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Original Article

ORIGINAL ARTICLE

Kidney effects of triple CFTR modulator therapy in people with cystic fibrosis

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ABSTRACT

Background. Elexacaftor/tezacaftor/ivacaftor (ETI) is a new cystic fibrosis transmembrane conductance regulator (CFTR) modulator that has transformed the respiratory prognosis of people with cystic fibrosis (pwCF). However, its impact on other organs such as the kidneys, where CFTR is expressed, remains unclear. Since pwCF are risk of both kidney disease and urolithiasis, we aimed to study the potential effects of ETI on renal function, volume status, and risk factors for urolithiasis.

Methods. This prospective, observational, single-center, before–after cohort study, involved adult pwCF eligible for ETI. The changes in plasma and urinary profiles were assessed by comparing renal function (using 2021 CKD-EPI$_{creatinine}$ and 2021 CKD-EPI$_{creatinine\text{-}cystatin\ C}$ formulas), volume status (using aldosterone/renin ratio and blood pressure), and risk factors for urolithiasis, at the time of ETI introduction (M0) and 7 months after (M7).

Results. Nineteen pwCF were included. No significant change in renal function was observed between M0 and M7 (2021 CKD-EPI$_{creatinine}$: 105.5 ml/min/1.73 m² at M0 vs. 103.3 ml/min/1.73 m² at M7; $P = .17$). There was a significant reduction in aldosterone level (370.3 pmol/l at M0 vs. 232.4 pmol/l at M7; $P = .02$) and aldosterone/renin ratio (33.6 at M0 vs. 21.8 at M7; $P = .03$). Among the risk factors for urolithiasis, a significant reduction in magnesuria level was found (4.6 mmol/d at M0 vs. 3.8 mmol/d at M7; $P = .01$).

Conclusion. These findings suggest that ETI seem to have no short-term impact on the renal function of adult pwCF and appears to correct secondary hyperaldosteronism due to excessive sweat losses. Further investigations are needed to determine the potential impact of decreased magnesuria observed under ETI therapy on the risk of urolithiasis.

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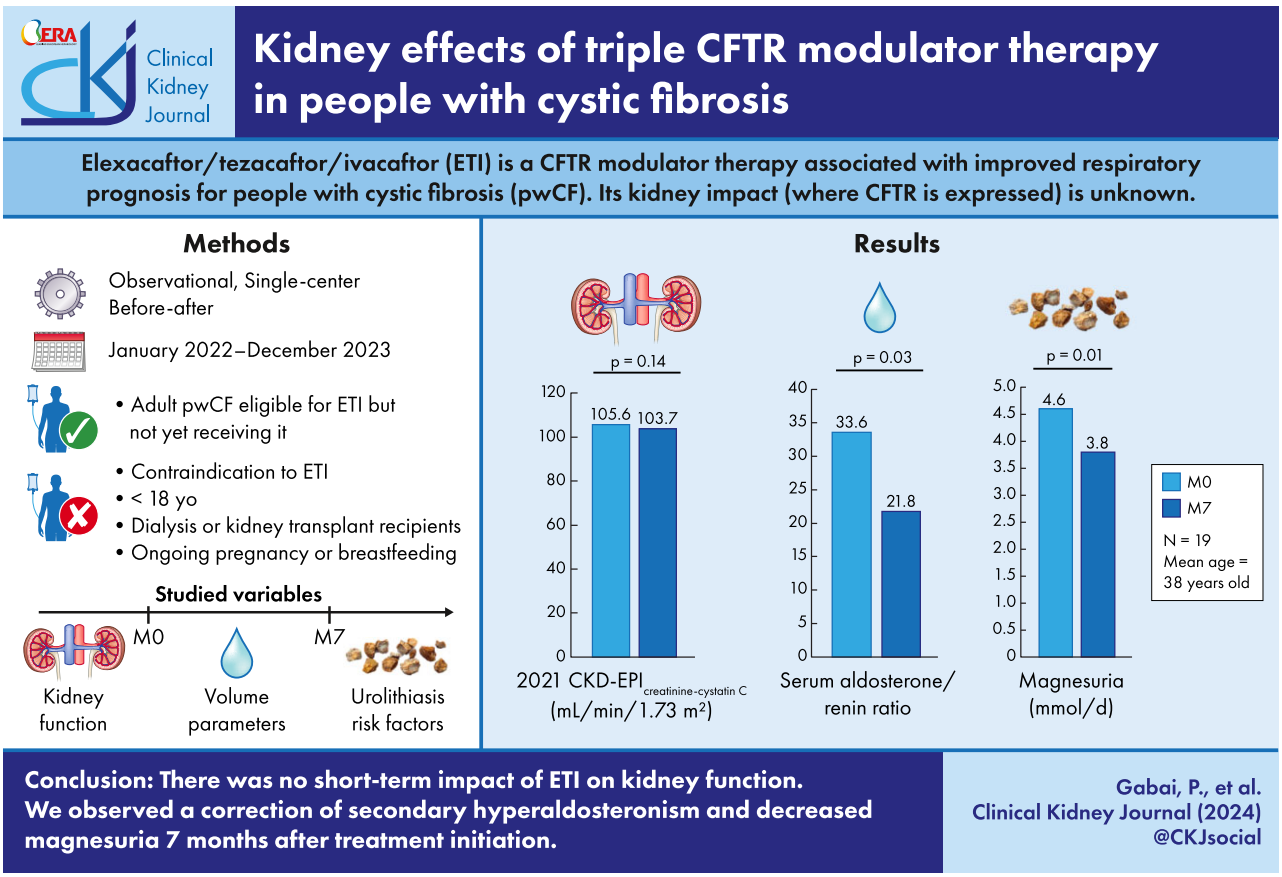
GRAPHICAL ABSTRACT



Keywords: cystic fibrosis, elexacaftor/tezacaftor/ivacaftor, glomerular filtration rate, risk of urolithiasis, secondary hyperaldosteronism

KEY LEARNING POINTS

What was known:

- Elexacaftor/tezacaftor/ivacaftor (ETI), a new triple transmembrane conductance regulator (CFTR) modulator, improves respiratory function in adult people with cystic fibrosis (pwCF) after 7 months of treatment.

This study adds:

- ETI has no short-term impact on the renal function of adult pwCF when assessed by estimated glomerular filtration rate.

Potential impact:

- ETI appears to correct secondary hyperaldosteronism due to excessive sweat losses and seems to lead to decreased magnesuria, the impact of which on the risk of urolithiasis needs to be further elucidated.

INTRODUCTION

Cystic fibrosis (CF) is a systemic autosomal recessive disorder that was estimated to affect more than 7700 individuals in France in 2022 [1]. It is caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) protein, leading to CFTR protein dysfunction [2]. CFTR codes for an epithelial anion channel that transports both Cl^- and HCO_3^- across the epithelial surface [3], mainly expressed in the respiratory tract, causing progressive pulmonary failure [4].

CFTR is also expressed in the gastrointestinal system including the pancreas, liver and bile ducts, sweat glands, and the genital tract [4]. CFTR is likewise described in all segments of the nephron [5], where its role remains unclear. The renal function of adult people with CF (pwCF) before lung transplantation seems preserved despite the repeated

administration of aminoglycosides for pulmonary exacerbations [6]. However, it has been widely observed that urolithiasis is more common in pwCF than in the general population [7], mainly due to hyperoxaluria, which is favored by exocrine pancreatic insufficiency and repeated antibiotic therapy [8–10, 11]. Additionally, sweat and digestive losses lead to hypovolemia and low diuresis, which also favors urolithiasis [12].

Until recently, the most effective treatment for advanced respiratory insufficiency in pwCF was pulmonary transplantation. The median survival following lung transplantation in pwCF is 9.5 years [13]. However, the access to lung transplantation is limited [14] and this technique poses a high risk of complications, including surgical complications, the risk of rejection, opportunistic infections, and complications related to chronic immunosuppressive treatments [15]. Additionally, a considerable loss in renal function has been reported after pulmonary transplantation, leading to maintenance dialysis requirement [16].

CFTR modulators have recently been developed to restore the function of the defective protein and have transformed the prognosis of pwCF. These medications include correctors, allowing CFTR protein expression at the membrane, and potentiators, which improve the function of abnormal CFTR proteins already present at the apical surface of the cell [17]. The first triple-combination of CFTR modulators (elexacaftor/tezacaftor/ivacaftor, ETI) obtained marketing authorization in the USA in October 2019 [18]. The impressive clinical effectiveness of ETI on respiratory function has been shown to lead to a decrease in the rate of pulmonary exacerbations and a reduced need for lung transplantation [19, 20].

Nevertheless, questions remain about the effects of ETI outside the lungs. While the correction of sweat Cl^- excretion has already been widely studied [19, 21], the renal impact of this new treatment has not been previously described, even in pivotal trials [19, 21]. The aim of this prospective before–after study was to describe the changes in renal function, volume status, risk factors for urolithiasis, and nutritional status of pwCF after the introduction of ETI.

MATERIALS AND METHODS

Study population and design

We conducted a prospective, observational, single-center, before–after cohort study, investigating the renal impact of ETI on adult pwCF, between 1 January 2022 and 31 December 2023. All adult pwCF eligible for ETI but not yet receiving it were included. Participants were enrolled following an extension of the French market authorization of ETI for pwCF with at least one DF508 mutation and those included in compassionate use programs.

Exclusion criteria were medical contraindication to ETI, age <18 years old, patients on maintenance dialysis (hemodialysis or peritoneal dialysis), kidney transplant recipients, ongoing pregnancy, breastfeeding, active cancer, and patients who objected to the collection of their medical data.

Relevant demographic characteristics, medical history, any concomitant medication, clinical and laboratory findings, and nutritional data were obtained following scheduled visits at the CF reference center. Data were collected from the patients' medical charts before the introduction of ETI (M0) and 7 months after (M7).

This study complied with the reference methodology of the French data protection agency (CNIL registration—MR004 no. 22–5080). The research fully complied with ethical standards and the principles of the Second Declaration of Helsinki. It obtained approval from the Scientific and Ethical Committee of the Hospices Civils de Lyon (CSE no. 22–5080). All participants involved in the study provided oral consent before enrollment. The study was registered on ClinicalTrials.gov (NCT06197490).

Variables

The following clinical variables were included in the analysis: systolic and diastolic blood pressure, presence of orthostatic hypotension (defined by a decrease in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg), weight and body mass index (BMI, defined by the weight-to-squared height ratio), and lung function assessed during a respiratory functional exploration, using predicted forced expiratory volume in 1 s (FEV1).

Laboratory measurements, assessed using standard methods in the routine clinical laboratory in blood and 24 h urine samples, were performed for renal function, volemic parameters, metabolic risk factors for urolithiasis, and nutritional status.

For renal function, the estimated glomerular filtration rate (eGFR), plasma urea level, and urinary sediment were assessed. The eGFR was calculated using the 2021 CKD-EPI$_{creatinine}$ and 2021 CKD-EPI$_{creatinine\text{-}cystatin\ C}$ formulas [22, 23], as well as the 2009 CKD-EPI$_{cystatin\ C}$ formula, the Schwartz formula, and measured creatinine clearance [clearance = (creatininuria × 24-hour diuresis)/(serum creatinine × duration)] [24]. Plasma urea level and urinary sediment were estimated by proteinuria (g/day), albuminuria/creatininuria ratio (mg/g), and urinary β2-microglobulin level (mg/day), on a 24-hour urine sample. Creatinine was assayed using an enzymatic method (Roche Diagnostics, Meylan, France), with calibrators assigned using isotope dilution mass spectrometry. Cystatin C was measured by immuno-nephelometry.

Volume parameters of interest were renin and aldosterone levels and aldosterone/renin ratio, natremia, natriuresis, kalemia, kaliuresis, chloremia, bicarbonatemia, sodium excretion fraction [= (natriuresis × serum creatinine)/(natremia × creatininuria)], brain natriuretic peptide level, hemoglobin level, and sodium intake estimated by the dietician and calculated using 24 h natriuresis.

The biological parameters of metabolic risk factors for urolithiasis considered were blood phosphorus and calcium metabolism (ionized calcium level, phosphoremia, magnesemia, parathyroid hormone level, and 25-OH vitamin D level); calciuria, oxaluria, uricosuria, magnesuria, citraturia, glycosuria, and phosphaturia, which were estimated on a 24-hour urine sample-; magnesium excretion fraction, calculated using the following formula: magnesium excretion fraction = (magnesuria × serum creatinine)/(magnesemia × creatininuria) × 100; protein intake calculated using 24 h urinary urea (protein intake = urinary urea/5/weight); calcium intake estimated by the dietician; and urinary pH, urinary density, and crystalluria measured in fresh urine.

Nutritional status was assessed using albumin level, measured by immunoturbidimetry, as well as pre-albumin level.

Statistical analysis

All statistical analyses were performed using GraphPad v.10 software.

Data are expressed as mean ± standard deviation (SD), mean (range), or absolute number and percentage. Simple comparisons between before (M0) and after (M7) the introduction of

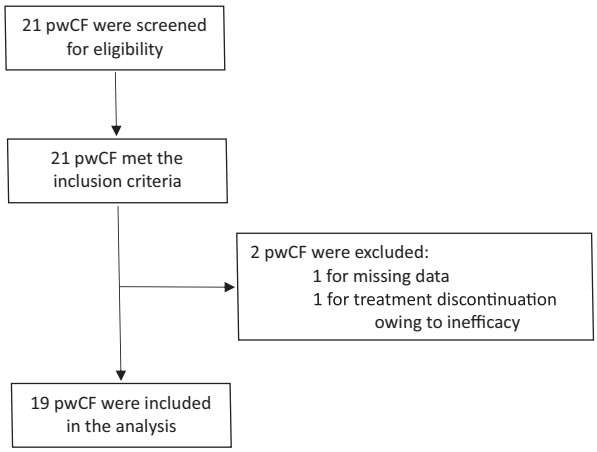


Figure 1: Study flow chart.

ETI parameters were made using the Student's paired *t*-test or Chi-square test. A *P* value <.05 was considered significant.

RESULTS

Study population

The study was conducted at our CF reference center between 1 January 2022 and 31 December 2023. A total of 19 adult pwCF were included for analysis (Fig. 1). The mean (range) age was 38 (18–67) years old and 52.6% of patients were women. Two patients (10.6%) were homozygous for DF508, 15 patients (78.8%) were heterozygous, and two patients (10.6%) had other mutations. The mean (range) age at CF diagnosis was 23.6 (0–67) years. In terms of previous therapy, 13 patients (68.4%) had no history of other CFTR modulator therapy, one (5.3%) had previously benefited from ivacaftor, one (5.3%) from lumacaftor + ivacaftor, and four (21%) from tezacaftor + ivacaftor (Table 1).

Table 1: Demographic and clinical characteristics of the population at baseline.

	Total population $n = 19$
Sex (male/female)	9/10
Mean age (range) in years	38 (18–67)
Mean BMI (range) (kg/m²)	24.1 (18.5–32.2)
Percentage of predicted FEV_1 from theory	
Mean (range)	76.1 (26–122)
Distribution, *n* (%)	
<40%	3 (15.8)
40–<70%	4 (21)
70–<90%	5 (26.3)
≥90%	7 (36.9)
Age at CF diagnosis (years)	
Mean (range)	23.6 (0–67)
Distribution, *n* (%)	
<1 year	3 (15.8)
>1 year	16 (84.2)
DF508 mutation, *n* (%)	
Homozygous	2 (10.6)
Heterozygous	15 (78.8)
None	2 (10.6)
Protein therapy prior to ETI, *n* (%)	
None	13 (68.4)
Ivacaftor	1 (5.3)
Lumacaftor + ivacaftor	1 (5.3)
Tezacaftor + ivacaftor	4 (21)
Medical history, *n* (%)	
Urolithiasis	0 (0)
Diabetes	1 (5.3)
High blood pressure	2 (10.6)
Dyslipidemia	0 (0)
Heart failure	0 (0)
Chronic kidney disease	0 (0)
Treatment, *n* (%)	
Diuretics	0 (0)
Inhibitors of the renin–angiotensin–aldosterone system	1 (5.3)
Other antihypertensive drugs	1 (5.3)
Pancreatic extracts	12 (63.2)
Vitamin D supplementation	10 (52.6)

Lung function

As expected, the mean percentage from theory of predicted FEV1 significantly increased under treatment by 13.9% (76.1% at initiation vs. 86.7% at M7; $P < .01$), reflecting a good respiratory effectiveness of ETI.

Renal function and urinary sediment

The mean serum creatinine level significantly increased by 5.2% between M0 and M7 (71.2 vs. 74.9 µmol/l, respectively, $P = .04$). There was no significant difference in serum cystatin C level between the two time points (0.85 vs. 0.87 mg/l, $P = .35$).

No significant difference was found in terms of eGFR using both the 2021 $CKD\text{-}EPI_{creatinine}$ and 2021 $CKD\text{-}EPI_{creatinine\text{-}cystatin\ C}$ formulas (Table 2 and Fig. 2), nor using the other formulas (Supplementary Data).

There was no significant difference in serum urea level, proteinuria, albuminuria/creatininuria ratio, and urinary β2-microglobulin level between M0 and M7 (Table 2).

Volume status

The mean serum aldosterone level was decreased by 137.9 pmol/l between M0 (370.3 pmol/l) and M7 (232.4 pmol/l), reflecting a 37.2% reduction ($P = .02$; Fig. 3). A 35.1% reduction in the serum aldosterone/renin ratio was found (33.6 at M0 vs. 21.8 at M7, $P = .03$; Fig. 3). No significant difference was found in systolic and diastolic blood pressure, serum renin level, natremia, natriuresis, kalemia, kaliuresis, chloremia, bicarbonatemia, sodium excretion fraction, brain natriuretic peptide level, hemoglobin level, and sodium intake (calculated and measured), between M0 and M7 (Table 3). Moreover, there was no significant difference in the prevalence of orthostatic hypotension between M0 and M7 (Chi squared test >0.99).

Metabolic risk factors for urolithiasis

The mean magnesuria level was 4.6 mmol/d at M0 and 3.8 mmol/d at M7, reflecting a 0.8 mmol/d reduction ($P = .01$; Fig. 4). There was a significant increase of 13.9 nmol/l in 25-OH vitamin D level (58.3 at M0 vs. 72.2 nmol/l at M7, $P = .01$; Fig. 4), while calcium intake estimated by the dietician decreased

Table 2: Changes in renal function and urine analysis between the introduction of ETI (M0) and 7 months after (M7).

	M0 (mean ± SD)	M7 (mean ± SD)	Paired *t*-test
Serum creatinine level (µmol/l)	71.2 ± 10.3	74.9 ± 12.6	0.04
Serum cystatin C level (mg/l)	0.85 ± 0.21	0.87 ± 0.19	0.35
2021 CKD-EPI$_{creatinine}$ (ml/min/1.73 m²)	105.5 ± 18.1	103.3 ± 19.6	0.17
2021 CKD-EPI$_{creatinine\text{-}cystatin\ C}$ (ml/min/1.73 m²)	105.6 ± 22.4	103.7 ± 21.6	0.14
Serum urea level (mmol/l)	4.9 ± 1.2	5.4 ± 1.6	0.20
Proteinuria (g/d)	0.16 ± 0.09	0.16 ± 0.09	0.72
Albuminuria/creatininuria ratio (mg/d)	18.4 ± 39.4	12.6 ± 16.3	0.27
Urinary β2-microglobulin level (mg/d)	0.07 ± 0.04	0.09 ± 0.08	0.44

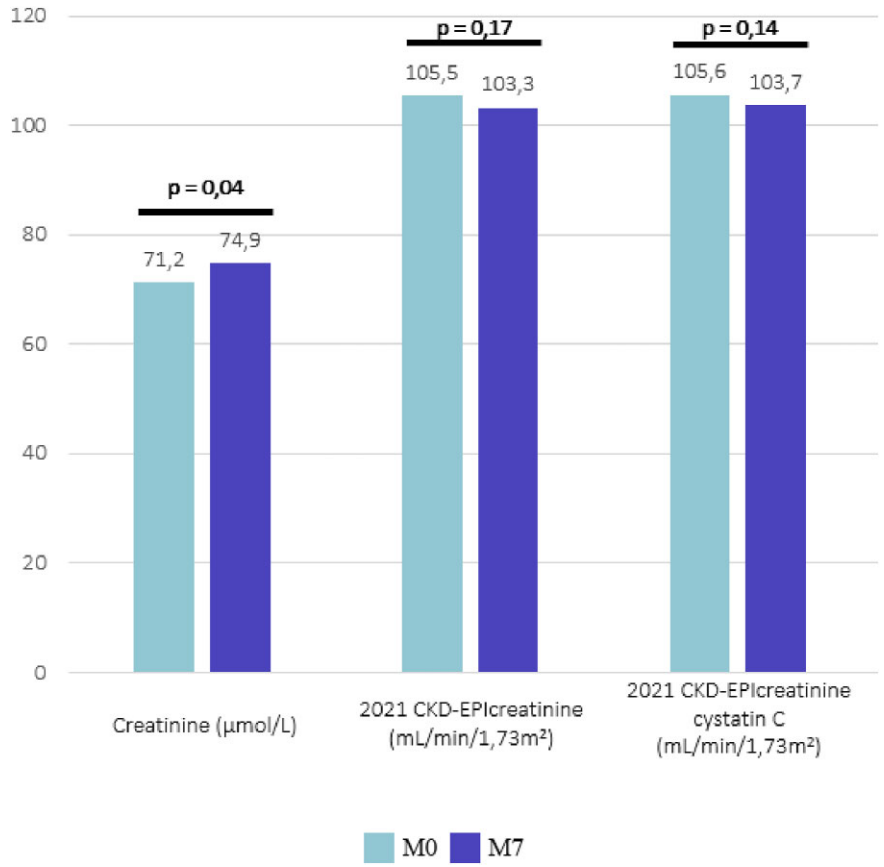


Figure 2: Changes in creatinine levels and eGFR using 2021 CKD-EPI$_{creatinine}$ and 2021 CKD EPI$_{creatinine\text{-}cystatin\ C}$ formulas between the introduction of ETI (M0) and 7 months after (M7).

significantly between M0 and M7 (1.03 vs. 0.80 g/d, respectively, $P = .03$). There was no significant difference in serum ionized calcium level, phosphoremia, magnesemia, parathyroid hormone level, diuresis, urinary pH, urinary specific gravity, calciuria, oxaluria, uricosuria, citraturia, glycosuria, phosphaturia, magnesium excretion fraction, and protein intake calculated between M0 and M7 (Table 4).

There was no significant difference in the presence of crystalluria between M0 and M7 (Chi squared test 0.60): at M0, three patients were positive (one had amorphous phosphate crystals, one had whewellite crystals, and one had both whewellite and weddellite crystals), compared to only one patient at M7 (persistent amorphous phosphate crystals for the first patient).

Nutritional status

No significant increase in BMI (24.1 kg/m² at M0 vs. 24.5 kg/m² at M7, $P = .06$) nor weight (68.1 kg at initiation vs. 69.4 kg at M7, $P = .07$) was observed. The pre-albumin level significantly increased between M0 and M7 (0.26 vs. 0.31 g/l, respectively, $P = .01$), whereas albumin level, which was normal at baseline, did not undergo significant changes throughout the study (40.3 at M0 vs. 40.5 g/l at M7, $P = .79$).

DISCUSSION

The present prospective before–after cohort study is the first to investigate the renal effects of ETI by examining a wide range of

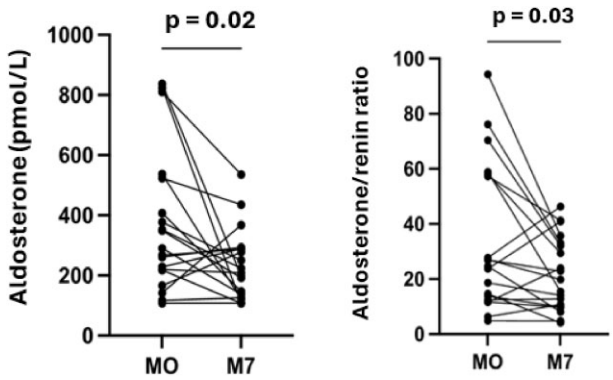


Figure 3: Changes in aldosterone levels and aldosterone/renin ratio between the introduction of ETI (M0) and 7 months after (M7).

parameters, including changes in renal function, volume status, and risk factors for urolithiasis, as well as nutritional status.

In the present cohort, all patients maintained normal eGFR throughout the study period, confirming the previous findings by our group that renal function, measured using either inulin or iohexol, is largely preserved before lung transplantation [6].

The slight increase in serum creatinine level observed herein could be related to changes in the muscle mass of patients rather than an actual change in kidney function. This is confirmed by the absence of modification in plasma levels of cystatin C, a biomarker of renal function independent of muscle mass. Moreover, eGFR using both the 2021 CKD-EPI$_{creatinine}$ and 2021 CKD-EPI$_{creatinine\text{-}cystatin\ C}$ formulas remained largely unchanged between the introduction of ETI and the end of the study. As shown by Al-Aloul *et al.*, eGFR based on creatinine cannot be used to reliably assess renal function in pwCF [25]. However, the stability of cystatin C throughout the study, a biomarker independent of muscle mass, is reassuring concerning the stability of renal function in the present cohort of pwCF.

Furthermore, no change in the level of proteinuria was observed in the present cohort; proteinuria was negative for all patients except one presenting with tubular proteinuria, which was persistent throughout the study.

To our knowledge, the present study is the first to demonstrate a correction of secondary hyperaldosteronism after the introduction of ETI in adult pwCF, as demonstrated by the significant reduction in plasma aldosterone level and aldosterone/renin ratio after ETI initiation. PwCF are known to present secondary hyperaldosteronism as a consequence of excessive sweat losses [26]. We hypothesize that the restoration of CFTR function in sweat glands due to ETI [19, 21] may have resulted in a decrease of salt losses, leading to a correction of the hypovolemia, and thus a decrease in aldosterone secretion. This correction of secondary hyperaldosteronism does not seem to be linked to a reduction of renal salt wasting, as both natriuresis and sodium excretion fraction remained unchanged during the study period. Despite the clear change in the aldosterone level and aldosterone/renin ratio, no significant modification of blood pressure or the presence of orthostatic hypotension was observed. This, however, may be because the study might be underpowered. Of note, one patient was taking a renin–angiotensin–aldosterone system inhibitor; the exclusion of this patient from the statistical analysis however, did not alter the significant decrease in aldosterone level and aldosterone/renin ratio observed. The correction of secondary hyperaldosteronism might indirectly enhance lung function in patients by mitigating the adverse effects of aldosterone on airways and associated inflammation [27]. Nevertheless, these findings would need to be confirmed by body composition measurement using impedancemetry, which could not be performed here due to technical considerations and the observational nature of the study.

Regarding plasma bicarbonate, the present findings are not in line with previous studies, showing that pwCF often present with a reduction in renal bicarbonate secretion, potentially leading to metabolic alkalosis, which could in turn induce a decrease in pulmonary function through alveolar hypoventilation [28]. The observation that plasma bicarbonate levels remained normal throughout the study period herein may be because the present cohort included people with milder forms of CF.

Although pwCF are known to be at an increased risk of urolithiasis, mainly because of enteric hyperoxaluria and low diuresis [7–11, 12], no patient herein presented with asymptomatic kidney stone on available ultrasound imaging. However, this imaging technique is not the most sensitive to explore urolithiasis. Since no systematic computed assisted tomodensitometry was available in the present study, this might have led to an underestimation of the prevalence of urolithiasis.

Table 3: Changes in volume parameters between the introduction of ETI (M0) and 7 months after (M7).

	M0 (mean ± SD)	M7 (mean ± SD)	Paired *t*-test
Systolic blood pressure (mmHg)	122.8 ± 19.4	124.8 ± 15.4	0.60
Diastolic blood pressure (mmHg)	76.0 ± 11.8	80.9 ± 10.9	0.06
Serum renin level (ng/l)	15.9 ± 10.7	14.2 ± 9.8	0.26
Serum aldosterone level (pmol/l)	370.3 ± 234.8	232.4 ± 118.6	0.02
Serum aldosterone/renin ratio	33.6 ± 26.8	21.8 ± 13.4	0.03
Natremia (mmol/l)	139.6 ± 2.0	140.0 ± 1.6	0.27
Natriuresis (mmol/d)	108.0 ± 48.7	115.3 ± 35.6	0.83
Kalemia (mmol/l)	4.1 ± 0.3	4.1 ± 0.4	0.65
Kaliuria (mmol/l)	47.8 ± 28.7	36.5 ± 14.5	0.16
Chloremia (mmol/l)	106.3 ± 2.9	107.8 ± 2.6	0.07
Bicarbonatemia (mmol/l)	23.6 ± 2.6	24.4 ± 2.9	0.21
Sodium excretion fraction (%)	5.6 ± 3.0	5.6 ± 2.2	0.81
Brain natriuretic peptide level (ng/l)	18.7 ± 10.9	21.1 ± 16.6	0.66
Hemoglobin level (g/l)	143.0 ± 13.6	142.6 ± 12.4	0.75
Sodium intake estimated by the dietician (g/d)	9.9 ± 3.3	9.3 ± 2.1	0.60
Sodium intake calculated (g/d)	6.4 ± 2.9	6.8 ± 2.1	0.83

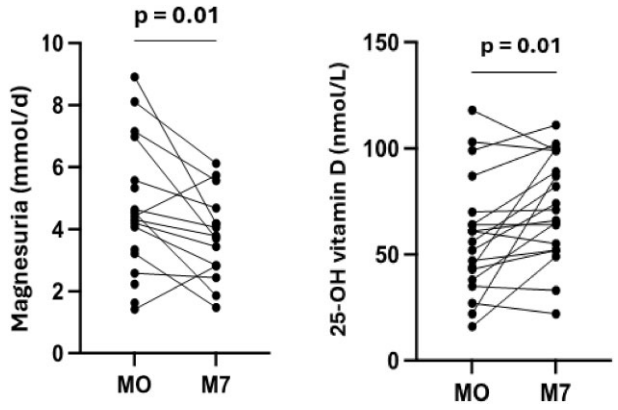


Figure 4: Changes in magnesuria and 25-OH vitamin D levels between the introduction of ETI (M0) and 7 months after (M7).

Regarding the metabolic risk factors for urolithiasis, magnesuria decreased under triple CFTR modulator therapy, although without significant change in magnesemia, which remained normal throughout the study. Hypomagnesuria is known to be a risk factor for urolithiasis [29]. However, in the present cohort, the mean magnesuria remained well above the risk threshold for urolithiasis (<1.5 mmol/day), even at M7, suggesting that the decrease in magnesuria might have limited consequences on the risk of urolithiasis in pwCF. Of note, previous research has shown that in case of CFTR mutation, the transient receptor potential (TRP) channel, expressed notably in the gastrointestinal tract [30], is overexpressed to stimulate the faulty CFTR channel (through extracellular signal transmission) [31, 32]. This leads to a reduced magnesium absorption in the digestive tract, with 50% of pwCF presenting hypomagnesemia [33]. Since both TRP and CFTR are expressed in the kidneys as well [5, 34], we hypothesize that there could be a reduced renal reabsorption of magnesium when CFTR is deficient. Triple CFTR modulator therapy could potentially correct these anomalies, explaining the decrease in magnesuria observed under treatment. These hypotheses require further investigation for a more detailed understanding of intestinal and renal magnesium handling in pwCF.

Concerning other urinary risk factors for urolithiasis, calciuria remained stable throughout the study and well below the lithogenic threshold (>0.1 mmol/kg/day). Surprisingly, no hyperoxaluria was observed, with oxaluria below the urolithiasis risk threshold (>350 µmol/l) before and after ETI initiation. Additionally, citraturia remained above the lithogenic threshold (<1 mmol/l), before and after ETI initiation.

As for classical dietary risk factors for urolithiasis, it is noteworthy that the sodium and protein intake of the patients herein remained stable throughout the study and below the risk

Table 4: Changes in metabolic risk factors for urolithiasis between the introduction of ETI (M0) and 7 months after (M7).

	M0 (mean ± SD)	M7 (mean ± SD)	Paired *t*-test
Serum ionized calcium level (mmol/l)	1.23 ± 0.04	1.24 ± 0.04	0.16
Phosphoremia (mmol/l)	1.01 ± 0.15	0.99 ± 0.11	0.54
Magnesemia (mmol/l)	0.82 ± 0.04	0.81 ± 0.04	0.22
Parathyroid hormone level (ng/l)	26.0 ± 8.7	26.3 ± 8.5	0.90
25-OH vitamin D level (nmol/l)	58.3 ± 27.8	72.2 ± 24.8	0.01
Diuresis (l/d)	1.5 ± 0.7	1.4 ± 0.4	0.18
Urinary pH	5.6 ± 0.7	5.7 ± 0.7	0.72
Urinary specific gravity (g/ml)	1.017 ± 0.004	1.025 ± 0.026	0.27
Calciuria			
mmol/d	3.34 ± 1.60	3.62 ± 2.03	0.93
mmol/kg/d	0.05 ± 0.03	0.05 ± 0.03	0.64
Calciuria (mmol/l)/creatininuria (mmol/l)	0.32 ± 0.16	0.31 ± 0.14	0.31
Oxaluria			
µmol/l	267.1 ± 155.7	244.2 ± 110.2	0.81
µmol/d	327.9 ± 149.9	295.9 ± 100.7	0.43
Uricosuria			
µmol/l	2416.3 ± 975.9	2182.4 ± 670.9	0.80
µmol/d	3141.9 ± 1046.7	2908.1 ± 831.3	0.40
Magnesuria			
mmol/l	3.5 ± 1.8	3.0 ± 1.4	0.12
mmol/d	4.6 ± 2.1	3.8 ± 1.4	0.01
Citraturia			
mmol/l	1.8 ± 1.3	1.7 ± 1.3	0.74
mmol/d	2.3 ± 1.4	2.2 ± 1.5	0.36
Glycosuria			
mmol/l	0.8 ± 2.5	0.2 ± 0.1	0.75
mmol/d	1.0 ± 3.0	0.3 ± 0.1	0.49
Phosphaturia			
mmol/l	20.6 ± 11.6	20.9 ± 10.4	0.26
mmol/d	26.5 ± 10.7	26.1 ± 10.1	0.75
Magnesium excretion fraction (%)	3.3 ± 2.8	2.7 ± 2.0	0.83
Protein intake calculated (g/kg/d)	1.0 ± 0.4	1.0 ± 0.3	0.89
Calcium intake estimated by the dietician (g/d)	1.03 ± 0.30	0.80 ± 0.35	0.03

threshold conventionally considered (>8 g/day for sodium and >1.2 g/kg/day for protein intake). Moreover, the diuresis of these patients remained stable around 1.5 l/day throughout the study, whereas it is usually recommended to maintain urine output >2 l/day to prevent urolithiasis.

In line with previous reports, we also observed a significant increase in 25-OH vitamin D level, which could partly be explained by an enhancement in the digestive absorption of fat-soluble vitamins and diet modifications after the introduction of ETI [35]. Nevertheless, it is challenging to attribute this increase to a specific effect of ETI, as it could be linked to either nutritional or seasonal factors. Additionally, 10 patients were supplemented with vitamin D at the start of the study and two patients started supplementation during the study period, which could have biased the results.

Finally, a significant increase in pre-albumin levels was also observed, while albumin levels remained normal and stable throughout the study. This reflects an improvement in the nutritional status of pwCF under triple CFTR modulator therapy. Additionally, unlike previous findings demonstrating an increase in BMI in pwCF under ETI [36], only a non-significant increase was observed in the present study, which could be partly explained by a lack of statistical power due to a small sample size as well as the already elevated BMI at ETI initiation of the pwCF included herein (surpassing 24 kg/m²). Moreover, nutritional status assessment lacked precise dietary surveys, appetite level evaluation, body composition, and assessment of muscle strength, fat, or pancreatic elastase from stool samples, further limiting the interpretation of nutritional status in pwCF under ETI.

The present study has several limitations

First, the observational before–after cohort design of the study and the limited number of pwCF followed-up over a short period prevents us to draw conclusions about causal relationships. However, proposing a randomized clinical trial would not have been ethically justifiable, considering the clear benefits of triple CFTR modulator therapy on lung status already demonstrated in numerous studies [19, 21]. Long-term prospective data are necessary to evaluate the consequences of ETI on renal function, volume status, and risk factors for urolithiasis.

Second, it is worth noting that the pwCF included in the present cohort mostly suffered from late-stage CF forms, with mostly mild or moderate manifestations. Since the study began several months after the French market release of ETI, most of the more severe pwCF were already under ETI at the start of the study. Furthermore, six out of the 19 pwCF included were already undergoing protein therapy before the start of the study, with five of them receiving a combination therapy involving a corrector and a potentiator, which could have resulted in an underestimation of the extra-pulmonary effects of ETI. However, since the significant improvement in pulmonary function observed herein after ETI introduction was comparable to that of the pivotal trials [19, 21], we can hypothesize that the findings regarding extra-pulmonary effects of ETI are reliable, even if their magnitude is potentially reduced compared to more severe patients.

Finally, only the use of measured GFR with, for instance, iohexol clearance instead of eGFR formulas, could have definitely confirmed the stability of renal function in this cohort but could not be performed due to technical considerations and the observational nature of the study. Furthermore, delaying ETI introduction to perform such measurements would also have been unethical. Additional data are needed to confirm the long-term renal safety of ETI therapy after the first 7 months of treatment.

CONCLUSION

This 7-month before–after study, involving 19 adult pwCF undergoing ETI found a correction of secondary hyperaldosteronism, probably linked to the reduction of pathological sweat losses in pwCF. The findings also suggest that ETI may not have a short-term impact on renal function. Finally, a substantial decrease in magnesuria was observed but without significant modification of other metabolic risk factors for urolithiasis. Long-term prospective studies are needed to explore the long-term consequences of ETI on renal function, volume status, and risk factors for urolithiasis.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

Resources, Q.R., R.N.-J. and I.D.; writing, P.G. and E.N.-C.; review, E.N.-C., Q.R. and S.P.; supervision, D.F, L.K. and I.D. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

CONFLICT OF INTEREST STATEMENT

D.F. has received speaker fees or travel support from AstraZeneca, Astellas, Lilly and Fresenius Kabi. I.D. declares an activity as a clinical trial investigator for Vertex and acknowledges having received support for conference travel from Viatris. L.K. having received grants from Fresenius Kabi, Nestlé, Lallemand, AstraZeneca and consultancy or speaker fees or travel support from AstraZeneca, Lilly, Baxter, Bayer, and Fresenius Kabi. P.G., E.N.-C., Q.R., R.N.-J., and S.P. declare no conflicts of interest.

REFERENCES

1. Registre français de la mucoviscidose—Bilan des données 2022. Vaincre la Mucoviscidose. Paris. Septembre 2023.
2. Kerem B, Rommens JM, Buchanan JA *et al*. Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989;**245**:1073–80. https://doi.org/10.1126/science.2570460
3. Quinton PM. Cystic fibrosis: impaired bicarbonate secretion and mucoviscidosis. *Lancet* 2008;**372**:415–7. https://doi.org/10.1016/S0140-6736(08)61162-9
4. Elborn JS. Cystic fibrosis. *Lancet* 2016;**388**:2519–31. Epub 2016 Apr 29. https://doi.org/10.1016/S0140-6736(16)00576-6

5. Crawford I, Maloney PC, Zeitlin PL *et al*. Immunocytochemical localization of the cystic fibrosis gene product CFTR. *Proc Natl Acad Sci USA* 1991;**88**:9262–6. https://doi.org/10.1073/pnas.88.20.9262
6. Novel-Catin E, Pelletier S, Reynaud Q *et al*. Aminoglycoside exposure and renal function before lung transplantation in adult cystic fibrosis patients. *Nephrol Dial Transplant* 2019;**34**:118–22. https://doi.org/10.1093/ndt/gfy084
7. Matthews LA, Doershuk CF, Stern RC *et al*. Urolithiasis and cystic fibrosis. *J Urol* 1996;**155**:1563–4. https://doi.org/10.1016/S0022-5347(01)66126-3
8. Perez-Brayfield MR, Caplan D, Gatti JM *et al*. Metabolic risk factors for stone formation in patients with cystic fibrosis. *J Urol* 2002;**167**:480–4. https://doi.org/10.1016/S0022-5347(01)69068-2
9. Hoppe B, Hesse A, Brömme S *et al*. Urinary excretion substances in patients with cystic fibrosis: risk of urolithiasis? *Pediatr Nephrol* 1998;**12**:275–9. https://doi.org/10.1007/s004670050452
10. Dharmsathaphorn K, Freeman DH, Binder HJ *et al*. Increased risk of nephrolithiasis in patients with steatorrhea. *Dig Dis Sci* 1982;**27**:401–5. https://doi.org/10.1007/BF01295647
11. Sidhu H, Hoppe B, Hesse A *et al*. Absence of Oxalobacter formigenes in cystic fibrosis patients: a risk factor for hyperoxaluria. *Lancet* 1998;**352**:1026–9. https://doi.org/10.1016/S0140-6736(98)03038-4
12. Yitgin Y, Asrak H, Tefik T. Role, importance and assessment of dietary habits in urolithiasis patient. *World J Urol* 2023;**41**:1229–33. Epub 2023 Jan 25. https://doi.org/10.1007/s00345-023-04277-3
13. Yusen RD, Edwards LB, Kucheryavaya AY *et al*. International Society for Heart and Lung Transplantation. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report—2014; focus theme: retransplantation. *J Heart Lung Transplant* 2014;**33**:1009–24. Epub 2014 Aug 14. https://doi.org/10.1016/j.healun.2014.08.004
14. Ramos KJ, Quon BS, Heltshe SL *et al*. Heterogeneity in survival in adult patients with cystic fibrosis with FEV1 < 30% of predicted in the United States. *Chest* 2017;**151**:1320–8. Epub 2017 Jan 20.
15. Lynch JP, 3rd, Sayah DM, Belperio JA *et al*. Lung transplantation for cystic fibrosis: results, indications, complications, and controversies. *Semin Respir Crit Care Med* 2015;**36**:299–320. Epub 2015 Mar 31. https://doi.org/10.1055/s-0035-1547347
16. Florens N, Dubourg L, Bitker L *et al*. Measurement of glomerular filtration rate in lung transplant recipients highlights a dramatic loss of renal function after transplantation. *Clin Kidney J* 2020;**13**:828–33. https://doi.org/10.1093/ckj/sfaa053
17. Lopes-Pacheco M. CFTR modulators: shedding light on precision medicine for cystic fibrosis. *Front Pharmacol* 2016 Sep 5;**7**:275. https://doi.org/10.3389/fphar.2016.00275
18. Hoy SM. Elexacaftor/Ivacaftor/Tezacaftor: first approval. *Drugs* 2019;**79**:2001–7. https://doi.org/10.1007/s40265-019-01233-7
19. Middleton PG, Mall MA, Dřevínek P *et al*. VX17-445-102 Study Group. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med* 2019;**381**:1809–19. Epub 2019 Oct 31. https://doi.org/10.1056/NEJMoa1908639
20. Burgel PR, Durieu I, Chiron R *et al*. French Cystic Fibrosis Reference Network Study Group. Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. *Am J Respir Crit Care Med* 2021;**204**:64–73. https://doi.org/10.1164/rccm.202011-4153OC
21. Barry PJ, Mall MA, Álvarez A *et al*. VX18-445-104 study group. Triple therapy for cystic fibrosis Phe508del-gating and -residual function genotypes. *N Engl J Med* 2021;**385**:815–25. https://doi.org/10.1056/NEJMoa2100665
22. Inker LA, Eneanya ND, Coresh J *et al*. Chronic kidney disease epidemiology collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021;**385**:1737–49. Epub 2021 Sep 23. https://doi.org/10.1056/NEJMoa2102953
23. Inker LA, Schmid CH, Tighiouart H *et al*. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012;**367**:20–9. Erratum in: N Engl J Med. 2012 Aug 16;367(7):681. Erratum in: N Engl J Med. 2012 Nov 22;367(21):2060. https://doi.org/10.1056/NEJMoa1114248
24. Schwartz GJ, Muñoz A, Schneider MF *et al*. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;**20**:629–37. Epub 2009 Jan 21. https://doi.org/10.1681/ASN.2008030287
25. Al-Aloul M, Jackson M, Bell G *et al*. Comparison of methods of assessment of renal function in cystic fibrosis (CF) patients. *J Cyst Fibros* 2007;**6**:41–7. Epub 2006 Jun 27. https://doi.org/10.1016/j.jcf.2006.05.004
26. Simopoulos A, Lapey A, Boat T *et al*. The Renin-angiotensin-aldosterone system in patients with cystic fibrosis of the pancreas. *Pediatr Res* 1971;**5**:626–32. https://doi.org/10.1203/00006450-197111000-00007
27. Gilbert KC, Brown NJ. Aldosterone and inflammation. *Curr Opin Endocrinol Diabetes Obes* 2010;**17**:199–204. https://doi.org/10.1097/MED.0b013e3283391989
28. Hegyi P, Seidler U, Kunzelmann K. CFTR-beyond the airways: recent findings on the role of the CFTR channel in the pancreas, the intestine and the kidneys. *J Cyst Fibros* 2023;**22**:S17–22. Epub 2023 Jan 6. https://doi.org/10.1016/j.jcf.2022.12.017
29. Peerapen P, Thongboonkerd V. Kidney stone prevention. *Adv Nutr* 2023;**14**:555–69. Epub 2023 Mar 9. https://doi.org/10.1016/j.advnut.2023.03.002
30. Yang H, Hou C, Xiao W *et al*. The role of mechanosensitive ion channels in the gastrointestinal tract. *Front Physiol* 2022;**13**:904203. https://doi.org/10.3389/fphys.2022.904203
31. Grebert C, Becq F, Vandebrouck C. Focus on TRP channels in cystic fibrosis. *Cell Calcium* 2019;**81**:29–37. Epub 2019 May 30. https://doi.org/10.1016/j.ceca.2019.05.007
32. Huguet F, Calvez ML, Benz N *et al*. Function and regulation of TRPM7, as well as intracellular magnesium content, are altered in cells expressing ΔF508-CFTR and G551D-CFTR. *Cell Mol Life Sci* 2016;**73**:3351–73. https://doi.org/10.1007/s00018-016-2149-6 Epub 2016 Feb 13.
33. Santi M, Milani GP, Simonetti GD *et al*. Magnesium in cystic fibrosis—systematic review of the literature. *Pediatr Pulmonol* 2016;**51**:196–202. Epub 2015 Dec 10. https://doi.org/10.1002/ppul.23356
34. Yan P, Ke B, Fang X. Ion channels as a therapeutic target for renal fibrosis. *Front Physiol* 2022;**13**:1019028. https://doi.org/10.3389/fphys.2022.1019028
35. Hergenroeder GE, Faino A, Bridges G *et al*. The impact of elexacaftor/tezacaftor/ivacaftor on fat-soluble vitamin levels in people with cystic fibrosis. *J Cyst Fibros* 2023;**22**:1048–53. Epub 2023 Aug 8. https://doi.org/10.1016/j.jcf.2023.08.002

36. Sutharsan S, Dillenhoefer S, Welsner M *et al*. German CF Registry of the Mukoviszidose e.V. and participating CF sites. Impact of elexacaftor/tezacaftor/ivacaftor on lung function, nutritional status, pulmonary exacerbation frequency and sweat chloride in people with cystic fibrosis: real-world evidence from the German CF Registry. *Lancet Reg Health Eur* 2023;**32**:100690. https://doi.org/10.1016/j.lanepe.2023.100690

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