*diabetology*

MDPI

*Article*

# Evaluation of Insulin Secretion and Continuous Glucose Monitoring in Patients with Cystic Fibrosis After Initiation of Transmembrane Conductance Regulator Modulator: A 52-Week Prospective Study

**Ane Bayona [1,2,3], Edurne Lecumberri Pascual [1], Saioa Vicente [4], Luis Maíz [3,4], Ana Morales [4], Adelaida Lamas [4], Cristina Sánchez Rodríguez [1], Rosa Yelmo [5], María Martín-Frías [5], Victoria Martínez Vaello [1], Enrique Blitz Castro [4] and Lía Nattero-Chávez [1,2,3,*]**

1 Department of Endocrinology and Nutrition, Hospital Universitario Ramón y Cajal, Carretera de Colmenar, Km 9.1, 28034 Madrid, Spain
2 Grupo de Diabetes, Obesidad y Reproducción Humana, Universidad de Alcalá & Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) & Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM). Av. Monforte de Lemos, 3-5. Pabellón 11. Planta 0, 28029 Madrid, Spain
3 Department of Medicine, Universidad de Alcalá de Henares, 28801 Madrid, Spain
4 Cystic Fibrosis Unit, Hospital Universitario Ramón y Cajal, 28034 Madrid, Spain
5 Pediatric Diabetes Unit, Hospital Universitario Ramón y Cajal, 28034 Madrid, Spain
* Correspondence: marialia.nattero@salud.madrid.org; Tel./Fax: +34-91-336-90-29

**Abstract: Introduction:** Limited studies have explored the impact of cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators on glucose tolerance and insulin secretion in patients with CF, yielding varied results. This study aims to assess alterations in glucose metabolism and insulin secretion over 24 and 52 weeks following CFTR modulator initiation in a cohort of pediatric and adult patients with CF. **Materials and Methods:** A prospective longitudinal study conducting oral glucose tolerance test (OGTT) with C-peptide and insulin levels. The insulin secretion rate at 60 min (ISR60) and the insulinogenic index (IGI) were calculated during the first 60 and 30 min of the OGTT, respectively. Glucose metabolism status was categorized as normal (NGT), indeterminate (INDET), impaired glucose tolerance (IGT), or cystic fibrosis-related diabetes (CFRD). Additionally, continuous glucose monitoring (CGM) was performed for 14 days at each visit. We employed a repeated-measures general linear model to assess changes in insulin secretion and CGM metrics, with glucose tolerance status as the between-subjects factor and visit (baseline, 24 and 52 weeks) as the within-subjects factor. **Results:** The study comprised 25 patients (11 adults and 14 pediatrics). At baseline, 2 patients (8%) had NGT, 8 (32%) had INDET, 10 (40%) had IGT, and 5 (20%) had CFRD. Overall, there were no significant changes in insulin and C-peptide area under the curve (AUC), IGI and DI after 52 weeks. However, we observed an increase in ISR60 among NGT patients (mean change: 1.766; 95% CI: 1.414; 2.118, $p < 0.001$). Consistently, average glucose exhibited a significant decrease in NGT patients between 24 and 52 weeks (mean change: −5.645; 95% CI: −4.233; −10.866, $p = 0.028$). **Conclusions:** Treatment with CFTR modulators potentially enhances insulin secretion in patients with CF NGT. Early initiation of treatment, as evaluated through long-term prospective trials, is essential to further investigate whether decreased glucose control is preventable or reversible.

**Keywords:** CFTR modulator; cystic fibrosis-related diabetes; cystic fibrosis; continuous glucose monitoring; insulin secretion

check for updates

**Citation:** Bayona, A.; Lecumberri Pascual, E.; Vicente, S.; Maíz, L.; Morales, A.; Lamas, A.; Sánchez Rodríguez, C.; Yelmo, R.; Martín-Frías, M.; Martínez Vaello, V.; et al. Evaluation of Insulin Secretion and Continuous Glucose Monitoring in Patients with Cystic Fibrosis After Initiation of Transmembrane Conductance Regulator Modulator: A 52-Week Prospective Study. *Diabetology* **2024**, *5*, 554–565. https://doi.org/10.3390/diabetology5060040

Academic Editor: Yoshifumi Saisho

Received: 19 August 2024
Revised: 10 October 2024
Accepted: 21 October 2024
Published: 24 October 2024

**Copyright:** © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

## 1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) gene [1]. A common complication of CF is

impaired glucose tolerance and CF-related diabetes (CFRD), which is observed in approximately one-fifth of adolescents and up to half of adult patients with CF [2–5]. CFRD results from progressive beta cell dysfunction, often occurring years before overt hyperglycemia is detected. The early hallmark of glucose metabolism disturbances in CF is an impaired first-phase insulin secretion, even in individuals with normal glucose tolerance. This defect reflects a loss of beta cell function, which is further exacerbated by chronic inflammation, pancreatic fibrosis, and the cumulative effects of recurrent infections. In the long term, these factors contribute to the development of CFRD. Understanding these early defects in insulin secretion is crucial for predicting and managing CFRD in the CF population [5,6]. Prevalence of CFRD in Europe and US is similar and it is estimated to be 0.73 and 0.79 cases per 10,000 habitants, respectively [7]. CFRD is an important comorbidity associated with overall increased mortality due to a negative impact on pulmonary function and nutritional status especially, underlining the importance of research in prevention and management of this complication [4,5]. The most significant risk factors associated with CFRD are age, female sex, type and severity of the genetic mutation (with patients homozygous for the Phe508del mutation being the most susceptible to CFRD), concomitance of exocrine pancreatic insufficiency and glucocorticoid therapy [4,5].

In recent years, the introduction of CFTR modulators provided a novel approach for the treatment of CF [8,9]. These new drugs target the CFTR protein, increase the quantity and activity of CFTR reaching the cell surface, and enhance its stability and function [8–11]. CFTR modulators fall into two categories: correctors and potentiators. Correctors, such as lumacaftor (LUM), tezacaftor (TEZ), and elexacaftor, assist with the proper folding and trafficking of CFTR to the cell surface, while potentiators like ivacaftor (IVA) enhance the ion transport through CFTR once it reaches the membrane [8,9]. When used in combination, these drugs can improve the functionality of the CFTR protein. The introduction of highly effective modulator therapies, which combine correctors and potentiators, has transformed CF management, significantly improving clinical outcomes including pulmonary function and reducing hospitalizations [9,10]. In Spain, IVA, LUM/IVA and TEZ/IVA have been prescribed to all individuals homozygous for the Phe508del mutation or other eligible mutations, irrespective of symptoms, since 2020.

With the drastic improvement in overall health with modulator therapy, this begs the question of the impact on other complications of CF, such as CFRD [12]. However, the clinical trials of CFTR modulators generally have not included diabetic or glycemic outcomes and the rapid emergence and dynamic evolution of these therapies has made the study of their impact on CFRD a "moving target" [12]. The role of CFTR in CFRD pathogenesis is inadequately understood and research aimed at deciphering the underlying mechanisms of CFRD continues to evolve [12]. While several studies have investigated the impact of CFTR modulators on glucose tolerance and insulin secretion, many of these have been retrospective in nature, with small sample sizes and short durations. The results of these studies are often inconclusive and show inconsistent outcomes, particularly regarding the modulators' long-term effects on glucose metabolism [13–29]. In light of these limitations, our study seeks to address these gaps by offering a prospective, year-long analysis with continuous glucose monitoring (CGM) data, providing a more detailed assessment of the modulators' impact on glucose dynamics over time. Hence, our primary objective was to evaluate changes in glucose metabolism and insulin secretion assessed by the oral glucose tolerance test (OGTT) at 24 and 52 weeks after initiation of CFTR modulators in patients with CF. Secondly, we evaluated the change in CGM metrics from baseline to the end of follow-up.

## 2. Material and Methods

### *2.1. Design of the Study and Patient Selection*

We conducted a prospective, single-center, observational study in patients with CF attended by the Cystic Fibrosis Unit of a tertiary hospital in Madrid, Spain. The study included patients who met the criteria for initiating CFTR modulators in accordance with

current regulations in our country. Since 2020, in Spain, IVA, LUM/IVA, and TEZ/IVA have been prescribed to all individuals homozygous for the Phe508del mutation or other eligible mutations, regardless of symptoms. IVA (Kalydeco®, Vertex Pharmaceuticals, Boston, MA, USA) is indicated for patients with at least one gating mutation. Patients homozygous for the Phe508del mutation are eligible for LUM/IVA (Orkambi® Vertex Pharmaceuticals, Boston, MA, USA) and TEZ/IVA (Symkevi® Vertex Pharmaceuticals, Boston, MA, USA). Additionally, TEZ/IVA is approved for certain patients with CF who are compound heterozygous for Phe508del and have a mild mutation. Recruitment concluded before the introduction of triple therapy with elexacaftor/TEZ/IVA at our hospital; hence, this study does not include patients receiving third-generation triple therapy with CFTR modulators.

Finally, we recruited 25 patients who initiated CFTR modulator therapy with IVA, LUM/IVA, and TEZ/IVA between February and June 2020, and who provided written consent to participate in the study. Exclusion criteria included pregnancy, solid organ transplantation, recent pulmonary exacerbation or oral glucocorticoid use within the previous 4 weeks, severe disease, or terminal illness. Specifically, this includes uncontrolled cardiovascular disease (e.g., heart failure or significant arrhythmias), severe liver dysfunction (e.g., cirrhosis), renal failure requiring dialysis, or any condition requiring long-term hospitalization or intensive care support.

To mitigate sampling bias, we employed consecutive sampling, inviting all eligible patients with CF to participate.

Throughout the 52-week study period, there were no instances of loss to follow-up or discontinuation of CFTR modulators.

### *2.2. Clinical Parameters and Laboratory Measures*

Demographic and clinical data of the study population were collected. CF-related variables were also recorded: presence of lung, liver and exocrine pancreas involvement; number of pulmonary exacerbations before and after CFRD diagnosis; and number of acute pulmonary exacerbations, hospitalizations and time to first pulmonary exacerbation after the initiation of CFTR modulators. We collected the last forced expiratory volume in one second ($FEV_1$). Spirometry was performed according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines [30]. $FEV_1$ was expressed as a percentage of the reference values [31].

Physical exam and laboratory analyses were performed at baseline, 24 and 52 weeks following the initiation of CFTR modulators. OGTT was performed using a 1.75 g/kg dose of glucose (maximum 75 g), given orally over 5 min, and samples were withdrawn at 0, 30, 60, 90 and 120 min for glucose (mg/dL), insulin (µUI/mL) and C-peptide (ng/mL) measurements. Subjects fasted for at least 8 h before the test. Plasma insulin and C-peptide levels were measured by chemiluminescent immunoassay. For those on long-acting insulin, the basal insulin dose was maintained as per their usual schedule, ensuring that no significant adjustments were made in the 48 h prior to the OGTT. Patients did not administer long-acting insulin on the day of the OGTT, as per protocol. No patients in our cohort were using insulin pumps or automated closed-loop delivery systems. All patients were advised to avoid any major dietary or physical activity changes in the days leading up to the OGTT. Area under curve (AUC) values for glucose, insulin and C-peptide were calculated as the AUC value above the fasting value over the 2 h sampling period using the trapezoidal estimation. Insulin secretion rate within 60 min (ISR60) was calculated as the change in insulin levels divided by the change in glucose in the first 60 min of the OGTT [32]. To further evaluate beta cell function and early insulin response, we calculated the insulinogenic index (IGI) based on the OGTT data. The IGI was calculated as the ratio of the change in insulin to the change in glucose during the first 30 min of the OGTT:

$$IGI = \Delta Insulin_{30-0} / \Delta Glucose_{30-0}$$

This index reflects the early phase of insulin secretion and provides insight into the functional capacity of pancreatic beta cells. It has been used in previous studies to assess

beta cell function and early insulin response in patients with cystic fibrosis and normal glucose tolerance (NGT) [33]. HOMA-β was calculated as an index representing insulin resistance and β-cell function by [fasting plasma insulin (μIU/mL) × 360/(fasting plasma glucose (mg/dL)–63] [34]. In addition, insulin resistance was calculated by homeostasis model assessment of insulin resistance (HOMA-IR) [35].

Glucose tolerance classification followed the 2018 International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines [36]. Glucose tolerance status was determined based on baseline OGTT results and defined as NGT: fasting glucose < 100 mg/dL and 2 h glucose < 140 mg/dL; indeterminate glucose tolerance (INDET): 1 h glucose ≥200 mg/dL and 2 h glucose <140 mg/dL; impaired glucose tolerance (IGT): 2 h glucose ≥140 mg/dL and <200 mg/dL, and CFRD: 2 h glucose ≥ 200 mg/dL [2]. Glucose tolerance status was reassigned at 24 and 52 weeks of follow-up.

Baseline metabolic control was assessed by $A_{1c}$ levels (high performance ion-exchange chromatography, HA-8160 analyzer, A. Menarini diagnostics, Italy) and continuous interstitial glucose monitoring (CGM) data (Freestyle libre 2, Abbott, EEUU). We downloaded the following CGM metrics: percentage of time spent in hypoglycemia [time below range (TBR) < 70 mg/dL and <54 mg/dL], normoglycemia [time in range (TIR) between 70 and 180 mg/dL], and hyperglycemia [time above range (TAR) > 180 mg/dL, >250 mg/dL)]; mean glucose concentration measured by the CGM (mg/dL), glucose management indicator (GMI), coefficient of variation (CV), standard deviation (DS) and percent sensor usage. Fourteen days of data from the CGM were analyzed at baseline, 24 and 52 weeks after the initiation of CFTR using Libreview™ platform.

### *2.3. Ethical Considerations*

The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments, and agreed with national regulations. The Ethics Committee of Hospital Universitario Ramón y Cajal approved the study (protocol ID: ENDDRFQ002, date of approval: 14 May 2020). Written informed consent to use the clinical and biochemical data for research was obtained from each participant. In patients aged < 18 years, the informed consent was obtained from parents and/or legal tutors. Patients' confidentiality was assured following good clinical practice, and anonymization of patients was conducted assigning a numeric code for data collection.

### *2.4. Statistical Analysis*

Descriptive summary statistics were calculated and presented as medians (interquartile range [IQR]) or fractions. Binary variables were compared using $\chi^2$ test or Fisher's exact test, depending on calculated expected frequencies. Total AUC for glucose was calculated over the 2 h sampling period using the trapezoid method. To analyze the entire study cohort, we employed multivariate linear mixed models with a random intercept. The dependent variables included assessments of insulin secretion and GCM values, while the independent variable was time measured in weeks. Patient ID served as the grouping variable. We used a repeated-measures general linear model to evaluate the changes in insulin secretion and CGM metrics between baseline and study visits: glucose tolerance status (NGT/INDET/IGT and CFRD) was the between-subjects factor, and visit (baseline, 24 and 52 weeks) was the within-subjects factor. Major effects and interactions were analyzed. For longitudinal changes in the glucose tolerance status throughout the study, we used generalized estimating equations (GEEs). We used intention-to-treat analysis including all patients; for missing observations, we carried forward the last valid value observed. A significance level of $p < 0.05$ was used for all tests.

## 3. Results

### *3.1. Baseline Characteristics*

The baseline characteristics of 25 patients included are summarized in Table 1. Among them, thirteen were male (57%). Eleven participants were adults, with a mean age of

38 ± 13 years, while the remaining fourteen were pediatric patients, with a mean age of 10 ± 4 years. Most patients (76%) were homozygous for the F508del mutation. At baseline, the median (IQR) FEV1 was 81% (31). In the pediatric subset, BMI z-score data were collected. Regarding glucose metabolism status, at baseline, 2 patients (8%) had NGT, 8 patients (32%) had INDET, 10 patients (40%) had IGT, and 5 patients (20%) had CFRD (Table 1). There were no subjects in our cohort with isolated impaired fasting glucose (fasting glucose between 100–125 mg/dL). The median age at diagnosis of glucose metabolism alteration was 34 years (IQR 17) in adult patients and 8 years (IQR 8) in pediatric patients. All patients diagnosed with CFRD were undergoing insulin treatment, with all of them receiving intensive insulin therapy regimens. Notably, none of these patients had developed CFRD-related complications.

**Table 1.** Baseline characteristics of patients included (*n* = 25). Data are presented as median ± DS or median (interquartile range) for quantitative variables and as number (percentage) for qualitative variables.

| Variable | Total (*n* = 25) | Adults (*n* = 11) | Pediatrics (*n* = 14) |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 16 (35) | 38 ± 13 | 10 ± 4 |
| Men (n, %) | 13 (57) | 6 (54) | 7 (50) |
| BMI z-score * | - | NA | −0.6 (0.5) |
| Homozygous F508del (n, %) | 19 (76) | 6 (55) | 13 (93) |
| **Glucose tolerance status** (n, %) | | | |
| NGT | 2 (8) | 2 (18) | 0 (0) |
| INDET | 8 (32) | 2 (18) | 6 (43) |
| IGT | 10 (40) | 3 (27) | 7 (50) |
| CFRD | 5 (20) | 4 (36) | 1 (7) |
| Insulin treatment (n, %) | 5 (20) | 4 (36) | 1 (7) |
| $A_{1c}$ (%) ¶ | - | 5.85 ± 0.55 | NA |
| $FEV_1$ (%) | 81 (31) | 66 ± 21 | 88 ± 11 |
| Pancreatic insufficient | 22 (88) | 8 (73) | 14 (100) |

$A_{1c}$, glycated hemoglobin (¶ $A_{1c}$ was only available for adults); BMI, body mass index (* BMI z-score was only available for pediatric patients); CFRD, cystic fibrosis-related diabetes; $FEV_1$, forced expiratory volume in one second; IGT, impaired glucose tolerance; INDET, indeterminate glucose tolerance; NA, data not available; NGT, normal glucose tolerance. (-) No data are available because they are only available for the pediatric population.

### *3.2. OGTT Results for Glucose and Insulin Secretion*

Analyzing the entire cohort, we found that median fasting, and 1 h and 2 h OGTT glucose levels did not exhibit significant changes between baseline, 24, and 52 weeks after the initiation of treatment with CFTR modulators (Table 2). Additionally, there were no significant alterations in glucose AUC from baseline to the end of the follow-up period. Estimates of insulin secretion derived from OGTT, including insulin AUC, fasting C-peptide levels and IGI, also showed no significant variation from baseline to 24 and 52 weeks (Table 2). Furthermore, there were no observed changes in HOMA-IR.

When analyzed according to baseline glucose tolerance status, as expected, patients with CFRD exhibited a greater glucose AUC compared to patients with NGT and those with INDET glucose tolerance, as shown in Table 3. However, no changes were observed over the 52-week follow-up period for the glucose AUC, insulin AUC, or C-peptide AUC. Nevertheless, we found a significant increase in ISR60 in the subgroup of patients with NGT (mean change: 1.766; 95% CI: 1.414; 2.118, $p < 0.001$), as shown in Table 3 and Figure 1. Similarly, we found a significant increase in HOMA-IR at 52 weeks to follow-up in the subgroup of patients with CFDR, as shown in Table 3.

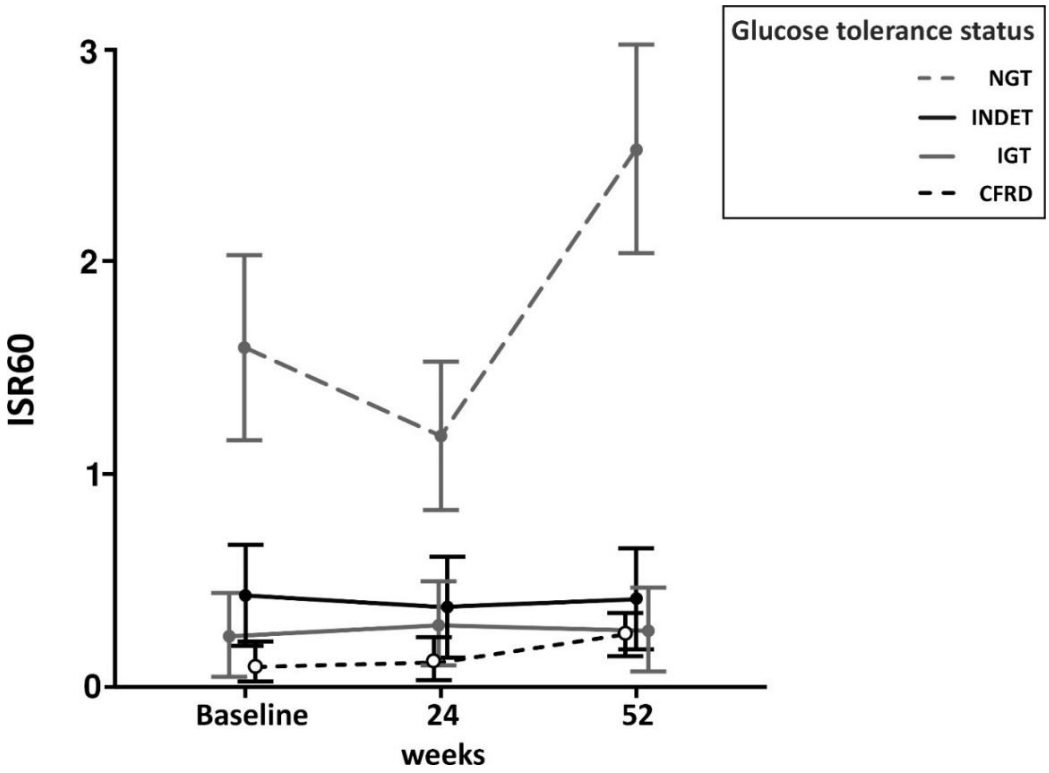


**Figure 1.** Insulin secretion rate within 60 min (ISR60) at baseline, 24 and 52 weeks after CFTR modulator initiation according to baseline glucose tolerance status. (NGT): normal glucose tolerance; (INDET): indeterminate glucose; (IGT): impaired glucose tolerance; and (CFRD): cystic fibrosis-related diabetes.

**Table 2.** Glycemic outcomes 24 and 52 weeks after CFTR modulator initiation. Data are presented as median (IQR).

| Outcome | Baseline | 24 Weeks | 52 Weeks | Mixed Model Coefficient (95% CI) | *p* Value |
|---|---|---|---|---|---|
| Fasting glucose (mg/dL) | 94 (16) | 94 (10) | 95 (14) | 0.002 (−0.086, 0.089) | 0.972 |
| 1 h OGTT glucose (mg/dL) | 196 (60) | 220 (90) | 236 (103) | 0.079 (−0.317, 0.474) | 0.697 |
| 2 h OGTT glucose (mg/dL) | 150 (90) | 157 (88) | 147 (84) | −0.188 (−0.562, 0.186) | 0.325 |
| Glucose AUC (mg/dL) | 8888 (6975) | 12,045 (6435) | 9180 (8190) | 3.040 (−25.907, 31.986) | 0.837 |
| Fasting C peptide (ng/mL) | 0.72 (0.67) | 1.01 (0.47) | 1.01 (0.53) | 0.001 (−0.002, 0.004) | 0.588 |
| C peptide AUC (ng/mL) | 325 (196) | 370 (299) | 345 (176) | 0.281 (−1.139, 1.701) | 0.698 |
| Insulin AUC (µUI/mL) | 2246 (1988) | 2417 (2819) | 2010 (1815) | 3.989 (−13.347, 21.325) | 0.652 |
| HOMA-IR (pmol/L × mol/L) | 0.86 (0.79) | 1.06 (0.73) | 1.33 (0.89) | 0.072 (−0.008, 0.153) | 0.077 |
| $A_{1c}$ (%) ¶ | 5.9 (0.4) | 5.6 (1.1) | NA | −0.009 (−0.020, 0.002) | 0.108 |

Abbreviations: $A_{1c}$, glycated hemoglobin (¶ $A_{1c}$ was only available for adults); AUC, area under curve; $FEV_1$, forced expiratory volume in one second; HOMA-IR: homeostatic model assessment of insulin resistance; NA, data not available; OGTT, oral glucose tolerance test.

Changes in glucose tolerance status from baseline to follow-up are illustrated in Figure 2. Two individuals showed an improvement in glucose tolerance (i.e., CFRD changed to IGT), while three individuals experienced a worsening of glucose tolerance (one patient changed from INDET to IGT, and two patients changed from IGT to CFRD). For twenty individuals, there was no change in glucose tolerance status.

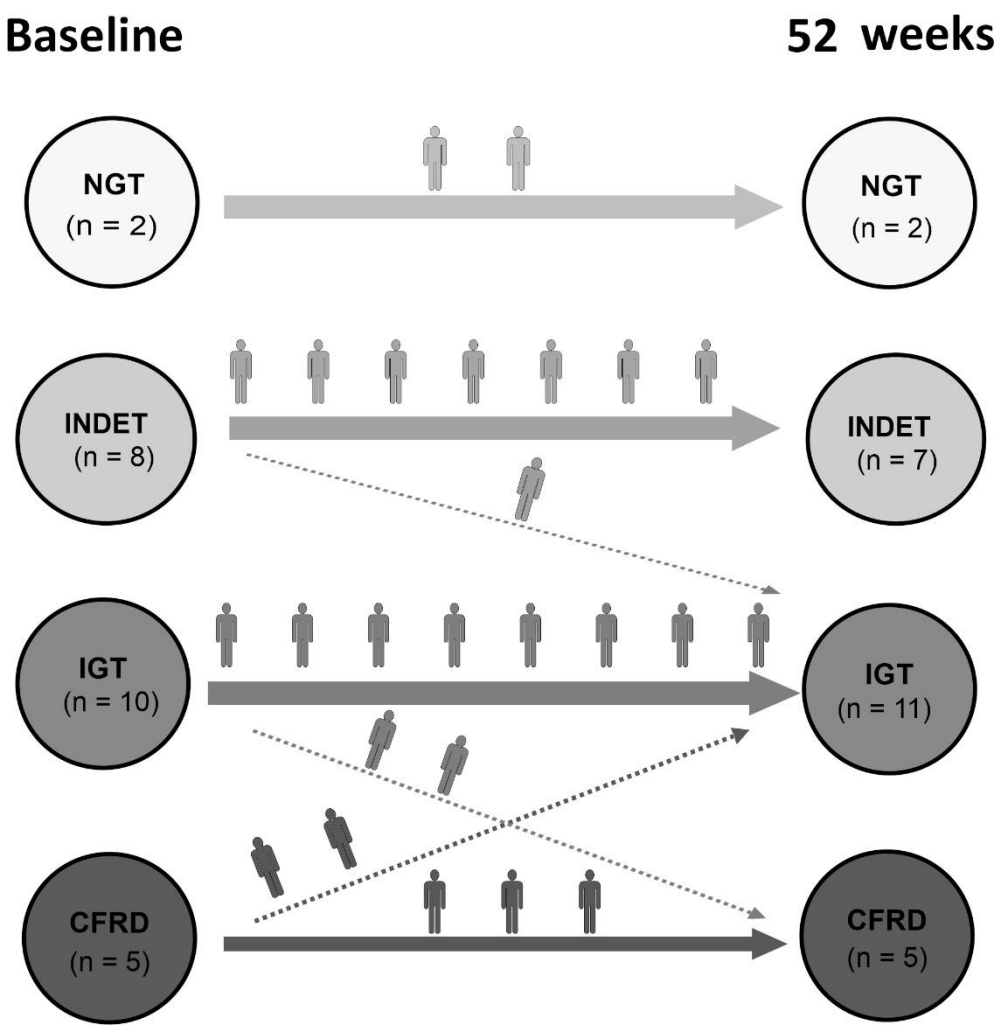


**Figure 2.** Changes in glucose tolerance category from baseline to 52 weeks after treatment initiation. Solid arrows indicate no change in the glucose tolerance category, while dashed arrows indicate a change in the glucose tolerance category. (NGT): normal glucose tolerance; (INDET): indeterminate glucose; (IGT): impaired glucose tolerance; and (CFRD): cystic fibrosis-related diabetes.

**Table 3.** Glycemic outcomes and CGM parameters at baseline, 24 and 52 weeks after CFTR modulator initiation according to baseline glucose tolerance status. Data are presented as mean (SD).

| Outcome | Baseline | | | | 24 Weeks | | | | 52 Weeks | | | | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NGT | INDET | IGT | CFRD | NGT | INDET | IGT | CFRD | NGT | INDET | IGT | CFRD | |
| Glucose AUC (mg/dL) [e, f, g] | 2948 (1983) | 6617 (1672) | 10667 (2834) | 16272 (4900) | 2813 (456) | 9527 (3987) | 11718 (3788) | 13269 (2052) | 2295 (870) | 7635 (1938) | 10565 (3996) | 16044 (5054) | **0.046** |
| C peptide AUC (ng/mL) | 474 (59) | 411 (275) | 394 (161) | 182 (145) | 569 (26) | 520 (317) | 438 (165) | 209 (165) | 573 (82) | 442 (277) | 401 (154) | 252 (120) | NS |
| Insulin AUC (µUI/mL) | 3364 (71) | 3206 (3487) | 3085 (1650) | 1589 (820) | 3319 (438) | 4292 (4429) | 3727 (2104) | 1723 (944) | 3491 (109) | 3521 (3629) | 3238 (2024) | 2451 (3030) | NS |
| ISR60 [b,c,d,e,f] | 1.59 (1.01) | 0.43 (0.36) | 0.24 (0.16) | 0.82 (0.56) | 1.18 (0.04) | 0.38 (0.38) | 0.29 (0.24) | 0.10 (0.06) | 2.53 (0.32) | 0.41 (0.36) | 0.26 (0.13) | 0.24 (0.37) | **<0.001** |
| HOMA-IR (pmol/L × mmol/L) [b,c,f,g] | 0.83 (0.08) | 0.73 (0.24) | 1.30 (0.54) | 1.15 (0.66) | 1.26 (0.32) | 0.86 (0.34) | 1.62 (0.80) | 1.27 (0.34) | 0.81 (0.11) | 0.82 (0.33) | 1.50 (0.79) | 10.50 (26.38) | **0.003** |
| Insulinogenic index | 0.84 (0.47) | 0.28 (0.22) | 0.21 (0.11) | 0.13 (0.15) | 0.76 (0.04) | 0.25 (0.25) | 0.23 (0.16) | 0.13 (0.10) | 0.84 (0.50) | 0.28 (0.22) | 0.27 (0.76) | 0.20 (0.28) | NS |
| Fasting glucose (mg/dL) [d,e,f,g,h] | 70 (5) | 91 (5) | 93 (9) | 104 (15) | 84 (5) | 89 (6) | 93 (4) | 109 (8) | 76 (4) | 92 (7) | 94 (8) | 97 (10) | **0.003** |
| TIR 70–180 (%) | 97 (3) | 96 (6) | 93 (5) | 85 (13) | 96 (5) | 92 (10) | 91 (8) | 88 (9) | 99 (1) | 97 (6) | 96 (3) | 88 (7) | NS |

**Table 3.** *Cont.*

| Outcome | Baseline | | | | 24 Weeks | | | | 52 Weeks | | | | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NGT | INDET | IGT | CFRD | NGT | INDET | IGT | CFRD | NGT | INDET | IGT | CFRD | |
| Mean glucose (mg/dL) [c,f] | 95 (2) | 103 (6) | 108 (12) | 110 (13) | 95 (3) | 97 (8) | 101 (11) | 125 (20) | 89 (6) | 106 (8) | 112 (7) | 122 (19) | **0.004** |
| GMI (%) | 5.6 (0.1) | 5.7 (0.1) | 5.8 (0.4) | 6.0 (0.4) | 5.4 (0.1) | 5.6 (0.1) | 5.7 (0.4) | 6.3 (0.5) | 5.6 (0.1) | 5.8 (0.2) | 6.0 (0.2) | 6.3 (0.4) | NS |
| TAR > 180 (%) [f,g,h] | 0.0 (0.0) | 0.8 (0.8) | 3.6 (3.8) | 12.3 (9.2) | 0.0 (0.0) | 0.8 (0.9) | 2.2 (2.2) | 13 (12) | 0.0 (0.0) | 1.0 (1.1) | 3.3 (2.1) | 13.3 (9.5) | **0.001** |
| TBR < 70 (%) | 3.0 (2.8) | 2.0 (1.4) | 4.3 (3.3) | 8.0 (9.3) | 5.0 (4.2) | 9.0 (12.1) | 8.0 (9.4) | 1.5 (2.3) | 1.5 (0.7) | 0.3 (0.5) | 0.5 (0.8) | 1.0 (1.4) | NS |
| SD (mg/dL) [f,g] | 14 (4) | 22 (5) | 28 (8) | 34 (7) | 10 (4) | 22 (5) | 26 (8) | 35 (9) | 11 (5) | 22 (5) | 27 (6) | 36 (13) | **0.004** |
| CV (%) [f] | 14 (3) | 22 (5) | 25 (7) | 31 (7) | 12 (5) | 23 (5) | 26 (6) | 29 (7) | 12 (4) | 21 (5) | 24 (6) | 29 (5) | **0.013** |

[a] Significant differences between baseline with 24 weeks; [b] Significant differences between baseline with 52 weeks; [c] Statistically significant differences between 24 with 52 weeks; [d] Significant differences between NGT with INDET; [e] Significant differences between NGT with ICG; [f] Significant differences between NGT with CFRD; [g] Significant differences between CFRD with INDET; [h] Significant differences between CFRD with IGT. Abbreviations: CFRD, cystic fibrosis-related diabetes; HOMA IR: homeostatic model assessment of insulin resistance; IGT, impaired glucose tolerance; INDET, indeterminate glucose tolerance; GMI, glucose management indicator; SD, standard deviation; NA, data not available; NGT, normal glucose tolerance; TAR, time above range; TBR, time below range; TIR, time in range.

### *3.3. CGM Parameters and $A_{1c}$*

CGM data for 14 days were available at baseline, 24 and 52 weeks for 23 patients (92%). Metrics from the CGM according to baseline glucose tolerance status observed between baseline visit and follow-up visit are described in detail in Table 3. TIR 70–180 mg/dL and TBR < 70 mg/dL did not change significantly between baseline, 24 and 52 weeks after treatment initiation. As expected, patients with CFRD exhibited a higher TAR > 180, SD and CV compared to patients with NGT and those with INDET glucose tolerance, as shown in Table 3. Average glucose showed a significant decrease only in the subgroup of patients with NGT between 24 and 52 weeks of follow-up (mean change: −5.645; 95% CI: −4.233; −10.866, $p = 0.028$), as shown in Table 3.

$A_{1c}$ levels were available for adult patients ($n = 10$) at baseline and 24 weeks after CFTR modulator initiation, and did not show any significant changes from baseline to 24 weeks after treatment initiation (5.85% (0.4) at baseline and 5.6% (1.1) at 24 weeks, $p = 0.108$), as shown in Table 2.

## 4. Discussion

This study aimed to evaluate changes in glucose metabolism, insulin dynamics, and C-peptide levels during a standard OGTT following the initiation of CFTR modulators. Analysis of the entire cohort revealed no significant changes in median fasting, 1 h, and 2 h OGTT glucose levels between baseline, 24, and 52 weeks after initiating CFTR modulator treatment. Similarly, estimates of insulin secretion derived from OGTT, including insulin and C-peptide AUC, showed no significant variation over the same period. However, when stratified by baseline glucose tolerance status, a significant increase in the insulin secretion rate at 60 min was observed in patients with NGT. Additionally, patients with NGT exhibited a significant decrease in average glucose levels measured by CGM between 24 and 52 weeks of follow-up. Although in our study very few patients had NGT, a larger study specifically including patients with NGT or early glucose intolerance is warranted to confirm our results.

Previous studies by Bellin et al. [13] and Kelly et al. [20] demonstrated improvements in insulin secretion following 1 and 4 months of monotherapy with IVA in smaller cohorts with gating mutations from North America and Italy. However, these studies also were limited by their sample sizes and wide age ranges. In a French study by Misgault et al. (21), glucose tolerance improved in 40 patients with CF homozygous for the F508del mutation after 1 year of LUM/IVA therapy. These findings are consistent with our results, suggesting a beneficial impact of CFTR modulators on glucose metabolism, particularly in enhancing early first-phase insulin secretion [13].

However, other studies investigating the effect of CFTR modulators in patients with CF did not find improvements in glucose tolerance status and insulin secretion [15,22,28]. The discrepancies in reported outcomes may be attributed to several factors. Firstly, the underlying defect in the pathophysiology of CFRD has not been definitively elucidated, leading to uncertainty regarding whether insulin insufficiency arises from irreversible changes secondary to pancreatic inflammation and fibrosis or reversible defects resulting directly from CFTR dysfunction [37]. Secondly, there is a lack of robust clinical data on the influence of novel CFTR modulators on glucose metabolism and insulin secretion, with studies often characterized by small sample sizes and short durations.

The varying results in the existing data [12–28] may also be explained by differences in the degree of inflammation and insulin resistance among different cohorts, particularly due to the wide age range of participants in the studies. While it is theoretically more likely for pancreatic endocrine function to recover in children due to less advanced disease progression, our analysis did not find a difference when separating adult and pediatric populations. The benefit of improved insulin secretion appears to be observed in patients (regardless of age) with NGT.

Some researchers suggest that the CFTR protein may have a modest yet significant impact on insulin secretion [38–40]. Animal models have shown that CFTR is expressed in pancreatic β-cells, and its absence results in changes in glucose tolerance and the initial phase of insulin release [39,41]. Augmenting CFTR activity could potentially enhance the immediate release of stored insulin in response to high blood sugar levels. In childhood, individuals with CF may compensate for this deficiency as their β-cell mass remains relatively intact. However, as pancreatic islet cells are progressively lost over time due to fibrosis of the exocrine pancreas and chronic stress on β-cells from inflammation and recurrent infections, the role of CFTR in insulin secretion becomes increasingly crucial [13].

The potential for CFTR modulators to enhance insulin secretion may depend on the duration of treatment exposure and the chronicity of CFRD. This highlights the potential benefit of initiating CFTR modulator therapy during childhood, potentially reducing the risk of developing CFRD. Moreover, our findings suggest that, from a glucose-focused perspective, initiating therapy prior to the onset of carbohydrate metabolism disorders may be advantageous.

There are several limitations to our study, primarily stemming from its observational design, small sample size with no control group, inclusion of only two adult patients with NGT, and reliance on data from a single center. All patients with NGT were adults, which restricts the generalizability of our findings to the pediatric population. Additionally, the small number of participants in each glucose tolerance category necessitates cautious interpretation of the results. A significant limitation of our study is the inclusion of adolescent patients, whose pubertal status may have influenced insulin sensitivity over the course of the 52-week follow-up. Puberty is known to cause considerable fluctuations in insulin sensitivity, which may have affected the metabolic responses observed in this subgroup. Additionally, the variation in BMI status between pediatric and adult participants could have contributed to differences in insulin secretion and sensitivity, potentially obscuring the overall results. Furthermore, the lack of significant changes in the insulinogenic index should be considered a limitation, as these metrics are crucial for assessing early-phase insulin secretion and beta cell function. One of the main limitations of our study is the exclusion of third-generation triple therapy. While this treatment has shown significant benefits in patients with CF, our study was limited to evaluating earlier generation modulators. The lack of triple therapy use may have influenced the results obtained, and future studies should consider its inclusion to more comprehensively assess the effects on glycemic control and insulin secretion. Future studies should take these variables into account to provide a more comprehensive analysis of the impact of CFTR modulators on glucose metabolism. However, our study also possesses several strengths. Our study stands out due to its prospective design, the inclusion of CGM data, and its year-long follow-up. The use of CGM allows us to capture subtle changes in glucose dynamics that may not be

evident through traditional glucose tolerance tests alone, thus offering a more in-depth understanding of the modulators' effects over time. Furthermore, OGTTs were conducted at baseline, and 24 and 52 weeks post-therapy initiation, with glucose metabolism status reassessed at each visit. Additionally, a subset of patients underwent CGM for 14 days at each visit. The stratification and analysis based on glucose tolerance status further enhance our findings.

## 5. Conclusions

In individuals with CF and normal glucose tolerance, there appears to be a potential enhancement in insulin secretion facilitated by CFTR modulators. Conducting long-term prospective trials for early treatment initiation is imperative to comprehensively evaluate the impact of the CFTR modulator on pancreatic endocrine function, particularly in individuals without CFRD. These studies are essential for elucidating the potential role of these medications in preventing and managing early glucose metabolism abnormalities.

**Author Contributions:** Conceptualization, E.L.P., L.M. and A.L.; methodology, L.N.-C.; formal analysis, S.V. and L.N-C; investigation, A.B., E.L.P., L.M., A.M., A.L., C.S.R., R.Y., M.M.-F., V.M.V. and E.B.C., L.N.-C.; data curation, E.L.P.; writing—original draft preparation, A.B.; writing—review and editing, L.M., A.L. and L.N.-C.; visualization, L.N.-C.; project administration, E.L.P. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work has been supported by grants from Fondo de Investigación Sanitaria (PI22/00616 and INT23/00051) from Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness. The funding organization played no role on the study design, collection, analysis, and interpretation of data, on the writing of the report, nor on the decision to submit the report for publication.

**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Ramón y Cajal Hospital (protocol code ENDDMFQ002, date of approval 14 May 2020).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author, [LN-C], upon reasonable request. The data are not publicly available because they containing information that could compromise the privacy of research participants.

**Conflicts of Interest:** The authors declare no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with, the subject matter or materials discussed in the manuscript.

## References

1. Fonseca, C.; Bicker, J.; Alves, G.; Falcão, A.; Fortuna, A. Cystic fibrosis: Physiopathology and the latest pharmacological treatments. *Pharmacol. Res.* **2020**, *162*, 105267. [CrossRef] [PubMed]
2. Boudreau, V.; Reynaud, Q.; Dubois, C.L.; Coriati, A.; Desjardins, K.; Durieu, I.; Rabasa-Lhoret, R. Screening for Cystic Fibrosis-Related Diabetes: Matching Pathophysiology and Addressing Current Challenges. *Can. J. Diabetes* **2016**, *40*, 466–470. [CrossRef] [PubMed]
3. Boudreau, V.; Coriati, A.; Hammana, I.; Ziai, S.; Desjardins, K.; Berthiaume, Y.; Rabasa-Lhoret, R. Variation of glucose tolerance in adult patients with cystic fibrosis: What is the potential contribution of insulin sensitivity? *J. Cyst. Fibros.* **2016**, *15*, 839–845. [CrossRef] [PubMed]
4. Putman, M.S.; Norris, A.W.; Hull, R.L.; Rickels, M.R.; Sussel, L.; Blackman, S.M.; Chan, C.L.; Ode, K.L.; Daley, T.; Stecenko, A.A.; et al. Cystic Fibrosis-Related Diabetes Workshop: Research Priorities Spanning Disease Pathophysiology, Diagnosis, and Outcomes. *Diabetes* **2023**, *72*, 677–689. [CrossRef]
5. Moran, A.; Becker, D.; Casella, S.J.; Gottlieb, P.A.; Kirkman, M.S.; Marshall, B.C.; Slovis, B. Epidemiology, pathophysiology, and prognostic implications of cystic fibrosis-related diabetes: A technical review. *Diabetes Care* **2010**, *33*, 2677–2683. [CrossRef]
6. Moran, A.; Brunzell, C.; Cohen, R.C.; Katz, M.; Marshall, B.C.; Onady, G.; Robinson, K.A.; Sabadosa, K.A.; Stecenko, A.; Slovis, B. Clinical care guidelines for cystic fibrosis-related diabetes: A position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care* **2010**, *33*, 2697–2708. [CrossRef]
7. Farrell, P.M. The prevalence of cystic fibrosis in the European Union. *J. Cyst. Fibros.* **2008**, *7*, 450–453. [CrossRef]

8. Clancy, J.P.; Cotton, C.U.; Donaldson, S.H.; Solomon, G.M.; VanDevanter, D.R.; Boyle, M.P.; Gentzsch, M.; Nick, J.A.; Illek, B.; Wallenburg, J.C.; et al. CFTR modulator theratyping: Current status, gaps and future directions. *J. Cyst. Fibros.* **2019**, *18*, 22–34. [CrossRef]
9. Eckford, P.D.; Li, C.; Ramjeesingh, M.; Bear, C.E. Cystic fibrosis transmembrane conductance regulator (CFTR) potentiator VX-770 (ivacaftor) opens the defective channel gate of mutant CFTR in a phosphorylation-dependent but ATP-independent manner. *J. Biol. Chem.* **2012**, *287*, 36639–36649. [CrossRef]
10. Volkova, N.; Moy, K.; Evans, J.; Campbell, D.; Tian, S.; Simard, C.; Higgins, M.; Konstan, M.W.; Sawicki, G.S.; Elbert, A.; et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. *J. Cyst. Fibros.* **2020**, *19*, 68–79. [CrossRef]
11. Cutting, G.R. Cystic fibrosis genetics: From molecular understanding to clinical application. *Nat. Rev. Genet.* **2015**, *16*, 45–56. [CrossRef] [PubMed]
12. Merjaneh, L.; Hasan, S.; Kasim, N.; Ode, K.L. The role of modulators in cystic fibrosis related diabetes. *J. Clin. Transl. Endocrinol.* **2022**, *27*, 100286. [CrossRef] [PubMed]
13. Bellin, M.D.; Laguna, T.; Leschyshyn, J.; Regelmann, W.; Dunitz, J.; Billings, J.; Moran, A. Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: A small pilot study. *Pediatr. Diabetes* **2013**, *14*, 417–421. [CrossRef] [PubMed]
14. Chan, C.L.; Granados, A.; Moheet, A.; Singh, S.; Vigers, T.; Arbeláez, A.M.; Yi, Y.; Hu, S.; Norris, A.W.; Ode, K.L. Glycemia and β-cell function before and after elexacaftor/tezacaftor/ivacaftor in youth and adults with cystic fibrosis. *J. Clin. Transl. Endocrinol.* **2022**, *30*, 100311. [CrossRef]
15. Colombo, C.; Foppiani, A.; Bisogno, A.; Gambazza, S.; Daccò, V.; Nazzari, E.; Leone, A.; Giana, A.; Mari, A.; Battezzati, A. Lumacaftor/ivacaftor in cystic fibrosis: Effects on glucose metabolism and insulin secretion. *J. Endocrinol. Investig.* **2021**, *44*, 2213–2218. [CrossRef]
16. Crow, H.; Bengtson, C.; Shi, X.; Graves, L., 3rd; Anabtawi, A. CGM patterns in adults with cystic fibrosis-related diabetes before and after elexacaftor-tezacaftor-ivacaftor therapy. *J. Clin. Transl. Endocrinol.* **2022**, *30*, 100307. [CrossRef]
17. Dagan, A.; Cohen-Cymberknoh, M.; Shteinberg, M.; Levine, H.; Vilozni, D.; Bezalel, Y.; Bar Aluma, B.E.; Sarouk, I.; Ashkenazi, M.; Lavie, M.; et al. Ivacaftor for the p.Ser549Arg (S549R) gating mutation—The Israeli experience. *Respir. Med.* **2017**, *131*, 225–228. [CrossRef]
18. Gaines, H.; Jones, K.R.; Lim, J.; Medhi, N.F.; Chen, S.; Scofield, R.H. Effect of CFTR modulator therapy on cystic fibrosis-related diabetes. *J. Diabetes Complicat.* **2021**, *35*, 107845. [CrossRef]
19. Hayes, D., Jr.; McCoy, K.S.; Sheikh, S.I. Resolution of cystic fibrosis-related diabetes with ivacaftor therapy. *Am. J. Respir. Crit. Care Med.* **2014**, *190*, 590–591. [CrossRef]
20. Kelly, A.; De Leon, D.D.; Sheikh, S.; Camburn, D.; Kubrak, C.; Peleckis, A.J.; Stefanovski, D.; Hadjiliadis, D.; Rickels, M.R.; Rubenstein, R.C. Islet Hormone and Incretin Secretion in Cystic Fibrosis after Four Months of Ivacaftor Therapy. *Am. J. Respir. Crit. Care Med.* **2019**, *199*, 342–351. [CrossRef]
21. Misgault, B.; Chatron, E.; Reynaud, Q.; Touzet, S.; Abely, M.; Melly, L.; Dominique, S.; Troussier, F.; Ronsin-Pradel, O.; Gerardin, M.; et al. Effect of one-year lumacaftor-ivacaftor treatment on glucose tolerance abnormalities in cystic fibrosis patients. *J. Cyst. Fibros.* **2020**, *19*, 712–716. [CrossRef] [PubMed]
22. Moheet, A.; Beisang, D.; Zhang, L.; Sagel, S.D.; VanDalfsen, J.M.; Heltshe, S.L.; Frederick, C.; Mann, M.; Antos, N.; Billings, J.; et al. Lumacaftor/ivacaftor therapy fails to increase insulin secretion in F508del/F508del CF patients. *J. Cyst. Fibros.* **2021**, *20*, 333–338. [CrossRef] [PubMed]
23. Mutyam, V.; Libby, E.F.; Peng, N.; Hadjiliadis, D.; Bonk, M.; Solomon, G.M.; Rowe, S.M. Therapeutic benefit observed with the CFTR potentiator, ivacaftor, in a CF patient homozygous for the W1282X CFTR nonsense mutation. *J. Cyst. Fibros.* **2017**, *16*, 24–29. [CrossRef] [PubMed]
24. Petersen, M.C.; Begnel, L.; Wallendorf, M.; Litvin, M. Effect of elexacaftor-tezacaftor-ivacaftor on body weight and metabolic parameters in adults with cystic fibrosis. *J. Cyst. Fibros.* **2022**, *21*, 265–271. [CrossRef]
25. Piona, C.; Mozzillo, E.; Tosco, A.; Volpi, S.; Rosanio, F.M.; Cimbalo, C.; Franzese, A.; Raia, V.; Zusi, C.; Emiliani, F.; et al. Impact of CFTR Modulators on Beta-Cell Function in Children and Young Adults with Cystic Fibrosis. *J. Clin. Med.* **2022**, *11*, 4149. [CrossRef]
26. Scully, K.J.; Marchetti, P.; Sawicki, G.S.; Uluer, A.; Cernadas, M.; Cagnina, R.E.; Kennedy, J.C.; Putman, M.S. The effect of elexacaftor/tezacaftor/ivacaftor (ETI) on glycemia in adults with cystic fibrosis. *J. Cyst. Fibros.* **2022**, *21*, 258–263. [CrossRef]
27. Steinack, C.; Ernst, M.; Beuschlein, F.; Hage, R.; Roeder, M.; Schuurmans, M.M.; Schmid, C.; Gaisl, T. Improved glucose tolerance after initiation of Elexacaftor/Tezacaftor/Ivacaftor in adults with cystic fibrosis. *J. Cyst. Fibros.* **2023**, *22*, 722–729. [CrossRef]
28. Thomassen, J.C.; Mueller, M.I.; Alejandre Alcazar, M.A.; Rietschel, E.; van Koningsbruggen-Rietschel, S. Effect of Lumacaftor/Ivacaftor on glucose metabolism and insulin secretion in Phe508del homozygous cystic fibrosis patients. *J. Cyst. Fibros.* **2018**, *17*, 271–275. [CrossRef]
29. Tsabari, R.; Elyashar, H.I.; Cymberknowh, M.C.; Breuer, O.; Armoni, S.; Livnat, G.; Kerem, E.; Zangen, D.H. CFTR potentiator therapy ameliorates impaired insulin secretion in CF patients with a gating mutation. *J. Cyst. Fibros.* **2016**, *15*, e25–e27. [CrossRef]
30. Miller, M.R.; Crapo, R.; Hankinson, J.; Brusasco, V.; Burgos, F.; Casaburi, R.; Coates, A.; Enright, P.; van der Grinten, C.P.; Gustafsson, P.; et al. General considerations for lung function testing. *Eur. Respir. J.* **2005**, *26*, 153–161. [CrossRef]

31. Quanjer, P.H.; Stanojevic, S.; Cole, T.J.; Baur, X.; Hall, G.L.; Culver, B.H.; Enright, P.L.; Hankinson, J.L.; Ip, M.S.; Zheng, J.; et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *Eur. Respir. J.* **2012**, *40*, 1324–1343. [CrossRef] [PubMed]
32. Park, S.Y.; Gautier, J.F.; Chon, S. Assessment of Insulin Secretion and Insulin Resistance in Human. *Diabetes Metab. J.* **2021**, *45*, 641–654. [CrossRef] [PubMed]
33. Elder, D.A.; Wooldridge, J.L.; Dolan, L.M.; D'Alessio, D.A. Glucose tolerance, insulin secretion, and insulin sensitivity in children and adolescents with cystic fibrosis and no prior history of diabetes. *J. Pediatr.* **2007**, *151*, 653–658. [CrossRef] [PubMed]
34. Radaelli, T.; Farrell, K.A.; Huston-Presley, L.; Amini, S.B.; Kirwan, J.P.; McIntyre, H.D.; Catalano, P.M. Estimates of insulin sensitivity using glucose and C-Peptide from the hyperglycemia and adverse pregnancy outcome glucose tolerance test. *Diabetes Care* **2010**, *33*, 490–494. [CrossRef]
35. Matthews, D.R.; Hosker, J.P.; Rudenski, A.S.; Naylor, B.A.; Treacher, D.F.; Turner, R.C. Homeostasis model assessment: Insulin resistance and ?-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **1985**, *28*, 412–419. [CrossRef]
36. Moran, A.; Pillay, K.; Becker, D.; Granados, A.; Hameed, S.; Acerini, C.L. ISPAD Clinical Practice Consensus Guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes* **2018**, *19* (Suppl. 27), 64–74. [CrossRef]
37. Hart, N.J.; Aramandla, R.; Poffenberger, G.; Fayolle, C.; Thames, A.H.; Bautista, A.; Spigelman, A.F.; Babon, J.A.B.; DeNicola, M.E.; Dadi, P.K.; et al. Cystic fibrosis-related diabetes is caused by islet loss and inflammation. *JCI Insight* **2018**, *3*, 19. [CrossRef]
38. Guo, J.H.; Chen, H.; Ruan, Y.C.; Zhang, X.L.; Zhang, X.H.; Fok, K.L.; Tsang, L.L.; Yu, M.K.; Huang, W.Q.; Sun, X.; et al. Glucose-induced electrical activities and insulin secretion in pancreatic islet β-cells are modulated by CFTR. *Nat. Commun.* **2014**, *5*, 4420. [CrossRef]
39. Edlund, A.; Esguerra, J.L.; Wendt, A.; Flodström-Tullberg, M.; Eliasson, L. CFTR and Anoctamin 1 (ANO1) contribute to cAMP amplified exocytosis and insulin secretion in human and murine pancreatic beta-cells. *BMC Med.* **2014**, *12*, 87. [CrossRef]
40. Ntimbane, T.; Mailhot, G.; Spahis, S.; Rabasa-Lhoret, R.; Kleme, M.L.; Melloul, D.; Brochiero, E.; Berthiaume, Y.; Levy, E. CFTR silencing in pancreatic β-cells reveals a functional impact on glucose-stimulated insulin secretion and oxidative stress response. *Am. J. Physiol. Endocrinol. Metab.* **2016**, *310*, E200–E212. [CrossRef]
41. Ode, K.L.; Moran, A. New insights into cystic fibrosis-related diabetes in children. *Lancet Diabetes Endocrinol.* **2013**, *1*, 52–58. [CrossRef] [PubMed]


**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.