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Original Article

Mutations with residual CFTR function are associated with better glucose tolerance and insulin secretion in people with Cystic fibrosis

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ABSTRACT

Background: People with Cystic Fibrosis (pwCF) often exhibit impaired insulin secretion, which may lead to Cystic Fibrosis-Related Diabetes (CFRD). The impact of CF variants in the complex relationship between CFTR channel function, pancreatic function, and glucose metabolism remains only partially understood.
Methods: In this multicenter study, 341 pwCF (57 % females, 79 % with pancreatic insufficiency; median age 19 yrs.) underwent an oral glucose tolerance test (OGTT) sampling glucose, insulin, and C-peptide every 30 min for 2 h to assess β-cell function, expressed by β-cell glucose sensitivity. Participants were grouped by having either a minimal function (MF) mutation on both alleles (256 pts, 75 %) or at least one residual function (RF) mutation (85 pts, 25 %). Each variant was then associated to the CFTR-chloride conductance (CC) values from the CFTR2 database. The highest CC value (from each allele) was selected as the patient' representative CC, and used to assess its relationship with β-cell glucose sensitivity.
Results: 162 pwCF (84 % of MF group) carried variants on both alleles with CC data available in the CFTR2 database. PwCF in the RF group exhibited better glucose tolerance and β-cell glucose sensitivity ($p \leq 0.001$). After adjustment for sex and age, a strong positive linear association was found between CFTR-CC values and β-cell glucose sensitivity ($p < 0.001$), without a significant interaction with pancreatic status.
Conclusions: Clinical data, OGTT results, and in vitro CC analysis demonstrate an independent relationship between the extent of CFTR channel dysfunction and β-cell function.

1. Introduction

Cystic fibrosis (CF) is a chronic autosomal recessive disorder that affects approximately 160,000 individuals worldwide, caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, which disrupt chloride ion transport across epithelial cells, particularly in the lungs, pancreas, gastrointestinal tract, and reproductive system [1]. Over 2000 mutant alleles have been identified, and the severity of the disease varies widely depending on the variant type, especially the extent of chloride transport loss and they are classified based on their impact on cystic fibrosis (CF) disease manifestation [2]. While the CFTR dysfunction's effects on exocrine pancreas function are well-established, its effects on endocrine pancreatic function and glucose metabolism remain an active area of research [3].

Cystic fibrosis–related diabetes (CFRD), the most common extrapulmonary complication in CF is expected to further increase with

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improving life expectancy of people with CF (pwCF). CFRD affects 40–50 % of adults, 2 % in children and 19 % in adolescents, contributing to poor health outcomes in pwCF [3]. Although CF is associated with varying levels of insulin resistance, CFRD is primarily driven by reduced β-cell function, resulting in insufficient insulin secretion and hyperglycemia [4–6].

The mechanisms through which CFTR variants lead to impaired insulin secretion remain contentious, with conflicting evidence in recent studies [7,8]. At the pancreatic level, it remains unclear whether CFTR is predominantly expressed in ductal cells indirectly influencing β-cell function or rather may influence insulin secretion in pancreatic β-cells. However, its expression in these cells is limited, and the functional impact remains a matter of debate [7,8]. These observations highlight the important role of CFTR in the maintenance of pancreatic functions beyond CF.

The severity of impairment caused by over 2000 CFTR variants and the molecular mechanisms through which they lead to channel dysfunction have been used to classify them into distinct classes [9,13]. Although phenotypes vary widely, CFTR2 database enables clinicians and researchers to better understand the relationship between genetic variants and disease expression.

According to the CFTR2 database, 1176 variants fall into three main categories: variants that have been demonstrated to cause cystic fibrosis (Disease Causing); variants that may or may not cause CF (Varying Clinical Consequences, VCC); variants that do not cause cystic fibrosis (Not Disease Causing) [10]. A simplified classification has been proposed that categorizes CFTR variants into those retaining residual channel function (residual function mutations, RF) and those having a more severe impact on the channel, resulting in minimal activity (minimal function mutations, MF), a distinction that has become particularly relevant in the era of highly effective modulator therapies (HEMT). Approximately 10–15 % of pwCF have mutations that exhibit residual CFTR ion channel activity, (RF) mutations, in contrast to 'minimal function' (MF) mutations, which are associated with little to no CFTR activity. PwCF carrying RF mutations typically exhibit sufficient pancreatic function to maintain normal nutritional status (pancreatic sufficiency), along with sweat chloride levels that may be normal, borderline, or slightly elevated, indicating partially preserved CFTR activity [11].

Further research is needed to better understand the mechanisms underlying the development of CFRD and the impact of CFTR channel dysfunction on pancreatic function and glucose metabolism. Although improvements in diabetes management are leading to decreases in mortality, the underlying mechanisms of CFRD are complex and multifactorial, involving both genetic and environmental factors [12].

We sought to describe the relationship between CFTR variants and β-cell function in pwCF based on clinical data from our cohort and in vitro functional studies from the CFTR2 database [10]. These CFTR-chloride conductance (CC) in vitro measurementsrepresent the maximal capacity for chloride transport elicited by different CFTR variants. These findings aim to provide deeper insights into the complex relationship between the degree of CFTR channel dyfunction, pancreatic function, and glucose regulation in CF.

2. Material and methods

2.1. Study design and participants

This cross-sectional study included Italian pwCF consecutively enrolled from 2016 to 2020 across three CF centers representing different regions of Italy (Milan, Rome, Messina). Inclusion criteria were clinical stability for the preceding 3 weeks (no exacerbations, treatment changes, or antibiotic/steroid use) and absence of CFRD or use of glucose-lowering medications in the prior 6 months. The study adhered to the Declaration of Helsinki and received ethical approval from the University of Milan (protocol code 53/19). All participants provided informed consent.

2.2. CFTR channel function stratification

Participants were stratified based on their CFTR genotypes. Each CFTR allele was categorized as having "minimal" or "residual" channel function (MF and RF, respectively)according to the classification system that include CFTR defects, clinical features, and therapeutic strategies [9,13]. Therefore, pwCF were then grouped as two MF alleles, group MF associated to a more-severe disease, or at least one RF allele, group RF. Sensitivity analyses considered the distinction between one or two residual function alleles.

2.3. Variables and measurements

The study compared the following variables between CFTR function groups, adjusting for age, sex, and pancreatic status:

- Oral Glucose Tolerance Test (OGTT) parameters: Glucose, insulin, and C-peptide levels at baseline and 30, 60, 90, and 120 min post-glucose load.
- β-cell function: β-cell glucose sensitivity, basal insulin secretion, total OGTT insulin secretion.
- Insulin clearance: Basal and OGTT insulin clearance.
- Insulin sensitivity: Quantitative insulin-sensitivity check index (QUICKI) for basal sensitivity and 2-hour oral glucose insulin sensitivity index (2-h OGIS) for OGTT sensitivity.

2.4. CFTR variants and clinical assessment

CFTR variants were classified as MF and RF [9,13]. Clinical data collected included pancreatic status, infection history, transplantation history, and CFTR modulator therapy.

2.5. Anthropometric and pulmonary assessment

Body mass index (BMI) was calculated from measured height and weight. BMI z-scores were derived for pwCF under 20 years using CDC growth charts [14]. Participants were classified by BMI category (underweight, normal weight, overweight, obese) and according to CF Foundation recommendations, CFF [15]. BMI categories based on CDC growth charts for those under 20 years (underweight: <5th percentile; normal weight: 5th to <85th percentile; overweight: 85th to <95th percentile; obese: ≥95th percentile) and standard thresholds for adults. For adults with cystic fibrosis, the CFF recommends maintaining a body mass index (BMI) of at least 22 kg/m^2 for females and 23 kg/m^2 for males. For children and adolescents aged 2 to 20 years, the CFF suggests keeping the BMI at or above the 50th percentile according to the CDC growth charts. For infants and young children under 2 years of age, the CFF recommends achieving a weight-for-length measurement at or above the 50th percentile by the age of 2 years. Spirometry was conducted per ATS/ERS guidelines, with forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) expressed as percentages of predicted values.

2.6. OGTT and laboratory analyses

A 2-hour OGTT (1.75 g/kg glucose, maximum 75 g) was performed with blood sampling at baseline and 30-minute intervals for glucose, insulin, and C-peptide measurements. C-reactive protein and HbA1c were also assessed. Glucose tolerance categories were determined per ISPAD guidelines [16].

2.7. Modeling and calculations

β-cell function was modeled from OGTT glucose and C-peptide data

[17–19], yielding parameters for β-cell glucose sensitivity, basal insulin secretion, and total OGTT insulin secretion. Insulin clearance was calculated as the ratio of insulin secretion to concentration. QUICKI [20] and OGIS [21] indices were used for insulin sensitivity assessment. Area under the curve (AUC) was calculated for glucose, insulin, and C-peptide.

Basal State Assessment The following indices were used to characterize metabolism in the fasting state:

- **Basal Insulin Secretion:** This was one of the parameters derived from the mathematical modeling of OGTT data.
- **Basal Insulin Sensitivity:** Assessed using the Quantitative Insulin-Sensitivity Check Index (QUICKI), calculated from fasting insulin and glucose.
- **Basal Insulin Clearance:** Calculated as the ratio of the basal insulin secretion rate to the fasting insulin concentration.

Postprandial (OGTT-derived) Assessment The following parameters were calculated to assess dynamic glucose handling and insulin secretion in response to the glucose load:

- **β-cell Function:** A mathematical model was used to analyze glucose and C-peptide concentrations from the OGTT. This provided key parameters describing the efficiency and magnitude of the insulin secretion response, including β-cell glucose sensitivity and total OGTT insulin secretion.
- **Insulin Sensitivity:** Dynamic insulin sensitivity during the OGTT was assessed using the 2-hour oral glucose insulin sensitivity index (2-h OGIS).
- **Insulin Clearance:** Overall insulin clearance during the OGTT was calculated as the ratio of total insulin secretion to the corresponding insulin concentrations during the test.
- **Area Under the curve (AUC):** The total AUC was calculated using the trapezoidal method for glucose, insulin, and C-peptide concentrations throughout the 2-hour OGTT.

2.8. Chloride conductance studies

Participants were characterized according to the CFTR2 database's CFTR-chloride conductance (CC) data carried out in Fisher Rat Thyroid cells, FRT, and in Cystic Fibrosis Bronchial Epithelial cells, CFBE. Although these data are publicly available in principle, the compiled spreadsheet is not posted on the CFTR2 website and was obtained through direct request to the CFTR2 team. Participants' CC values of allele pairs performed in FRT and CFBE cells were associated to each patient stratified in groups: MF/MF function and MF/RF or RF/RF function. For each cell line, only participants with complete data were included in the analysis. For each patient, the higher of the two mean CC values (one for each allele) was used as representative of that patient's CC [10].

2.9. Bias and sample size

Potential biases included variations in OGTT screening practices and exclusion of diabetic participants from the OGTT. Survival bias was assessed by analyzing outcome variable trends. The minimum sample size ($n = 240$) was determined based on criteria by Riley et al. [22] for a multivariable model predicting β-cell glucose sensitivity.

2.10. Statistical analysis

All statistical analyses were conducted using R 4.4. A p-value of < 0.05 was considered statistically significant for all analyses. The primary, pre-specified hypothesis of this study was to test the relationship between the in vitro measure of CFTR channel function (CFTR-chloride conductance) and the most comprehensive in vivo measure of pancreatic endocrine efficiency (β-cell glucose sensitivity). All other statistical comparisons, such as group differences in individual OGTT time points or other derived metabolic parameters, were considered secondary and exploratory, intended to provide a richer physiological context for our primary finding.

Sample Size Calculation The minimum required sample size was determined a priori based on the criteria by Riley et al. [22] for developing a multivariable prediction model for β-cell glucose sensitivity, our primary outcome. The calculated minimum sample size was 240, which was exceeded by our enrolled cohort of 341 participants.

Data Presentation and Handling Continuous variables were presented as median and interquartile range (IQR), while discrete variables were reported as counts and proportions. To manage the effect of extreme values, all continuous outcome variables, excluding age, were winsorized at the 1st and 99th percentiles. Multiple imputation was used to handle missing data.

Comparison between CFTR Function Groups To assess differences in OGTT and modeled metabolic parameters between CFTR function groups, we used additive quantile regression models. This approach allowed us to model the effect of predictors on the 25th, 50th (median), and 75th percentiles of each outcome variable's distribution. For these models, the outcome variables were the OGTT parameters and derived indices (e.g., β-cell glucose sensitivity). The predictors included in the models were:

- CFTR MF and RF groups (categorical: "Minimal/minimal function" MF/MF vs. "Minimal/residual MF/RF or residual/residual function RF/RF")
- Age (continuous, transformed with a cubic spline basis)
- Sex (categorical: Female vs. Male)
- Pancreatic status (categorical: Pancreatic sufficient vs. Pancreatic insufficient)

Association with CFTR-Chloride Conductance The relationship between CFTR channel function and β-cell function was assessed using multivariable linear regression. In these models, β-cell glucose sensitivity was the dependent variable. The primary predictor was the patient's representative mean chloride conductance (as % of normal), with adjustments made for sex and age. Separate models were run for conductance data obtained from FRT and CFBE cells.

3. Results

3.1. Overall characteristics of the study population

Baseline characteristics and disease severity are summarized in Table 1. In total 341 pwCF were enrolled with a median (IQR) age of 19 [16,25] and almost equal distribution of sex (193 (57 %) females). The sample was prevalently pancreatic insufficient (271 (79 %)), and the BMI of 204 (60 %) participants was considered below target according Cystic Fibrosis Foundation recommendations. The majority of pwCF had normal glucose tolerance, NGT ($N = 207$, median age 18, 59 % females, 71 % PI). CFTR genotypes were also described by epidemiological prevalence (F508del homozygous, F508del heterozygous, other). Based on the CFTR mutations classification system [9,13], we enrolled most participants (255, 75 %) with both CFTR alleles with minimal function, and only 11 (3.2 %) with both alleles with residual function mutations. Partecipants enrolled under modulator treatments are indicated in Table 1, no pwCF enrolled was under ETI treatment.

3.2. Differences between pwCF with residual or minimal CFTR function

OGTT glucose and insulin data were stratified according to CFTR genotypes (MF group., Minimal/Minimal function or RF group, heterozygous with at least one residual function mutation, Minimal/Residual or Residual/Residual) of partecipants enrolled for determinations

Table 1
Patient characteristics in the overall sample, stratified by CFTR minimal and residual function mutation groups.

Characteristics	N	Overall $N = 341$[1]	MF/MF $N = 255$[1]	MF/RF or RF/RF $N = 86$[1]
Age (years)	341	19 (15, 24)	19 (14, 25)	19 (15, 23)
Sex	341			
Female		193 (57 %)	136 (53 %)	57 (66 %)
Male		148 (43 %)	119 (47 %)	29 (34 %)
FEV1 fraction of predicted (as %)	245	87 (71, 103)	83 (70, 101)	96 (82, 103)
Unknown		96	74	22
Pancreatic status	341			
Pancreatic sufficient		70 (21 %)	30 (12 %)	40 (47 %)
Pancreatic insufficient		271 (79 %)	225 (88 %)	46 (53 %)
BMI category	341			
Underweight		12 (3.5 %)	6 (2.4 %)	6 (7.0 %)
Normal weight		312 (91 %)	239 (94 %)	73 (85 %)
Overweight		14 (4.1 %)	9 (3.5 %)	5 (5.8 %)
Obese		3 (0.9 %)	1 (0.4 %)	2 (2.3 %)
BMI Cystic Fibrosis Foundation recommendations	341			
Below target		204 (60 %)	161 (63 %)	43 (50 %)
Above target		137 (40 %)	94 (37 %)	43 (50 %)
CFTR genotype	341			
F508del homozygous		90 (26 %)	90 (35 %)	0 (0 %)
F508del heterozygous		158 (46 %)	115 (45 %)	43 (50 %)
Other		93 (27 %)	50 (20 %)	43 (50 %)
CFTR function	341			
Minimal/minimal function		255 (75 %)	255 (100 %)	0 (0 %)
Minimal/residual function		75 (22 %)	0 (0 %)	75 (87 %)
Residual/residual function		11 (3.2 %)	0 (0 %)	11 (13 %)
CFTR modulator	341			
None		289 (85 %)	217 (85 %)	72 (84 %)
Ivacaftor		20 (5.9 %)	8 (3.1 %)	12 (14 %)
Lumacaftor/Ivacaftor		32 (9.4 %)	30 (12 %)	2 (2.3 %)

[1] Median (Q1, Q3); n (%)
Patient characteristics in the whole sample and stratified by the CFTR function mutations classes, MF and RF.

of plasma glucose, serum insulin, and C-peptide concentrations (Table 2). The glucose curve resulted consistently lower for pwCF with at least one RF mutation, and while no significant differences between the two groups is observed in the early stages of insulin secretion by insulin and C-peptide values during the OGTT. The relationship between glucose levels and insulin secretion was significantly different, and highlighted by the differences in β-cell glucose sensitivity, a parameter that most of all expresses the efficiency of insulin secretion. Insulin clearance, both basal and during OGTT, was lower in pwCF with preserved residual CFTR channel function (Table 2). Fitted values are displayed for pwCF with median age (19 years), female sex, and pancreatic insufficiency (Fig. 1). . The same differences are depicted in Fig. 1 and Fig. 2, showing the 25th and 75th percentiles. For a detailed visualization of the underlying data and model fits for each of these parameters, see **Supplementary Figures 2–5**. The complete statistical outputs for the quantile regression models at the 25th, 50th, and 75th percentiles are provided in **Supplementary Tables 1–4**." To ensure our findings were not confounded by treatment differences, we performed a sensitivity analysis by including CFTR modulator therapy as a covariate in our models. The inclusion of this variable did not alter the significant differences observed between the MF and RF groups. The effect of modulator therapy itself was not consistently significant across all metabolic parameters, as detailed in the Supplementary Materials.

3.3. Patient characteristics and their relationship with CFTR-chloride conductance and β-cell glucose sensitivity

Out of 341 partecipants enrolled, 162 had both CFTR variants tested in FRT cells (84 % MF group, 86 % PI, median age 20 years (range 15–25), 51 % females), and an overlapping subset of 102 carrying both CFTR variants tested in CFBE cells (94 % MF group, 86 % PI, median age 21 years (range16–26), 45 % females) for chloride conductance, CC with data collected in the CFTR2 database [10].Characteristics of pwCF with available mean CC data of both CFTR variants are provided in Table 3, and the relationship between mean CC and β-cell glucose sensitivity is displayed in Table 4. Mean CC values show a positive and statistically significant relationship with β-cell glucose sensitivity. This association remains robust even after adjusting for multiple variables known to influence β-cell glucose sensitivity, such as age, sex, and other relevant clinical factors, This relationship is consistent regardless of the cell line used to measure chloride conductance, indicating that higher CFTR function (RF group), as reflected by increased chloride conductance, is closely linked to improved β-cell function.They display better glucose tolerance at all OGTT time points (all $p \leq 0.05$), and better β-cell glucose sensitivity with a difference of 21 $pmol \times min^{-1} \times m^{-2} \times mM^{-1}$ between groups (Table 2). Although worse β-cell function is associated with exocrine PI, CFTR-chloride conductance is quantitatively related to β-cell function in pwCF (Table 4). This positive and statistically significant linear relationship is visualized in **Supplementary Figure 1**, which plots the individual participant data against the model's fitted lines.

4. Discussion

In our study, we highlighted differences in insulin secretion and glucose metabolism between pwCF with at least one residual function mutation (RF group), and those with MF mutations on both alleles (MF group). The study population is representative of the broader pwCF population, encompassing a diverse range of ages, disease severities, and genetic variants, thereby reflecting the heterogeneity commonly observed in clinical practice (Table 1) [23,24].

We employed in vitro data of CFTR-chloride conductance, CC studies in FRT and CFBE cell lines stored in the CFTR2 database, a comprehensive online resource for both clinical features and functional testing of CFTR variants [10]. After adjusting for key variables known to influence glucose tolerance and insulin secretion, the RF group showed better glucose tolerance during OGTTs and exhibited more robust, timely insulin secretion, as indicated by higher β-cell glucose sensitivity compared to the MF group. This clinically significant improvement in glucose handling is clearly illustrated in Fig. 1, which shows a consistently lower glucose excursion in the RF group at all post-load time points during the OGTT. Additionally, in pwCF with available CC data, a positive linear correlation was observed between mean residual CC and β-cell glucose sensitivity. Research has shown that the severity of CFTR dysfunction correlates with the risk and severity of CFRD [7,11,16, 23–25]. Although the primary defect in CF stems from the dysregulation of CC due to CFTR variants, its effects may extend beyond the exocrine pancreas to impact endocrine function, particularly β-cell activity. Impaired CC could indirectly influence β-cell function, and data suggest that it may trigger a cascade of events contributing to the development of CFRD [25]. The extensive damage to the exocrine pancreas, marked

Table 2
OGTT glucose and insulin data stratified in two groups according to CFTR genotypes having minimal function, MF mutations on both alleles or at least one residual function, RF mutation on one allele.

Characteristics	N	Overall $N = 341$	MF/MF $N = 255$	MF/RF or RF/RF $N = 86$	Adjusted difference	95 % CI[1]	p-value
Fasting glucose (mg/dL)	338	84 (78, 91)	85 (78, 92)	83 (77, 89)	−1.5	1.1, −4.2	0.3
Glucose at 30 OGTT minutes (mg/dL)	338	149 (131, 173)	154 (133, 177)	136 (122, 157)	−14	−6.3, −22	**<0.001**
Glucose at 60 OGTT minutes (mg/dL)	336	163 (132, 197)	173 (142, 203)	134 (107, 160)	−24	−13, −35	**<0.001**
Glucose at 90 OGTT minutes (mg/dL)	337	133 (106, 174)	143 (114, 184)	109 (95, 135)	−21	−9.8, −33	**<0.001**
Glucose at 120 OGTT minutes (mg/dL)	336	109 (92, 139)	116 (95, 147)	99 (88, 119)	−14	−4.7, −22	**0.003**
Fasting insulin (μIU/mL)	298	6.7 (4.6, 9.7)	6.3 (4.4, 9.1)	7.4 (5.6, 10.7)	0.51	1.7, −0.66	0.4
Insulin at 30 OGTT minutes (μIU/mL)	291	31 (18, 52)	28 (17, 46)	43 (27, 60)	7.1	15, −0.58	0.070
Insulin at 60 OGTT minutes (μIU/mL)	298	45 (29, 71)	44 (27, 70)	53 (31, 83)	0.14	10, −10	>0.9
Insulin at 90 OGTT minutes (μIU/mL)	299	49 (31, 72)	50 (32, 71)	48 (31, 80)	−3.1	5.9, −12	0.5
Insulin at 120 OGTT minutes (μIU/mL)	301	39 (24, 65)	40 (24, 68)	38 (26, 60)	−4.6	3.2, −12	0.3
Fasting C-peptide (ng/mL)	337	1.39 (0.99, 1.78)	1.34 (0.95, 1.76)	1.49 (1.06, 1.87)	0.00	0.18, −0.17	>0.9
C-peptide at 30 OGTT minutes (ng/mL)	335	3.70 (2.59, 5.41)	3.50 (2.38, 5.00)	4.70 (3.19, 6.39)	0.63	1.3, −0.04	0.065
C-peptide at 60 OGTT minutes (ng/mL)	337	5.89 (4.07, 8.32)	5.60 (3.93, 8.06)	6.69 (4.50, 8.92)	0.33	1.2, −0.57	0.5
C-peptide at 90 OGTT minutes (ng/mL)	336	7.00 (4.87, 8.97)	7.08 (4.86, 8.97)	6.79 (4.88, 8.97)	−0.44	0.39, −1.3	0.3
C-peptide at 120 OGTT minutes (ng/mL)	335	6.52 (4.65, 8.64)	6.66 (4.67, 8.64)	5.99 (4.46, 8.55)	−1.1	−0.31, −1.9	**0.007**
Basal insulin secretion ($pmol \times min^{-1} \times m^{-2}$)	337	68 (48, 88)	64 (47, 87)	76 (53, 91)	−2.1	6.2, −10	0.6
Quantitative insulin sensitivity check index	297	0.37 (0.34, 0.39)	0.37 (0.34, 0.39)	0.36 (0.34, 0.38)	0.00	0.01, −0.01	0.5
Basal insulin clearance ($l \times min^{-1} \times m^{-2}$)	298	1.67 (1.25, 2.13)	1.71 (1.30, 2.18)	1.56 (1.16, 1.96)	−0.23	−0.04, −0.41	**0.016**
Glucose sensitivity ($pmol \times min^{-1} \times m^{-2} \times mM^{-1}$)	337	67 (46, 107)	60 (42, 96)	106 (65, 139)	21	33, 8.9	**<0.001**
Total insulin secretion ($nmol \times m^{-2}$)	337	50 (35, 62)	49 (35, 61)	51 (36, 63)	−5.0	0.85, −11	0.093
2-hours OGIS ($ml \times min^{-1} \times m^{-2}$)	271	473 (425, 511)	472 (423, 508)	482 (435, 519)	15	31, −2.3	0.090
OGTT insulin clearance ($l \times min^{-1} \times m^{-2}$)	336	1.27 (1.00, 1.59)	1.28 (1.07, 1.61)	1.15 (0.79, 1.51)	−0.14	−0.01, −0.27	**0.032**

[1] CI = Confidence Interval

Differences between patients with "MF/MF" and "MF/RF or RF/RF" from quantile regression of median of oral glucose tolerance parameters and modeled parameters. The characteristics column indicates the outcome for each quantile regression model; predictors included in the models: age (continuous, years, transformed with a smooth that have a cubic spline basis), sex (categorical: Female, Male), pancreatic insufficiency (categorical: Pancreatic sufficient, Pancreatic insufficient), CFTR function (categorical: minimal/minimal function, minimal/residual or residual/residual function).

by fibrosis and fatty replacement, creates a challenging microenvironment for the islets of Langerhans, disrupting cell-to-cell communication and impairing β-cell function [25]. Moreover, the altered composition and arrangement of the islets, alongside the loss of critical structures such as microvasculature and autonomic nerve fibers, may further compromise insulin secretion [7,11,25,26]. Finally, while CFTR is predominantly recognized for its role in exocrine pancreas, mutations in CFTR may compromise β-cell function, thereby contributing to the development of CFRD [7,25,28,30]). This possibility underscores the importance of further research to elucidate the potential direct impact of the degree of CFTR channel dysfunction on β-cell physiology. Furthermore, our observation of elevated insulin clearance in pwCF with minimal CFTR function is consistent with our previous findings in two independent CF cohorts (Table 2), as well as with external studies [7,20,25,28]. This suggests that CFTR dysfunction may play a critical role in modulating insulin dynamics, and it raises the possibility that early alterations in insulin clearance could be an early indicator of developing metabolic dysfunction in pwCF.

Furthermore, the recent suggestion that elevated insulin clearance could serve as a hallmark of a novel diabetes subtype in the general population raises the possibility that similar mechanisms could contribute to metabolic dysfunction in pwCF. Therefore, insulin clearance represents a potential factor to investigate in advancingour understanding of CFRD pathogenesis [29].

This study also underlines that the shape of the insulin curve during an OGTT provides crucial insights beyond overall insulin secretion. Indeed, an early insulin peak (at around 30 min) is vital for efficient glucose management [21,23,28]. Relying solely on measures as insulin AUC or total insulin secretion may be misleading, whereas modeled parameters such as β-cell glucose provide a more accurate representation of this dynamic process.

It is crucial, in the near future, that clinicians will be able to rely on standardized biomarkers to predict the development of CFRD for an early management, particularly in the context of newer highly effective CFTR modulators such as ETI and VTD (vanzacaftor/tezacaftor/ivacaftor) [30]. In this study, only 15 % of the sample was receiving a CFTR modulator (lumacaftor/ivacaftor) at the time of the OGTT and our models did not show a positive effect on glucose tolerance and insulin secretion parameters [27]. This will require further investigations, particularly regarding the highly effective CFTR modulator ETI or VTD to fully understand its role in modifying insulin dynamics, especially when treatment begins early in the life of pwCF.

This study benefits from a large cohort of pwCF, who underwent detailed characterization including OGTTs, enabling a comprehensive assessment of glucose tolerance and insulin secretion dynamics. However, it is important to acknowledge that CC studies were available in the CFTR2 database only for a subset of variants [10].

Taken together, our findings demonstrate that CFTR function associated to improved glucose tolerance and insulin secretion in pwCF, emphasizing CFTR's dual role in **both** pancreatic exocrine and endocrine functions. The observed correlation between CFTR-dependent chloride conductance and β-cell glucose sensitivity suggests a potential mechanism **underlying its influence** on insulin secretion. Future studies, **ideally integrating assessments of** β-cell function and chloride conductanceideally in patient-derived cells, will be crucial to further **elucidate** clarify the complex interplay between CFTR channel activity, pancreatic function, and glucose metabolism in CF.

CRediT author contribution statement

Fabiana Ciciriello: Conceptualization; Resources; Data curation; Investigation; Writing - original draft; Visualization; Writing - review & editing. **Andrea Foppiani:** Methodology; Data curation; Visualization; Formal analysis; Writing - original draft; Writing - review & editing. **Federica Sileo**: Data curation; Investigation; Methodology. **Federico Alghisi**: Investigation; Data curation; Resources; Writing - original draft. **Maria Chiara Russo:** Investigation; Data curation; Resources. **Laura Elisabetta Claut:** Investigation; Data curation; Resources. **Arianna Bisogno:** Investigation; Data curation; Writing - original draft. **Stefano Costa:** Investigation; Data curation; Resources; Writing - original draft. **Maria Cristina Lucanto:** Investigation; Data curation; Resources; Writing - original draft. **Vincenzina Lucidi:** Investigation; Funding

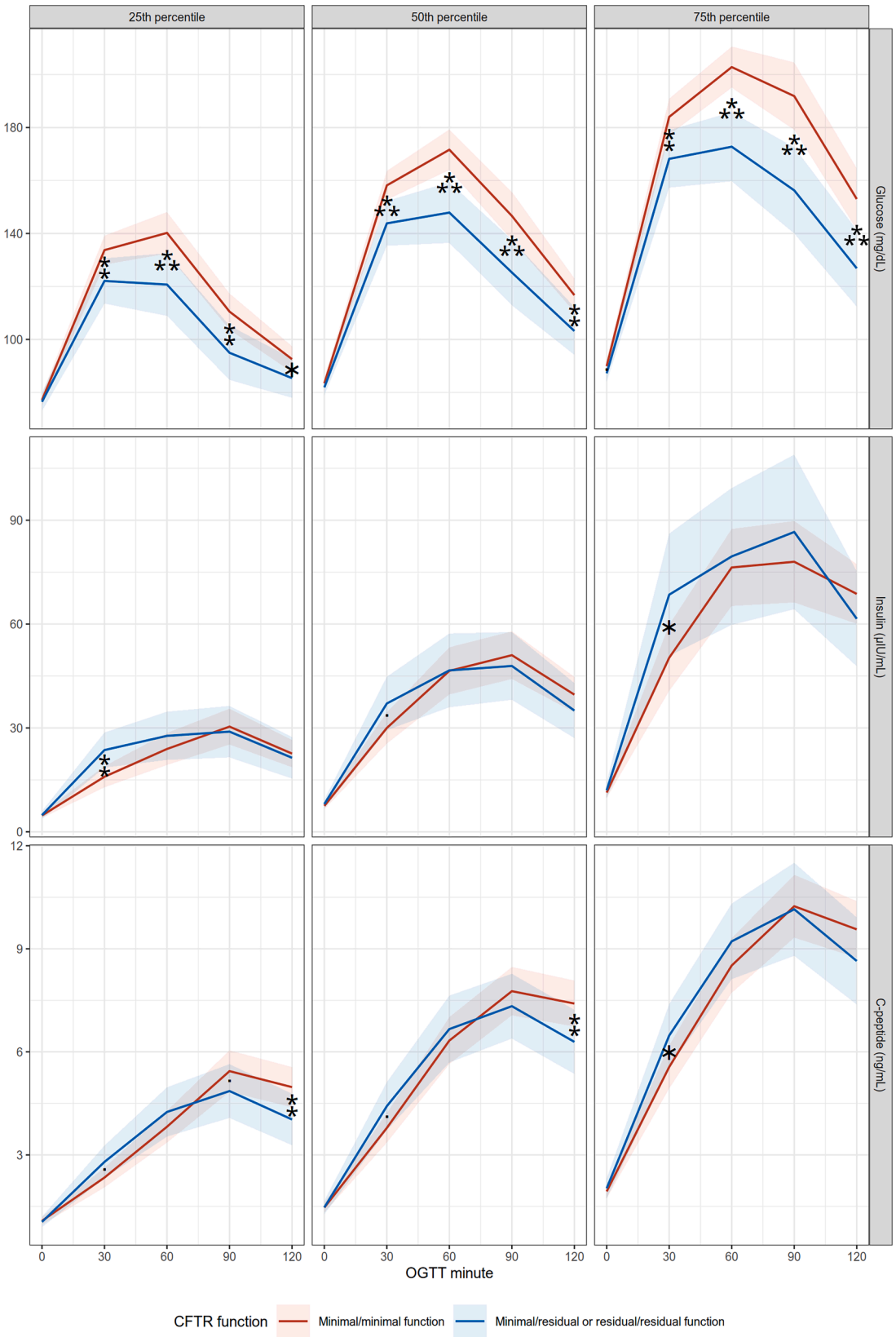

Fig. 1. Oral glucose tolerance test fitted results from quantile regression of quartiles of glucose, insulin, and C-peptide. Displaying fitted values for patients with median age (19 years), females, pancreatic insufficient. Shaded areas represent confidence intervals from quantile regression, data stratified by CFTR function, asterisks represent p-values from quantile regression for differences between 'Minimal/minimal function' and 'Minimal/residual or residual/residual function' categories (⁂: $p < 0.001$, ⁑: $p < 0.01$, *: $p < 0.05$, ·: $p < 0.1$).

Fig. 2. Fitted results from quantile regression of quartiles of oral glucose tolerance test modeled parameters. Displaying fitted values for patients with median age (19 years), females, pancreatic insufficient. Error bars represent confidence intervals from quantile regression, data stratified by CFTR function, asterisks represent p-values from quantile regression for differences between 'Minimal/minimal function' and 'Minimal/residual or residual/residual function' categories (⁂: $p < 0.001$, ⁑: $p < 0.01$, *: $p < 0.05$, ·: $p < 0.1$).

Table 3
Characteristics of pwCF with variants on both alleles tested for chloride conductance in the CFTR2 database.

Characteristic	FRT $N = 162$[1]	CFBE $N = 102$[1]
Age (years)	20 (15, 25)	21 (16, 26)
Sex		
Female	82 (51 %)	46 (45 %)
Male	80 (49 %)	56 (55 %)
pancreatic insufficiency		
Pancreatic sufficient	23 (14 %)	14 (14 %)
Pancreatic insufficient	139 (86 %)	88 (86 %)
BMI category		
Underweight	5 (3.1 %)	1 (1.0 %)
Normal weight	147 (91 %)	96 (94 %)
Overweight	9 (5.6 %)	5 (4.9 %)
Obese	1 (0.6 %)	0 (0 %)
BMI Cystic Fibrosis Foundation recommendations		
Below target	93 (57 %)	59 (58 %)
Above target	69 (43 %)	43 (42 %)
CFTR mutation		
F508del homozygous	90 (56 %)	90 (88 %)
F508del heterozygous	58 (36 %)	12 (12 %)
Other	14 (8.6 %)	0 (0 %)
CFTR function		
Minimal/Minimal function	136 (84 %)	96 (94 %)
Minimal/Residual function	25 (15 %)	6 (5.9 %)
Residual/Residual function	1 (0.6 %)	0 (0 %)
CFTR modulator		
None	112 (69 %)	64 (63 %)
Ivacaftor	19 (12 %)	8 (7.8 %)
Lumacaftor/Ivacaftor	31 (19 %)	30 (29 %)

[1] Median (Q1, Q3); n (%)

Patient characteristics in chloride conductance subsamples, stratified by cell line used.

Table 4
Linear regression of glucose sensitivity as predicted by chloride conductance, adjusted by sex, age. One model per cell line used.

	FRT	CFBE				
Characteristic	Beta	95 % CI[1]	p-value	Beta	95 % CI[1]	p-value
Sex						
Female	—	—		—	—	
Male	−18	−29, −6.2	**0.003**	−19	−32, −5.2	**0.008**
Mean chloride conductance, as % of normal	1.5	0.75, 2.3	**<0.001**	2.7	1.4, 4.0	**<0.001**
Age smooth			**<0.001**			**<0.001**

[1] CI = Confidence Interval

Linear regression of glucose sensitivity as predicted by chloride conductance, adjusted by sex, age. One model per cell line used.

acquisition; Resources; Writing - original draft; Writing - review & editing. **Carla Colombo:** Supervision; Funding acquisition; Resources; Writing - original draft; Writing - review & editing. **Alberto Battezzati:** Conceptualization; Funding acquisition; Project administration; Writing - original draft; Writing - review & editing.

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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2025.11.001.

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