of mutation of CFTR channel, HbA1c (%), forced expiratory volume in 1 s (FEV_1), weight, body mass index (BMI), and daily insulin doses. We did not consider lung function variables and nutritional features of interest if measured during acute respiratory exacerbations or illnesses. Hence, the closest measurements prior to, or after such episodes once clinical stabilization was notified, were considered. A respiratory exacerbation was considered according to the definition of Fuchs et al. (1994): intravenous antibiotherapy required for 4 of the following 12 signs or symptoms: sputum changes; new or increased haemoptosis; increased cough; increased dyspnea; malaise, fatigue or lethargy; fever (≥38 °C); anorexia or weight loss; sinus pain or tenderness; change in sinus drainage; change in physical examination of the chest; decrease in lung function of 10% or more from a previously recorded value; or X-ray changes indicative of a lung infection[29]. Last measurements before decline were collected for deceased patients. To assess on-treatment effects on insulin requirements, clinical and biological features were collected before initiation of modulators and during treatment.

Data on insulin requirements were collected from consultations reports in the EMR. All patients had fixed insulin doses recorded in the EMR and there was no data on insulin carb ratios, since the latter are not often used in Belgium to adapt insulin doses, which are generally modulated on the basis of retrospective glucometry following usual carbohydrate intakes.

At the initial evaluation, we considered the total daily dose as fixed by the therapist in accordance with the patient at the end of the visit. At the final evaluation, we considered total daily dose as fixed by the therapist in accordance with the patient at the end of the visit. If the reduction or increase of the insulin doses operated by the patient during the observation time seemed to be sufficient or appropriate by the hospital practitioner, such total daily dose was taken into account. On the other hand, if the practitioner judged that the doses injected were not appropriate, we took into account the final daily dose decided by the practitioner in agreement with the patient on the basis of hypoglycemia history (glucose level <70 mg/dl), patient's preference, CGM data or SMBG, all of which not systematically reported in the EMR.

HOMA2 indices (HOMA-B, HOMA-S, HOMA-[BxS] and loss rates) were determined prior to initiation of combined CFTR modulators (HOMA T_0, i.e. at initial evaluation) and on combined CFTR modulator therapy (HOMA T_1, i.e. at final evaluation). If available, we collected an additional HOMA (HOMA T_{-1}, modulator-naïve), prior to T_0, for an intra-subject multiple measures model. HOMA indices were calculated from fasting glucose (mg/dL) and insulinemia (pmol/L) from OGTT data, performed for CFRD screening. We used the HOMA2 calculator software (Oxford University). HOMA is a structural model of glucose/insulin feedback, structurally based on physiological responses of organs involved in glucose homeostasis through sets of simultaneous equations that assess the degree to which various combinations of impaired β-cell

function and insulin sensitivity affect glucose homeostasis. The model reproduces physiological reality in a reference individual by setting an equilibrium point of plasma glucose, insulin, C-peptide and proinsulin in the fasting state. In HOMA, B-cell function (%B) and peripheral and hepatic insulin sensitivity (%S) are each arbitrarily assigned a normal value of 100%[30–32]. Since insulin secretion (HOMA-B (normal = 100%) needs adjustment to individual insulin sensitivity (HOMA-S (normal = 100%)[33], HOMA-B was plotted as a function of HOMA-S defining it as a hyperbolic product area (HOMA-B × S; unit: $\%^2$; standardized normal value 100%). HOMA-BxS represents the true underlying residual BCF adjusted for individual IS. Individual BCF loss rate (%. $year^{-1}$) can be calculated as the ratio between the hyperbolic product [BxS] loss (100%-[BxS] (%)) and the age (year) at the time of HOMA modeling[32–34]. A negative loss rate was computed as 0.

The study protocol was approved by the *Comité d'Ethique Hospitalo-Facultaire Saint-Luc – UCL (CEHF: 2020/23JUI/337)*.

Statistical analyses were performed using IBM SPSS Statistics® version 27. Numerical variables are expressed as means (±SD) if normally distributed or median (IQR) for non-normal distribution. Categorical variables are expressed as rates or percentages depending on data availability. Inference tests were chosen according to variable type, sample size and if applicable to the distribution of variables. Normality was assessed by Shapiro-Wilk's test. To assess difference before and after initiation of combined CFTR modulator therapy, a Wilcoxon's test was used in case of non-normal distribution, and a paired Student's *t* test for normal distribution. We used ANOVA for multiple measures test or Friedman ANOVA according to distribution to determine treatment effects on HOMA indices.

Results

We reviewed 135 adult patients with CF. Seventeen patients met the inclusion criteria among 51 patients with CFRD. Among 84 CF patients without diabetes, 15 patients met the inclusion criteria (30 OGTTs; Fig. 1).

Results for the CFRD group

Among Patients with CFRD, homozygous cystic fibrosis genotype was dominant (15/17; 88%). One heterozygous patient had the F508del/D1507, and another the F508del/E831X genotype. All had pancreatic exocrine insufficiency. Twelve patients were male (sex assigned at birth; 70%) and mean age was 37±12 years. Diabetes duration was 15±10 years. Insulin therapy was immediately initiated after diabetes diagnosis (median: 0; IQR: 0). One patient had only mealtime insulin, whereas all others were treated with basal + bolus insulins scheme. They all had fixed mealtime insulin doses. All patients were modulator-naïve at initial evaluation. Four patients received ETI up front and were never treated with TI. Four patients received first TI before being switched to ETI. Having not yet been reassessed for the latter, the data used in this study were those under TI. The remaining 9 patients were initially on TI and switched to ETI by the end of the study.

The main results are summarized in Table 1. Median duration of combined CFTR modulator therapy between start and end of the study was 16 months (IQR: 4). Median duration of TI was 14.5 months (IQR: 5) and 1.75 month (IQR: 11) for ETI. All patients received the standard dose of CFTR modulator therapy. On-treatment insulin requirements decreased in 15 patients (88%). Average daily insulin requirements went from 50±16 to 44±20 units/day ($p = 0.017$). On a weight basis, insulin needs decreased from 0.85±0.3 to 0.71±0.3 U/kg ($p = 0.001$). None of these patients experienced severe hypoglycemia. Insulin requirements on a weight basis (U/kg) remained stable in 2 patients in whom no weight gain was recorded. All other patients experienced weight gain and reduction in daily insulin requirements. Two patients had a combined CFTR modulator therapy for only 1 month, yet they still experienced a reduction in insulin needs.

Table 1
Clinical and biological changes after CFTR modulator therapy in CFRD patients.

	Baseline, modulator-naïve population (n = 17)	On-treatment (n = 17)*	*p*
Weight (kg)	60 (18.05)	64 (20.25)	*0.001*
BMI (kg/m^2)	20.9 (1.90)	22.1 (3.70)	*0.014*
Insulin requirements (U/kg/day)	0.85±0.3	0.71±0.3	*0.001*
Total daily insulin dose (U/day)	50±16	44±20	*0.017*
FEV_1 (% predicted value)	67.9±19.5	79.3±20.3	*<0.001*
HbA1c (%)	7.7±1.6	7.3±1.1	*0.072*

Abbreviations: ETI, elexacaftor + tezacaftor + ivacaftor;TI, teazcaftor + ivacaftor; BMI, body mass index; FEV_1, forced expiratory volume in 1 s.
Results are presented as means ± SD or median (IQR); p value: statistical significance (<0.05 considered statistically significant).
* Four patients received ETI up front after initial evaluation and never received TI. Four patients received TI throughout the study, after initial evaluation. The remaining 9 patients started with TI after initial evaluation and then switched to ETI. Median follow-up was 16 (4) months.

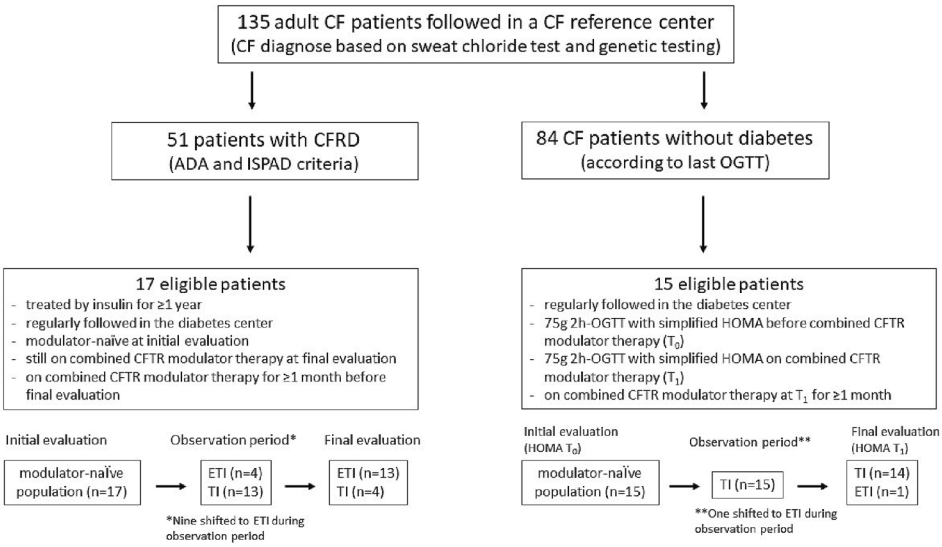

Fig. 1. All patient were modulator-naïve at initial evaluation. In the CFRD group, 4 patients received ETI up front and never received TI. Another 4 patients received TI throughout the study. The remaining 9 patients were initially on TI, before being switched to ETI. All but one of the patients were receiving TI at the time of second HOMA modeling. The sole patient on ETI at the second evaluation had been taking it for one month. He was previously receiving TI for one year. Abbreviations: TI, tezacaftor + ivacaftor; ETI, elexacaftor + tezacaftor + ivacaftor.

Among patients with a reduction of insulin on a weight basis, 8 had a reduction in both basal and bolus insulin, 2 in basal insulin only, 3 in bolus insulin only, and 2 had no change in insulin daily dose yet experienced weight gain and stable HbA1c. Eight patients reported improved appetite and 6 increased physical activities.

Eight patients reported a higher rate of daytime hypos on combined CFTR modulator therapy. Ten patients reported more frequent nocturnal hypoglycemias following treatment. Two patients had to be seen by the diabetic education nurse team between 2 follow up visits to adjust doses due to hypoglycemias occurring after starting therapy. Four patients had a TBR ≥5% after TI initiation. Two patients had a TBR ≥5% on ETI.

On-treatment, BMI improved significantly (20.9 (IQR: 1.90) *vs* 22.1 kg/m^2 (IQR: 3.70); $p = 0.014$). Weight increased significantly 60 (IQR: 18.05) *vs* 64 kg (IQR: 20.25); $p = 0.001$). HbA1c tended to improve (7.7 ±1.6 *vs* 7.3±1.1%; $p = 0.072$). FEV_1 increased from 67.9±19.5 to 79.3 ±20.3% ($p < 0.001$).

After omitting the 4 patients on TI during the entire observation period, the difference in insulin requirements remained significant (0.83 ±0.3 *vs* 0.72±0.3 U/kg; $p < 0.001$; n = 13). Difference in HbA1c was not statistically significant (7.15 (IQR: 2.17) *vs* 7.15 % (IQR: 1.40); $p = 0.075$). By adding the 4 patients for whom data on treatment shift (transition from TI to ETI) were available to the 4 patients who only had ETI, considering thus only the observation period on ETI, the difference in insulin requirements was still significant (0.74±0.3 *vs* 0.67±0.3 U/kg; $p = 0.014$; n = 8;). A Wilcoxon's test showed no significant difference in HbA1c ($p = 0.075$). A third sub-analysis, covering only the period on TI, showed a significant difference in insulin requirements (0.87±0.3 *vs* 0.73±0.4 U/kg; $p = 0.030$; n = 8). Wilcoxon test showed no significant difference in HbA1c (7 (IQR: 2.40) *vs* 7.2 % (IQR: 1.50) ($p = 0.878$). These data suggest that the ETI patients as a subgroup was not pulling the overall results towards significance.

Results for the CF without diabetes group

Among CF patient without diabetes, the homozygous genotype was also dominant (14/15; 93%). One heterozygous patient carried the F508del/2789 + 5G->A mutation. All patients had pancreatic exocrine insufficiency. Ten were male (10/15; 67%), and median age was 22 years (IQR: 11), mean age was 25±8 years. Three patients had impaired glucose tolerance (IGT) based on 120 min post-OGTT glycemia >140 and <200 mg/dl. All, but one patient on ETI, were on TI at final evaluation (T_1). The only patient who was taking ETI had been taking it for 1 month. He had previously been on TI for 1 year.

The main results are summarized in Table 2. Mean duration of CFTR modulator therapy during observation time was 10±5 months. The mean interval between the 2 HOMAs (T_0 and T_1) was 2.5±1.3 years. OGTT categories (NGT, IGT, IFG) hardly changed over time, since all patients with previous glucose intolerance remained as such, except for one with normoglycemia at baseline who became glucose intolerant. At time point 0′, mean glucose level increased from 83±9 to 86±7 mg/dl ($p = 0.099$) and insulin levels did not change with statistical significance (52.2 (IQR: 48.20) *vs* 37.80 pmol/L (IQR: 47.30) ($p = 0.532$). At time point 120′, mean glucose level increased from 107±29 to 121±27 mg/dl ($p = 0.038$) and insulin levels did not changer either (259.1 (IQR: 267.2) *vs* 324.8 pmol/L (IQR: 245.1) ($p = 0.609$). There were no differences in HOMA indices prior to (T_0) and following CFTR modulator therapy (T_1). On-treatment HOMA-B changes were not significant (129.2 (IQR: 84.8) *vs* 103.5 % (IQR: 66.3) nor were HOMA-S changes (from 94±64 to 95 ±49%). HOMA-BxS decreased from 112±45 to 104±29% (NS). Wilcoxon test showed no difference in HOMA-BxS loss rate 0.0 (IQR: 0.80) *vs* 0.07 %/year (IQR: 0.71).

We collected an additional HOMA (T_{-1}) for 12 of them. They were included in an intra-subject multiple measures model to determine whether there was a decrease of HOMA-BxS loss rate on combined CFTR modulator therapy. The average time between T_{-1} and T_0 was 26±14 months. The average time between T_0 and T_1 was 34±15 months. T_{-1} HOMA-BxS loss rate was 0.3±0.6 %/year but the difference between means was not statistically significant ($p = 0.239$). HOMA-S loss between T_{-1} and T_0 was 11±51%/year. HOMA-S loss between T_0 and T_1 was 1.5±30%/year ($p = 0.638$). BxS loss between T_{-1} and T_0 was 5.3 ±40.5%/year. BxS loss between T_0 and T_1 was 2.2±6.6 %/year ($p = 0.800$). On-treatment BMI significantly increased from 21.9±3 to 23.1 ±3.5 kg/m^2 ($p = 0.047$). Weight increased from 60.5±13.1 to 64.3 ±14.2 kg ($p = 0.022$). HbA1c was unchanged (5±0.5 to 5±0.5%). FEV_1 increased from 81.7±20.6 prior to therapy to 89.1±22.2% on-treatment ($p = 0.013$).

Table 2
Clinical and biological changes on CFTR modulators therapy in CF patients without diabetes.

	Baseline, modulator-naïve population T_0 (n = 15)	On-treatment T_1 (n = 15)*	*p*
Weight (kg)	60.5±13.1	64.3±14.2	*0.022*
BMI (kg/m^2)	21.9±3	23.1±3.5	*0.047*
HOMA-B (%)	129.2 (84.8)	103.5 (66.3)	*NS*
HOMA-S (%)	94±64	95±49	*NS*
HOMA-BxS (%)	112±45	104±29	*NS*
BxS loss rate (%/year)	0.0 (0.80)	0.07 (0.71)	*NS*
HbA1c (%)	5.0±0.5	5.0±0.5	–
FEV_1 (% predicted value)	81.7±20.	89.1±22.2	*0.013*

Abbreviations: TI, tezacaftor + ivacaftor; ETI, elexacaftor + tezacaftor + ivacaftor; BMI, body mass index; FEV_1, forced expiratory volume in 1 s.
Results are presented as means ± SD or median (IQR); p value: statistical significance (<0.05 considered statistically significant).
* All but one patient received TI at the time of second HOMA evaluation. The sole patient taking ETI at the time of second evaluation had been taking it for one month. He had previously been receiving TI for one year. The average duration of CFTR modulator therapy was 10±5 months. The time interval between the two HOMAs was on average 2.5±1.3 years.

Discussion

In this retrospective study, total daily insulin dose of patients with CFRD significantly decreased following combination therapy with CFTR modulators. Alongside the reduction in insulin needs, weight gain and improvement in respiratory function were observed. We assumed that HOMA2 could be used to assess glucose homeostasis determinants in the context of CF based on previous studies[35–39]. Of note, there were no significant changes in HOMA-derived estimates of BCF and IS in patients without diabetes after treatment with CFTR modulators, even though they gained weight and improved lung function.

These seemingly contradictory findings must be interpreted in the light of an equally disparate literature, comparison with previous reports being hampered by heterogeneity of study designs. Ours appears to be the first study having evaluated the effect of combination therapy on glucose homeostasis determinants, including insulin requirements over time and multiple HOMA indices, in a well-characterized CF population with and without diabetes.

There have been conflicting results in studies examining the effect of CFTR modulators on diabetes control, on the one hand, and on glucose homeostasis in non-diabetic patients, on the other hand. One case report and a handful of numerically small studies previously hinted that treatment with IVA resulted in diabetes remission, or improvement of glycemic control. These authors based their conclusions from conventional OGTT results[18–20,23]. Additionally, analyses of US and UK CF registries indicated favorable trends in glycemic control in CFRD patients treated with IVA compared to untreated patients. These analyses revealed a lower prevalence of CFRD over time suggesting that IVA treatment may improve BCF[7,8]. Other small-scale studies found no improvement in diabetes control on treatment with LI[16,21,22].

However, one recent study of 40 CF patients with abnormal glucose tolerance reported, after one year of treatment with LI, improved glucose tolerance, as indicated by a decrease of 1 h and 2 h OGTT glucose levels[15]. Paradoxically, LI seems to increase fasting blood glucose level although it remained within normal[24,25]. Equally mixed conclusions were reached as regards ETI. On the one hand, Scully et al. prospectively demonstrated improvement in continuous glucose monitoring (CGM) data (blinded to patients) and HbA1c in 23 diabetic and non-diabetic patients on triple combination[5]. Patients without diabetes on-treatment spent less time with interstitial glucose levels >200 mg/dL. Korten et al. retrospectively showed improvement in OGTT results with regression to glucose intolerance stage without changes in CGM data[9]. Similarly, Steinack et al. showed the same outcomes, with additional improvement in HbA1c[27]. Chan et al reported a significant decrease of HbA1c 10.5 months after initiation of ETI in 22 patients (including different glucose tolerance stages) but CGM data didn't change and OGTT changes were variable[26]. On the other hand, Crow et al. did not report differences in CGM data nor in HbA1c after 3 and 6 months of treatment in 11 diabetic patients in a retrospective analysis [17]. Total daily insulin requirements decreased, but the decrement was not statistically significant. They concluded that insulin needs were unchanged by triple modulators therapy, although their data were unadjusted for weight gain. This suggests that insulin needs may have decreased on a unit-per-weight basis. Gaines et al. also showed that 30% of their patients became insulin-independent after 2.5 years of CFTR modulator therapy[6]. In the present study, mean CFTR modulator therapy duration was 14 months and 2 patients experienced exogenous insulin requirements reduction on treatment within a mere 1 month. Several studies have reported a rapid-onset benefit of CFTR modulators on lung function within 2 to 4 weeks[40]. We assumed that a period twice as long as that required for lung improvement would be empirically sufficient to induce changes in whole-body carbohydrate homeostasis, even though this may be too short as regards pancreatic endocrine function. It is often reported that insulin requirements rapidly decrease on CFTR modulators therapy[6,18]. These observations indirectly suggest that the effect of CFTR modulators on glucose homeostasis could be equally rapid, but more evidence is required, since many confounding factors could be involved. It cannot be ruled out that longer exposure to CFTR modulators could have had a greater impact on glucose homeostasis, inducing discontinuation of insulin in some patients.

Age is a two-sided confounder, as it represents a longer time spent suffering from CF, pancreatic fibrosis, as well as more duration of residual insulin secretion loss. Further, any improvement in the latter would be relative, depending on baseline residual insulin secretion. Long-standing diabetic patients would not benefit as much of a similar relative improvement in BxS on treatment as would younger diabetic patients or patients with shorter diabetes duration, due to greater B cell loss at baseline. We were not able to make subgroups analyses based on diabetes duration (or on BxS loss) due to limited sample size. It is unlikely that CFTR channels are directly involved in insulin secretion[13]. Improved IS, whatever its underlying mechanism, may account for better BxS function rather than improved insulin secretion, as BxS incorporates both insulin secretion and IS as a product of each other. Unfortunately, we could not retrieve data in the EMR on physical activity level from baseline to follow-up. We could neither assess, from our data set, whether CFTR modulators had a beneficial impact on pancreatic fibrosis over the study period. However, in this scenario, improvement in absolute insulin secretion would be relative, depending on baseline residual insulin secretion. Thus, older diabetic individuals would not benefit as much from potential recovery in BCF compared to younger diabetic individuals, given their greater loss of BCF and smaller residual islets mass. Conversely, patients without diabetes would benefit less from the effect of CFTR modulators on glucose homeostasis compared patients with diabetes given their greater muscle mass and therefore lower potential of improvement in IS. Since mean diabetes duration was long (15 years) the decrease in insulin requirements among CFRD patients would be more consistent with improved IS rather than enhanced insulin secretory function but this needs to be further explored.

Our results regarding BCF and IS are consistent with the four studies having explored residual BCF through mathematical modeling, even though the CFTR modulators combinations were not the same as in the present study. As mentioned, one of these was a retrospective control study that aimed at investigating 1-year bitherapy with LI in 13 homozygous F508del non-diabetic patients. There was no statistically significant difference between pre- and on treatment data regarding BCF, IS, and insulin clearance[24]. Their assessment used a model of insulin secretion extracting multiple indexes of BCF from a physiological meal test[41]. Piona et al. did not show any difference in glucose homeostasis determinants among non-diabetic children and young adults with CF treated with combined CFTR modulators for a median of 16.3 months. Sixteen received LI and 5 received ETI[25]. BCF and insulin clearance were assessed by conventional 75 g OGTT-based mathematical modeling and IS was estimated by the Oral Glucose Sensitivity Index. HbA1c levels of patients on triple therapy decreased. In addition, neither these studies nor ours showed significant changes in glucose tolerance brought about by combined CFTR modulators. We observed that one among non-diabetic patients transitioned from NGT to IGT over a 3-year period. A conversion rate from NGT to IGT of 27% over a 2-year period was reported in an adult cohort with an average age of 27y[42]. We found a lower conversion rate of 8% in our cohort. Due to limited cohort size, we cannot determine the conversion rate from NGT to IGT with statistical power. As mentioned, glucose levels at time point 120′, on average 2.5 years after the previous OGTT, increased significantly in the non-diabetic group. This could suggest that either CFTR modulators do not prevent deterioration of glucose homeostasis in CF, and/or that they increase glucose uptake by the gut during OGTT.

There is no data on the rate of BCF loss in CF patients. The 2.5 years' time-span between the two OGTTs is sufficient to account for the observed 2 h-OGTT blood sugar elevation as a result of the inherent pathophysiological process of CF, added on top of the secular BxS loss experienced by all individuals. CFTR channel modulators may counter this decline. HOMA-BxS loss rate non significantly decreased in this study. Improvement of lung function, conducive to increased physical activity, could promote muscle mass gain and improved IS, this being indirectly supported by the fact that patients gained weight without worsening insulin resistance. Another possible explanation would be a reduction in BCF loss as a result of lesser pancreatic inflammation. Further we did not evaluate body composition nor leisure-time physical activity since these data are not routinely collected in the EMR. Recently, Granados et al. have provided the first elements of an answer by studying body composition changes through dual-energy X-ray absorptiometry fat-free mass and fat mass adjusted for height, before and after HEMT (ETI). They showed fat gain without muscle mass changes which contradict our assumptions above[43]. Finally, Chan et al. showed no improvement in BCF, measured through the oral disposition index, and showed a worsening of IS through $OGTT_{C\text{-}pep}$ index[26]. Steinack et al. showed no difference in BCF and IS in a small single-center observational study including 33 CF patients with different glucose tolerance status treated with ETI)[27]. They used the insulinogenic index to determine BCF according to Wareham et al.[44] and the whole-body sensitivity index was calculated according to Matsuda and De Fronzo[45].

Our study has several inherent limitations, beyond its retrospective design, with small sample size and short duration of follow-up. Firstly, the cohort was heterogeneous in terms of modulators administered, which may have differed in their individual or combined effects on the variables under study. We hypothesized that a class effect of CFTR modulators would be operative which is why we gathered all patients irrespective of modulators number. Moreover, ETI was only recently approved in Belgium (September 2022) while IT was available as of April 2021. Only a few patients had access to ETI prior to 2022, and for

compassionate use. Nevertheless, the sub-analyses suggested an independent effect of TI and ETI. Secondly, the time elapsed between the T_0 HOMA modeling and treatment initiation may have contributed to further loss of residual insulin secretion, as assessed by HOMA-BxS, and we did not take into consideration diabetes duration in the CFRD group. Thirdly, we arbitrarily assigned the patients a [BxS] function of 100% at birth, and we cannot ascertain whether a nil [BxS] value de facto equates with an endocrine pancreatic function that is immutable. As a result, [BxS] loss rate may have been underestimated in some patients. Moreover, we did not analyze the effect of combined CFTR modulator therapies on leisure-time physical activity which may lead to decreased insulin needs as a consequence of raised exercise level and/or higher skeletal muscle mass, nor on body composition or appetite. Thus, CF patients may experience exercise intolerance, from acquired sarcopenia & abnormal oxygen transport within skeletal muscles where the CFTR channel is expressed[46]. Low muscle mass is associated with insulin resistance, and CF patients with IGT have lower skeletal muscle mass than NGT patients[47]. Exercise-based interventions are beneficial for CF patient in terms of muscle strength and cardiorespiratory endurance [48]. Muscle strength and power improved alongside VO_2 max and maximal workload after one year of either LI or TI[49]. Similar results regarding levels of aerobic workout were demonstrated in patients on ETI[50]. Improved physical condition could lead to more recreative or occupational (including intensive) physical activity, thereby generating a virtuous circle with improved IS as outcome. There was no data on insulin-carbohydrate ratios. However, it is much easier to estimate total daily insulin dose with fixed mealtime insulin doses than with ratios. Data on changes in carbohydrate intake per meal could have given an insight into increased appetite and IS. From this perspective, the lack of carb counting is a little limitation as is the lack of CGM or SMBG data. The fact that HbA1c remained stable or decreased supports the decisions made regarding the reduction of insulin doses. Physical activity and appetite, although evaluated on a subjective basis in the CFRD group, seemed to improve in this study but no conclusion can be drawn. The limited sample size of this study could explain the non-statistical achievement in non-diabetics as regards HOMA indices. Trends seen in HOMA-S and BxS loss need to be further explored. Finally, HOMA indices must ideally be calculated from the mean of median of triplicate pairs of glucose-insulin measurements to decrease analytic variation and the impact of pulsatile insulin secretion.

In conclusion, this retrospective study showed a trend towards improved glycemic control with lesser insulin doses, without concurrent severe hypoglycemias in patients with CFRD on combined CFTR modulators. HOMA indices in CF patients without diabetes treated with combined CFTR modulator therapies showed no improvement in insulin secretion. These results could indicate, in line with recent literature, a potential benefit of new generation CFTR modulators in CF patients with diabetes. Such benefit may lie in increased physical activity, with secondary improvement in IS. CFTR modulators did not modify glucose homeostasis determinants in CF patients without diabetes, although limited sample size may have blunted the statistical significance of the observed changes. Further data collection and prospective analyses are needed for in-depth assessment of the benefits of CFTR modulators on glucose homeostasis in CF patients.

CRediT authorship contribution statement

Fabian Lurquin: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Visualization. **Sophie Gohy:** Resources, Writing – original draft. **Michel P. Hermans:** Conceptualization, Writing – original draft, Validation, Supervision. **Vanessa Preumont:** Conceptualization, Resources, Writing – original draft, Validation, Supervision.

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.

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