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Original research

The role of modulators in cystic fibrosis related diabetes

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ABSTRACT

The development and introduction of modulator therapies have completely shifted the paradigm for the treatment of cystic fibrosis (CF). Highly effective modulator therapies have driven marked improvements in lung function, exacerbation rate, weight and quality of life in CF patients. However, their effect on CF related diabetes (CFRD) is not well delineated. The role of CF transmembrane conductance regulator (CFTR) in CFRD pathogenesis is inadequately understood and research aimed at deciphering the underlying mechanisms of CFRD continues to evolve. In this review, we summarize what is known regarding the effect of CFTR modulators on CFRD. Small studies using ivacaftor monotherapy in gating mutations have revealed improvement in insulin secretion, glucose tolerance and/or decrease in insulin requirement. However, lumacaftor/ivacaftor studies (primarily in delta F 508 homozygous) have not revealed significant improvement in CFRD or glucose tolerance. No studies are yet available regarding the effect of the highly effective triple therapy (elexacaftor/tezacaftor/ivacaftor) on CFRD or insulin secretion. CFTR modulators might affect development or progression of CFRD through many mechanisms including improving insulin secretion by correcting the CFTR defect directly, improving ductal function, reducing islet inflammation, and improving incretin secretion or by enhancing insulin sensitivity via reduced systemic inflammation and increased physical activity driven by improved lung function and quality of life. On the other hand, they can stimulate appetite and improve gastrointestinal function resulting in increased caloric intake and absorption, driving excessive weight gain and potentially increased insulin resistance. If the defect in insulin secretion is reversible then it is possible that initiation of CFTR modulators at a younger age might help prevent CFRD. Despite the advances in CF management, CFRD remains a challenge and knowledge continues to evolve. Future studies will drive better understanding of the role of highly effective CFTR modulators in CFRD.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) gene leading to abnormality of chloride (Cl) channels in mucus and sweat producing cells and affecting multiple organs with lungs most severely affected. CF related diabetes (CFRD) is the most common secondary complication of CF. It occurs in 19% of adolescents and 40–50% of adults with CF [1]. CFRD is associated with increased morbidity and mortality [2]. Patients with CFRD have worse lung function, more frequent pulmonary exacerbations and worse nutritional status compared to patients with CF without diabetes [3].

Historically, treatment of CF has been focused on individual organ systems. More recently, modulator therapies, small molecules that directly target the underlying defect of CF, modulating or correcting the function of the CFTR gene, have been developed. These molecules, given their direct interaction with the protein, are mutation- specific [4]. Because the most effective of these drugs bring about a near "cure" for CF, the introduction of highly effective modulator therapy (HEMT) has dramatically changed the landscape of CF care, resulting in substantial improvements in lung function, reduction in hospitalization and mortality.

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. However, the clinical trials of HEMT generally did not include diabetic or glycemic outcomes and the rapid emergence and

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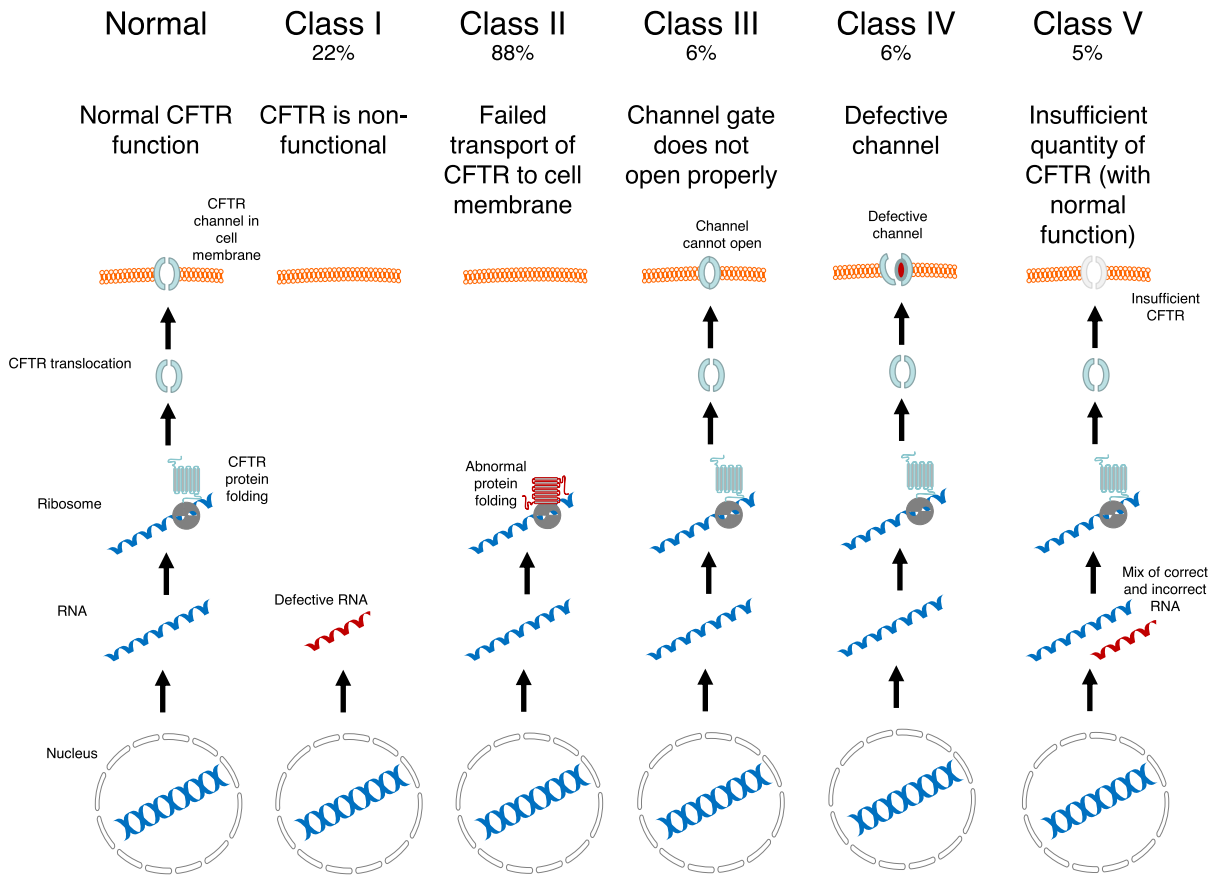

Fig. 1. The mutation classes of the CFTR gene leading to CFTR dysfunction.

dynamic evolution of these therapies has made the study of their impact on CFRD a "moving target." This review will discuss what is known about the effect of modulator therapy on glucose metabolism and CFRD and current knowledge gaps along with future directions of research.

CFTR function and mutations

CF is caused by mutations in the CFTR gene, located on the long arm of chromosome 7. CFTR functions as a regulated Cl channel at the cell surface [5]. Its dysfunction results in abnormal transport of Cl and bicarbonate ions across secretory epithelia, resulting in thickened and viscous secretions in the bronchi, pancreas and intestines leading to multisystem disease. CFTR protein is made in the endoplasmic reticulum, processed in the Golgi apparatus, and secreted in vesicles that are carried by chaperone proteins to the cell membrane, where it must be inserted and then must function normally. Mutations of the CFTR gene are classically grouped into six classes of mutations based on the mechanism underlying the lack of adequate function of the CFTR protein [6] (Fig. 1).

Class I mutations lead to lack of functional CFTR protein synthesis due to nonsense, frame shift or splicing mutations. Class II mutations lead to a misfolded protein that fails to achieve conformational stability to transport to the plasma membrane, resulting in severe reduction of CFTR activity. This class includes F508 del, the most prevalent mutation in the CFTR gene in Western countries [7]. Class III mutations referred to as "gating" mutations lead to defective gating of the Cl channel, preventing Cl- transport across the membrane. G551D is the most common CFTR gating mutation. Class IV mutations reduce CFTR dependent Cl transport due to channel conductance defect, but still permit a degree of residual function. Class V mutations cause decreased synthesis and/or inefficient protein maturation resulting in reduction, but not elimination of functional CFTR protein. Class VI mutations affect CFTR stability at the plasma membrane level, thus reducing the protein expression and recycling at the apical surface. Mutations in classes I, II, and III are associated with more severe disease and higher CFRD prevalence, whereas others are related to milder phenotypes.

CFTR modulator therapies

CFTR modulators are drugs that enhance and/or restore the expression, function, or stabilize the defective CFTR protein. Initially, modulator therapy was only available for gating mutations where only a single drug was required to improve CFTR function. However, the most common mutation, F508 del, requires multiple areas to be addressed to increase function. Most of the mutated protein does not make it to the cell membrane, and what mutated protein does make it to the membrane does not conduct. Therefore, multiple small molecules with different targets were developed- correctors to bring the protein to the cell surface, and potentiators to increase opening of the ion channel. Currently available modulators include the potentiator ivacaftor, and the correctors lumacaftor, tezacaftor, and elexacaftor, which improve the processing and trafficking of functional CFTR protein to the cell surface, increasing its amount and enhancing ion transport.

Table 1 summarizes the available modulator therapies by chronological order of FDA approval year, their indications and their effects on lung function and exacerbation frequency compared to placebo. Both elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) and ivacaftor (when used in gating mutations) are considered highly effective modulator therapies (HEMT) because of the significant improvements seen in lung function with these therapies compared to other modulator therapies.

The role of CFTR in CFRD pathophysiology

Both the pathophysiology of CFRD and the specific role of CFTR in

Table 1
Summary of the available modulator therapies.

Modulator therapy (brand name)	FDA approval	Age	Mutation	Effects compared to placebo
Ivacaftor (Kalydeco)	2012	4 months and older	One of 97 specific gating mutations (4–5% of CF)	-Increase in FEV1% predicted of >10% from baseline. -Reduction in pulmonary exacerbations by 55%(19)
Lumacaftor/ ivacaftor (Orkambi)	2015	2 years and older	Homozygous for F508 del	-Increase in FEV1% predicted of 2.6–4% from baseline. -Reduction in pulmonary exacerbations by 30–39% [36]
Tezacaftor/ ivacaftor (Symdeco)	2018	6 years and older	Two copies of F508 del mutation or a single copy of one of 154 specific mutations	-Increase in FEV1% predicted of 4% from baseline. -Reduction in pulmonary exacerbations by 35% [37]
Elexacaftor/ tezacaftor/ ivacaftor (Trikafta)	2019	6 years and older	At least one copy of the F508del mutation or one copy of 177 specific mutations (95% of CF patients)	-Increase in FEV1% predicted of 14% from baseline. -Reduction in pulmonary exacerbations by 63% (38)

the pathophysiology of CFRD are incompletely understood, leading to uncertainties whether restoring CFTR function using modulator therapy will improve glucose metabolism in CF.

It has been established that dysfunctional insulin secretion is the primary defect leading to CFRD [8]. It is also clear that the insulin secretion defects seen in CF are not merely consequences of fibrosis and scarring of the surrounding exocrine pancreas, as pancreas autopsies from CFRD patients show similar beta cell mass to CF patients without CFRD [9]. Whether CFTR dysfunction directly contributes to these functional defects is yet to be confirmed.

The presence of CFTR in islet cells remains controversial. CFTR expression has been identified in pancreatic alpha- and beta-cells in some studies [10,11] and has been shown to play a role in insulin exocytosis and regulation of membrane potential in beta-cells contributing to insulin secretion [12,13]. However, these findings are not consistent throughout the literature. In contrast, Hart et al. reported that CFTR deletion from mouse beta-cells did not affect glucose tolerance [14]. They also found minimal CFTR mRNA expression and no detectable CFTR protein in human islet cells, concluding that it does not play an important role in regulating insulin secretion. However, it has been suggested that there could be a direct paracrine effect of CFTR, expressed in the ductal epithelial cells of the exocrine pancreas, on the islets [15]. If this proves to be correct, then enhancing pancreatic ductal function by restoring CFTR might improve islet function and insulin secretion.

Alternatively, CFTR restoration could play an indirect role in CFRD through reducing inflammation. CF is associated with generalized and localized intra- and inter-islet inflammation. Increased IL-1β immunoreactivity was detected in pancreatic autopsies in CF patients with and without diabetes [9]. IL-1β inhibits beta-cell function in type 1 diabetes [16] and IL-1β inhibition is associated with improved beta-cell function in type 2 diabetes [17]. Systemic inflammation is also known to be associated with insulin resistance [18]. Modulator therapy reduces the inflammation associated with CF and as a result may improve islet function and insulin sensitivity. Another possibility is that restored CFTR might improve secretion of incretins from the gastrointestinal neuroendocrine cells, indirectly improving insulin secretion. This could occur via improvements in intestinal PH profile leading to enhanced pancreatic enzyme–replacement therapy efficiency and nutrient absorption.

A potential role for CFTR in glucose metabolism was suggested in the study by Sun et al. where Ivacaftor administration in utero and postnatally in ferret models of CF with homozygous gating mutations was shown to prevent pancreatic insufficiency (PI) and glucose abnormalities. Withdrawal of Ivacaftor postnatally in these pancreatic sufficient ferrets resulted in PI and varying degrees of glucose abnormalities. The findings also suggested that modulator therapy may prevent glucose abnormalities if started early enough. Additionally, 2 CF patients (one had CRFD and one did not) in the Ivacaftor arm of a randomized, placebo-controlled trial had hypoglycemia additionally suggesting a role for CFTR in glucose metabolism [19].

Discussion of the existing clinical data on modulators and glucose metabolism in CF (Table 2)

Large prospective studies on the effect of modulator therapy on CFRD and glucose metabolism in CF are lacking, and CFRD related endpoints were not included in the randomized controlled trials performed for approval of any of highly effective modulator therapies. To date, existent studies tend to be small or limited to case reports and case series. No published studies are yet available regarding the effects of ELX/TEZ/IVA on glucose metabolism in CF.

Ivacaftor studies

Bellin et al. were the first to evaluate the effect of ivacaftor on insulin secretion in a small pilot study conducted in CF patients with the gating G551D mutation [20]. Oral glucose tolerance tests (OGTT) and intravenous glucose tolerance tests (IVGTT) were performed at baseline and 4 weeks after daily ivacaftor therapy on five CF patients aged 6–52 (2 with normal glucose tolerance (NGT), 1 with abnormal glucose tolerance (AGT), 2 with CFRD). After 1 month on ivacaftor, insulin area under the curve (AUC) on OGTT improved by 66–178% in all subjects except the patient with long-standing diabetes. The patient with AGT improved to NGT but there was no change in the glucose tolerance category for the patients with CFRD. In response to IVGTT, 4/5 patients had improvement in insulin secretion by 51–346%, including partial restoration in 2 subjects who previously had no measurable acute insulin response. This small pilot study suggested that correction of CFTR activity improves insulin secretion in CF.

Subsequently, Hayes et al. reported on a 25-year-old male with CF (G551D gating mutation) and CFRD on insulin diagnosed 6 years before starting ivacaftor. CFRD resolved and insulin was discontinued within a year and OGTT was normal within 2 years after starting ivacaftor [21]. Tsabari et al. described two siblings with CF and S549R gating mutation (1 with diabetes and 1 indeterminate glycemia (INDET)) in whom ivacaftor therapy improved insulin secretion and resolved CFRD or INDET after 16 weeks [22]. Christian et al. described a 34-year-old male with CF due to G551D mutation and CFRD on insulin for 14 years who discontinued insulin within 6 months after starting ivacaftor because of recurrent hypoglycemia [23]. He remained off insulin for 3 years with good glycemic control after which he resumed insulin secondary to hyperglycemia. These case reports also suggested that restoration of CFTR function might resolve or improve CFRD.

Dagan et al. studied 8 CF patients (mean age 21 years) with the S549R gating mutation and varying degrees of glucose tolerance (1 NGT,

Table 2
Summary of the studies describing the effect of modulators on glucose metabolism in CF.

Study	Number of subjects	Age (years)	CFRD status	Tests	Outcomes
Ivacaftor for Gating Mutations					
Bellin et al. 2013	5	6–53	2 NGT, 1 AGT, 2 CFRD	OGTT and IVGTT before and after 4 weeks of therapy	-Improved insulin secretion on both OGTT and IVGTT in 4/5 subjects.
Banerjee et al. 2014* [38]	24		17 NGT, 3 AGT, 4 CFRD	Hba1c at 1,3 and 6 months after starting therapy	- Improvement in HbA1c from baseline to 6 months (median 42.5 mmol/L vs. 39.5 mmol/L, p = 0.004).
Dagan et al.2017	8	21 ±10	1 NGT, 3 AGT, 4 CFRD	OGTT before and after starting therapy	-Improvement in glucose tolerance: 2 CFRD became IGT, 3 IGT and one NGT were NGT.
Kelly et al 2019	12	6–42 (median 13.5)	7 NGT, 5 AGT	OGTT, MMTT and glucose-potentiated arginine tests before and after 16 weeks of therapy	-Improvement in first phase and glucose potentiation of arginine-induced insulin secretion assessed by acute C-peptide responses.
Volkova et al. 2020	US: 635 treated vs. 1874 untreated.UK: 247 treated vs. 1230 untreated.			Proportions of patients with CFRD in the ivacaftor and comparator cohorts over 5 years.	-Improvement in CFRD prevalence over 5 years: the increase in prevalence was lower in treated vs. comparator (12.1 vs 18.3% in US data and 2.4 vs. 8.2% in UK data)
Lumacaftor/ ivacaftor for F 508 del-Homozygous					
Thomassen et al. 2018	5	13–33	1 NGT, 4 AGT	OGTT and IVGTT before and after 6–8 weeks of therapy	-Worsening of glucose AUC in 3 patients on OGTT. -Worsening in insulin secretion in 3 and improvement in 2.
Li et al. 2019	9	11–15.6	3 NGT, 5 AGT, 1 CFRD	CGM, HbA1c and OGTT within 12 months before and within 12 months after starting therapy	-Worsening in HbA1c and fasting plasma glucose (p = 0.02). -No changes in OGTT or CGM measures.
Misgault et al. 2020	40	24 ± 10	31 AGT, 9 CFRD	OGTT 1 year after starting therapy	-Improvement in glucose tolerance -Improvement in 2-hour glucose from 171 to 139 mg/dL (p < 0.001).
Moheet et al. 2020	39	22 ±10	9 NGT, 15 AGT, 15 CFRD	OGTTs before and at 3, 6 and 12 months after starting therapy.	- No difference between fasting glucose, 2-hour glucose, glucose AUC, insulin AUC, time to peak insulin and c-peptide levels between baseline, 3, 6, and 12 months.
Colombo et al. 2021	13	21±5	7 NGT, 4 AGT, 2 CFRD	3-hour OGTT at baseline and after one year of therapy.	- No change in glucose tolerance categories. - No difference in insulin secretory parameters, clearance and sensitivity compared to matched controls.

* Available only in abstract.

3 AGT and 4 CFRD). They reported that 5 patients (3 AGT and 2 CFRD) had improvement in their glucose tolerance category after 1 year after ivacaftor therapy [24].

In a systematic study using OGTT, mixed-meal tolerance tests (MMTT), and glucose-potentiated arginine tests, Kelly et al compared measures before and 16 weeks after ivacaftor initiation in 12 CF subjects aged 6–42 years with at least one CFTR gating or conductance mutation [25]. Of the subjects, 7 had NGT and 5 had AGT. Glucose tolerance normalized in one AGT subject but otherwise, there was no change in the 1 or 2-hour glucose on OGTT. Ivacaftor treatment did not alter meal responses except for an increase in early phase C-peptide (P = 0.04). However, first-phase and glucose potentiation of arginine-induced C-peptide responses improved after treatment (p = 0.001 and 0.027 respectively). The disposition index relating the amount of insulin secreted for insulin sensitivity also improved (P = 0.04). Incretin secretion including GLP1 and GIP remained unchanged although both incretins showed trends in the right direction. The study included relatively young patients with normal to mild glycemic abnormalities which could explain the minimal changes see on OGTT and MMTT. Nonetheless, improved insulin secretion in this group of patients is significant and might have stronger implications in patients with more severe glycemic abnormalities.

Finally, Volkova et al. used data from the US and UK CF patient registries to assess CFRD prevalence in ivacaftor-treated vs untreated comparator cohorts matched by age, sex, and disease severity [26]. US analyses included 635 ivacaftor-treated patients and 1874 comparators and UK analyses included 247 ivacaftor-treated patients and 1230 comparators followed for 5 years from year 1 of market availability (2012–2016). They found favorable trends in increasing CFRD prevalence in ivacaftor-treated patients relative to comparators (CFRD prevalence increase: US data: 12.1% vs. 18.3%; UK data: 2.4% vs. 8.2%). These results should be interpreted with caution as they are confounded by the screening rates and by the fact that the groups were not matched by genotype; the comparator groups did have a significant proportion with class I-II mutations which carry a higher risk of CFRD compared to class III gating mutations.

The above studies had limitations including the small sample size, the different baseline glucose tolerance status of the subjects and the different endpoints evaluated in addition to the reporting bias in the case reports showing resolution of CFRD with ivacaftor. Despite their limitations, the results were promising in that Ivacaftor therapy (and potentially other modulators) may have a positive effect on insulin secretion and glucose metabolism in CF. However, studies done on lumacaftor/ivacaftor have been much less promising.

Lumacaftor/ivacaftor studies

Thomassen et al. were the first to study the effect of lumacaftor/ivacaftor in 5 CF patients with 508 del-homozygous (age 13–33) [27]. OGTT and IVGTT were done before and 6–8 weeks after starting treatment. They could not detect a significant improvement in glucose metabolism or insulin secretion as the results varied significantly between patients. On OGTT, the glucose AUC worsened in 3 patients and 1 patient changed from IGT to CFRD. On IVGTT, acute insulin secretion worsened in 3 and improved in 2.

Li et al. compared CGM measures, hemoglobin A1c (HbA1c) and OGTT glucose levels before and after starting lumacaftor/ivacaftor in 9 homozygous F508 del CF patients (age 11–15.6) [28]. They found no difference in continuous glucose monitoring (CGM) measures or 1 or 2-hour OGTT glucose levels but an increase in Hba1c and fasting glucose within a year after starting treatment.

In a study of 40 CF patients with homozygous F508 del (31 AGT and 9 CFRD), Misgault et al. compared OGTT done one year after starting treatment to OGTTs done before [29]. They reported improvement in glucose tolerance category with 50% of patients becoming NGT at follow up and improvement in the 2-hour glucose level (from 171 (153–197) to

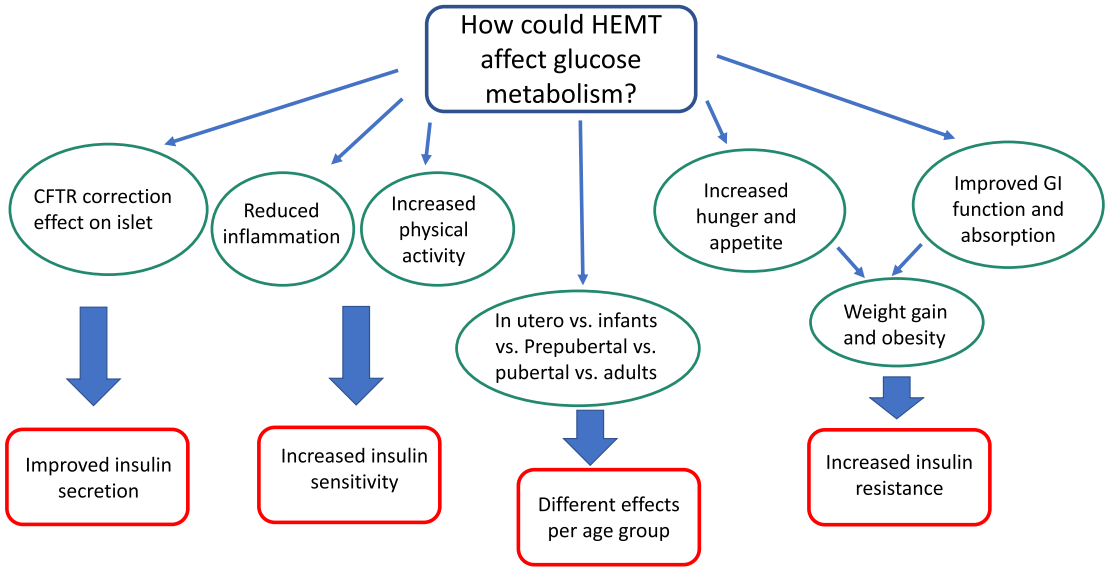

Fig. 2. The possible mechanisms in which highly effective modulator therapy (HEMT) might affect glucose metabolism in CF.

139 (117–162) mg/dL ($p < 0.001$). This study did not include patients with NGT to assess whether they had worsening of glucose tolerance [29].

In another study, Moheet et al. reported no improvement in glucose tolerance or insulin secretion after one year of lumacaftor/ivacaftor therapy in 39 CF patients with homozygous F508 del [30]. Their study included 9 NGT, 15 AGT and 15 CFRD patients and they performed OGTTs at baseline, 3, 6 and 12 months after starting therapy. They found no difference in fasting, 2-hour glucose or glucose AUC and no difference in insulin AUC and c-peptide levels between baseline and the subsequent OGTTs [30].

Similarly, Colombo et al. reported no change in glucose tolerance category, insulin secretory parameters, clearance or sensitivity in 13 CF patients with F 508 del homozygous (mean age 21 years) compared to controls with the same genotype after one year of lumacaftor/ivacaftor therapy [31].

The results of the lumacaftor/ivacaftor studies are less encouraging than the ivacaftor studies but are not completely unexpected. Lumacaftor/ivacaftor has less CFTR activating effects in F508 del patients than ivacaftor alone in patients with gating mutations, which likely explains the lack of improvement in glucose metabolism in most lumacaftor/ivacaftor studies.

In a study that evaluated the effects of 3 different modulator therapies on 14 patients with CFRD, Gaines et al retrospectively reviewed the change in insulin requirement after initiating therapy compared to 17 patients with CFRD not on modulators [32]. They included 2 patients with gating mutations on ivacaftor, 8 on lumacaftor/ivacaftor and 4 on tezacaftor/ ivacaftor. Of those, 4 patients completely stopped using insulin (2 on ivacaftor and 2 on lumacaftor/ivacaftor). Three of these patients continued to have hypoglycemia despite stopping insulin. Another patient (on lumacaftor/ivacaftor) went from using pre-prandial insulin three times a day to using insulin once a week. Home blood glucose and HbA1c values in these patients supported resolution of CFRD but no OGTTs were done to confirm NGT. There was no change to the insulin regimen in CFRD patients not on CFTR modulators. The patients on modulators that did not respond had the homozygous F508del CFTR mutation. Thus, the responders and non-responders had different defects in CFTR that would be expected to respond differently to CFTR modulator therapy. Remarkably, 3 of the patients with resolved CFRD had disease durations >8 years which supports that long-standing CFRD is not merely caused by islet loss and suggests that functional defects exist in the islet which have the potential to be reversed with CFTR modulator therapy. Average time to CFRD resolution was 8.4 months after starting modulator therapy suggesting that modulator therapy effects might take time to be realized and are more complex than a simple correction of the existing CFTR defect. Other factors such as systemic and local inflammation might have an important role in islet function which could explain the longer time to resolution of CFRD in these patients. This indicates that long term studies are needed to evaluate the effects of modulator therapy on glucose metabolism.

Knowledge gaps and future directions

Age may be a critical factor in the effect of HEMT on glucose metabolism. Younger children with CF may be able to compensate for their insulin secretion defect with larger beta cell mass and thus maintain close to normal glucose metabolism. However, over time, as islets are lost due to exocrine fibrosis and inflammation, the impact of CFTR on insulin secretion may become more important. Thus, it may be ideal to intervene at a young age to be able to preserve the healthy beta cells which will be better able to withstand the metabolic stresses that escalate over time. Future studies will help determine whether starting modulator therapy during childhood will delay or prevent the onset of diabetes. Additionally, it is possible that insulin secretion defects exist in the pancreatic islets prior to birth and even by the time of birth are too great a burden to maintain sufficient long-term function. Therefore, it could be envisioned that CFTR restoration may need to begin even before birth to prevent or minimize CFRD risk.

Furthermore, it is important to consider the effects of modulator therapy on weight gain [33]. Despite the improvements in insulin secretion that CFTR correction might mediate, and the possible improvement in insulin sensitivity resulting from reduced inflammation, increased physical activity and better quality of life, other factors should be considered. Improved appetite and increased caloric intake coupled with improved gut function and intestinal absorption can lead to excessive weight gain and obesity. This in turn can result in insulin resistance, placing more stress on the pancreatic islets. In fact, increasing insulin resistance with age is already described in people with CF [34]. Additionally, CF patients tend to consume high saturated fat and high glycemic index diets that can lead to beta-cell toxicity [35]. These factors might limit the ability of CFTR modulators to preserve healthy pancreatic islets over time. If HEMT proves to initially improve islet function, then efforts should be directed to preserve and prolong these effects. More attention should be paid to the diet consumed by CF

patients and dietary recommendations will need to change as more information is available. Fig. 2 describes the possible mechanisms in which HEMT might affect glucose metabolism.

Currently, there are no studies on the role of ELX/TEZ/IVA in glucose metabolism in CF. The Promise study is an ongoing prospective multicenter study that aims to evaluate the biological and clinical effects of significantly corrected CFTR function using ELX/TEZ/IVA. In its endocrine sub study, OGTTs are done before and at 1 and 2 years after starting therapy. Insulin secretory measures in addition to islet and gastrointestinal hormones are being evaluated. The results of this study will increase understanding of the effects of HEMT on glucose metabolism and will enable improved prediction of glycemic outcomes for those on HEMT therapy.

Until the role of CFTR in CFRD pathogenesis is fully delineated, the effect of CFTR modulator therapy on the development and course of CFRD will remain incompletely understood. The overarching question remains whether the causes of CFRD are fixed, reversible or partially recoverable. Animal studies will help uncover the mechanisms leading to CFRD and the role of CFTR and hopefully assist in answering this question. Once there is better understanding of the mechanisms underlying CFRD, hopefully modulator therapies will be used to more effectively manage and potentially prevent CFRD.

In summary, the effect of CFTR restoration through modulator therapy on glucose metabolism in CF is not yet well delineated. The exact role of CFTR in CFRD pathogenesis and its effects in different age groups remain inadequately understood. Ongoing large studies such as the Promise study will help answer these questions, but it is likely that ongoing questions will remain, especially as to whether glucose abnormalities will recur later if they do resolve initially or what the consequences of non-compliance with HEMT will be on glycemic risk. Until more information is available, efforts should continue to provide regular screening and appropriate treatment of CFRD to prevent its short- and long-term complications.

CRediT authorship contribution statement

Lina Merjaneh: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Sana Hasan:** Writing – original draft, Writing – review & editing. **Nader Kasim:** Writing – original draft, Writing – review & editing, Visualization. **Katie Larson Ode:** Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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