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REVIEW

Cardiometabolic insights in cystic fibrosis and highly effective modulator therapies: a narrative review

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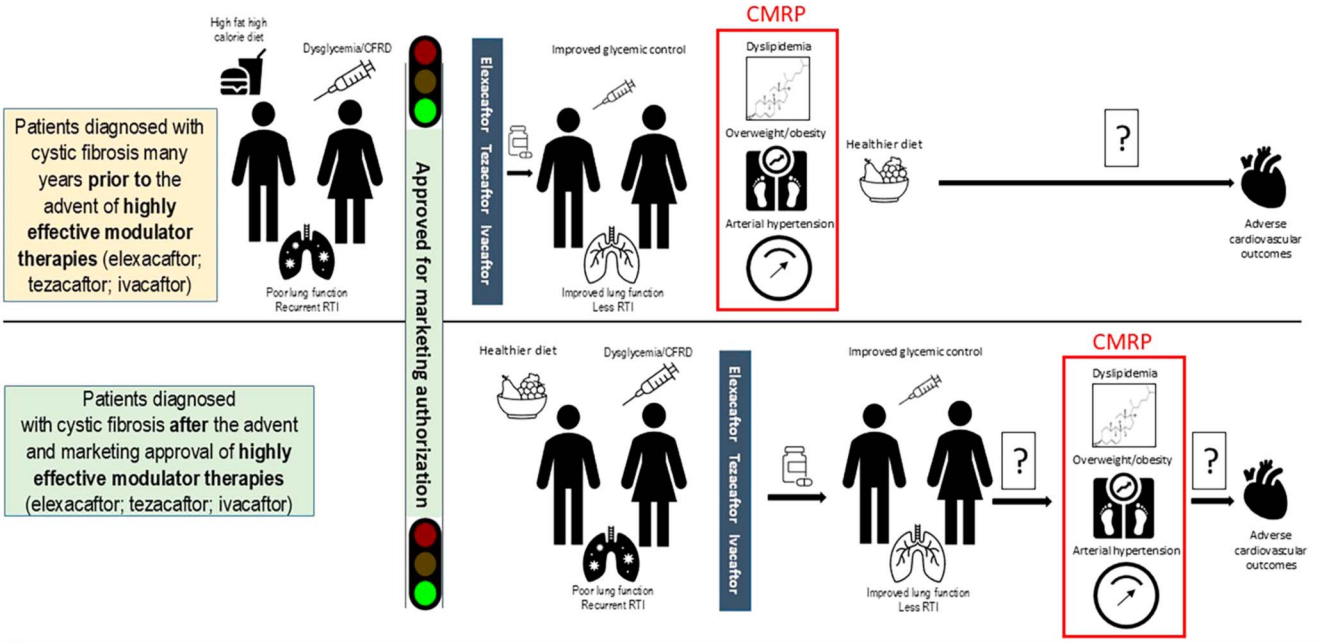
Graphical Abstract



Adverse cardiometabolic changes may occur in patients with cystic fibrosis treated with CFTR modulators. Two distinct phenotypes coexist. The first consists of patients advised to be on a high fat high calorie diet before the advent of CFTR channel modulators. They may experience adverse metabolic changes, including worsening of lipid profile, increased body fat, and higher risk of arterial hypertension, all of which may require lifestyle changes. While dysglycemia/cystic fibrosis-related diabetes often improves, these patients remain at risk of type 2 like diabetes. The second includes those diagnosed with CF after marketing approval of CFTR channel modulators, for whom current dietary recommendations are appropriate (CFRD, cystic fibrosis-related diabetes; CMRP, cardiometabolic risk phenotype; RTI, respiratory tract infections).

Abstract

Alongside pulmonary and nutritional benefits, highly effective modulator therapies (HEMT) can promote an increase in body fat and raise the prevalence of overweight/obesity, dyslipidemia, and hypertension in patients with cystic fibrosis. These metabolic changes will theoretically elevate cardiovascular risk in a population that has largely been unaffected by

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such complications until now. A rise in the prevalence of metabolic syndrome among HEMT-treated patients is expected, which has already prompted a review of dietary recommendations. Thus, a distinction must be made between patients with several years of care experience and those, especially younger patients or those with a late diagnosis of cystic fibrosis, who have not been educated on the principle of a high-calorie diet. Whether these metabolic changes will result in a greater incidence of cardiovascular events remains uncertain, underscoring the need to validate predictive risk scores in this context.

Keywords: cystic fibrosis; highly effective modulator therapy; metabolic syndrome; cardiovascular

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease present worldwide and the most common lethal inherited disorder among Western populations. Its highest prevalence is observed in North America, Europe, and Australia (1).

It is caused by a mutation in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene, which codes for the CFTR, a transmembrane channel found in the respiratory, digestive, and other tracts. This channel regulates water and electrolyte balance through anions such as chloride and bicarbonate handling in epithelial cells, ensuring optimal fluidity of secretions. Loss of this channel's function gradually leads to clogging of bronchi and digestive organs such as pancreatic ducts or the gastrointestinal tract, causing infections, chronic inflammation, undernutrition, and (multi)organ dysfunction.

The two main determinants of CF progression are respiratory function loss and malnutrition. Cystic fibrosis-related diabetes (CFRD) is among the most prevalent metabolic comorbidities, while respiratory complications are the leading cause of mortality in individuals with CF (2).

Recently, the advent of CFTR modulator therapies aimed at correcting the underlying cause of CF dramatically changed the paradigm of CF management and has proven a real game changer, with major improvements in respiratory function and nutritional status among patients benefiting from CFTR modulation (3, 4, 5, 6, 7).

Two types of modulators are currently prescribed, either alone or in combination. All are small molecules, classified as either potentiators, which open the channel (such as ivacaftor (IVA)), or correctors, which chaperone channel proteins during trafficking to the cell membrane (such as lumacaftor, tezacaftor, or elexacaftor). The choice of modulator type depends on the specific mutations affecting the patient. These mutations are stratified into six categories based on the dysfunction of the CFTR channel: i) absence of mRNA or absence of channel protein expression, ii) altered protein trafficking to the plasma membrane of epithelial cells, iii) defective channel opening, iv) reduced protein conductance, v) decreased protein abundance, and vi) decreased protein stability (2). Classes 1–3 are associated with more severe disease.

Triple combination therapy elexacaftor-tezacaftor-ivacaftor (ETI) has become the standard approach in managing CF in patients with at least one F508del mutation or a CFTR gene mutation responsive to ETI in some countries, while IVA stands alone for patients suffering from a gating mutation (class 3). They both are considered HEMT (highly effective modulator therapy), a term coined for CFTR modulators that greatly enhance the function of the defective CFTR protein in individuals with specific CF mutations.

Their beneficial effects on lung function and nutritional status are remarkable, marking the beginning of an era characterized by unprecedented advances in pulmonary function, nutritional status, and life expectancy (8, 9). However, this remarkable success has an important and unintended consequence: the unmasking of cardiometabolic comorbidities previously rare in this population (10).

As patients live longer and healthier lives, clinicians are now confronting a new frontier where the challenges of CF intersect with those of the general population, including obesity, dyslipidemia, hypertension, and metabolic syndrome (MetS), defined by the presence of at least three of the following five criteria: increased waist circumference (≥102 cm for men and ≥88 cm for women), high blood pressure (systolic >135 mmHg or diastolic >85 mmHg), impaired fasting blood glucose (100–125 mg/dL), and an abnormal lipid profile characterized by either low HDL-C (<40 mg/dL in men; <50 mg/dL in women) or elevated fasting triglycerides (>150 mg/dL) (11). The evidence for these changes is recent, rapidly emerging, and fragmented across the literature. Therefore, the purpose of this narrative review is to synthesize these disparate findings into a cohesive clinical picture of the emerging post-HEMT cardiometabolic phenotype. We will evaluate the impact of HEMT on the individual components of MetS, critically assess the potential drivers of this shift, and propose an integrated framework for cardiovascular (CV) risk assessment and management, bridging the gap between traditional CF care and preventive CV endocrinology.

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Methodology

We conducted a focused search of the PubMed/MEDLINE® database for articles published between 2020 and 2024 and reviewed the annual CF registries from Australia, Europe, the United States of America (USA), and Canada. The keywords used, individually or in combination, included cystic fibrosis, cystic fibrosis-related diabetes, CFTR modulators, elexacaftor, tezacaftor, ivacaftor, obesity, body composition, body weight, body mass index (BMI), metabolic syndrome, hypercholesterolemia, lipids, hypertension, insulin secretion and sensitivity, glucose tolerance, and β-cell function. This work was conceived as a narrative review, not a systematic review; therefore, our search was designed to capture the key literature to build a cohesive clinical narrative rather than exhaustively catalog every publication. The major themes discussed in this review emerged organically from this literature as the most consistently reported metabolic consequences of HEMT. Given the limited number of studies conducted to date, we chose to include cross-sectional and retrospective studies alongside the few prospective studies published so far. Conference papers were also recorded.

Effects of HEMT on abdominal obesity

MetS includes abdominal circumference, as visceral adiposity is linked to CV risk, and BMI alone can be misleading and may not accurately reflect this risk. However, studies do not account for this relevant data in the context of MetS, which is why we will focus on discussing the effects of HEMT on BMI and body composition, given the lack of precise data on abdominal circumference. In the absence of a more suitable definition in CF, overweight and obesity are defined in the same way as in the general population: a BMI between 25 and 29.9 kg/m^2 and a BMI >30 kg/m^2, respectively (according to the Centers for Disease Control and Prevention (CDC)) (12, 13). CFTR modulator therapies drastically improve the nutritional status of patients, which is one of the key points in CF daily care. Although overweight and obesity are not new issues, the rapid increase in the incidence of obesity in this population has become a serious concern worldwide in recent years (14). A longitudinal analysis by Stephenson on long-term nutritional trends at the Toronto CF Center found that the proportion of underweight (BMI <18.5 kg/m^2) individuals dropped from 21 to 11% between 1985 and 2011, while the percentage of those who were overweight or obese rose from 7 to 18% over the same period (15). Although the association between pulmonary outcomes and nutritional status has been well recognized in the literature since the 1970s, the systematic and intensified implementation of a high-calorie diet since the late 1980s has further contributed to improved nutritional status and pulmonary outcomes, resulting in higher mean body weight. In 1974, Crozier advocated a high-fat, high-calorie diet (16), in contrast to the low-fat, high-protein regimen recommended by Shwachman in 1977, the standard treatment in North American CF clinics at that time (17). Later, Corey *et al.* demonstrated the superiority of the high-fat diet (18), which subsequently became the standard of care in CF management (19). Accordingly, it is likely that not all patients included in Stephenson's study were following a high-fat diet before 1985, a period that may have represented a pivotal shift in nutritional practices.

According to the 2023 US CF Foundation Patient Registry Report, the prevalence of obesity among adults with CF (≥20 years) has continued to increase. The proportion of adults with CF classified by the CDC as overweight or obese rose from 17 to 41% between 2003 and 2023, with 28% overweight and 13% obese. During the same period, the prevalence of underweight decreased from 14 to 4.5%. In 2023, men showed a higher prevalence of overweight or obesity (45%) compared to women (38%) (20, 21). Numerous cases of extreme obesity (BMI >40 kg/m^2) have also been described (13, 22, 23).

The European Cystic Fibrosis Society (ECFS) Annual Patient Registry states that the 75th percentile of BMI in CF patients aged more than 18 years was 25 kg/m^2 in 2022 compared to 22.5 kg/m^2 in 2012. The median value of BMI Z score improved remarkably in 2022 compared to 2012 (the year when modulators were first introduced in the USA). Given frequent pretreatment CF-related undernutrition, the notable increase in BMI in 2022 from the age of 6 onward in Europe highlights the overall effectiveness of CFTR modulator therapy (22, 24).

The Australian Cystic Fibrosis Data Registry reported similar data in 2022. Overall, the median BMI among adults with CF increased steadily from 22 kg/m^2 to 23 kg/m^2 between 2017 and 2022. These trends indicate a general increase in BMI in the adult CF population over this period (25).

The 2022 annual data report of the Canadian Cystic Fibrosis Registry indicates similar trends for adults of both sexes. It highlights a gradual increase in overweight and obesity rates from 1992 to 2022, with a notable surge following the introduction of CFTR channel modulators. The proportion of adults with CF classified as having a normal weight decreased from approximately 66 to 61% between 2016 and 2022. During the same period, the percentage of underweight adults decreased from 9 to 5%, the proportion classified as overweight increased from 20 to 26%, and those classified as obese increased from 6 to 8%, approximately. There were significant changes in BMI categories between 2019 and 2022. Of the 2,071 adults with BMI data for both years, the majority (74%) remained in the same nutritional category. Around 143 (7%) individuals moved to a lower category, while 393 (19%) shifted to a category at least one step higher. Notably, 232 (11%) individuals who were considered to have a normal weight in 2019 became

overweight or obese by 2022. It is important to highlight that many of these individuals received highly effective modulator therapy during this period (26).

Thus, overweight and obesity in CF populations are on the rise worldwide, a trend that has sharply accelerated with modern therapeutic advancements. The underlying causes are multiple, including the historical promotion of a high-calorie, high-fat diet and increased life expectancy. More recently, the widespread introduction of HEMT, particularly ETI, has been a major driver of this surge, distinguishing their impact from earlier generations of modulators (13).

Data on body composition in CF are limited, and there is no established gold standard for its analysis. The literature indicates that patients on HEMT usually gain body fat without a corresponding improvement in lean body mass (27, 28, 29, 30, 31, 32). However, bone mineral density seems to improve according to a few studies on the effect of HEMT on bone metabolism, but this needs confirmatory validation (32, 33, 34). A retrospective study using fully automated thoracic computed tomography (CT) body composition assessed the impact of HEMT on thoracic bone, muscle, and adipose tissue divided by bone volume to obtain body size-adjusted ratios in adults with CF. The study identified substantial increases in adipose tissue across all compartments analyzed. Conversely, the overall study population showed only slight but statistically significant increases in muscle mass ratio. Participants initially classified as underweight demonstrated more notable increases in total adipose tissue ratio (35).

The pattern of adipose tissue gain remains poorly studied. This question is crucial, as the link between obesity and CV disease risk is largely attributed to excess visceral fat and thus assessed by waist circumference (36). A prospective study examined, using CT scans, the impact on body composition after at least 6 months of HEMT among 26 subjects. The authors first demonstrated a strong correlation between the various CT compartments and different bioelectrical impedance measures. They concluded, as expected, that the increase in body mass was primarily due to an increase in fat mass and, more importantly, that the largest increase represented visceral fat (cm^2/m^2) (30). Another previous study from the same group found an increase in visceral fat area after 6 months of ETI (28). These results are particularly concerning, as it was reported that untreated patients with CF tend to have more visceral adipose tissue than healthy individuals (37, 38, 39). A recent study found an increase in the rate of metabolic syndrome 1 year after the introduction of ETI, but this rise was not attributed to an increase in abdominal circumference (40).

The link between obesity and overweight with CV risk is well established in the general population. However, these associations have been less extensively studied in CF. Nonetheless, research has shown that obesity and overweight in CF are associated with a greater accumulation of CV risk factors (RF) such as high LDL-C and hypertension (41, 42).

Effect of HEMT on lipids

CF significantly disrupts lipid metabolism in patients who are prone to hypocholesterolemia and essential fatty acid deficiencies, which contribute to enhanced inflammation. Interest in lipid disturbances in CF has been rekindled by findings that CFTR modulators, ranging from IVA to the latest ETI, modulate lipid metabolism, particularly phosphatidylcholine (PC) and ceramides, in both humans and CF cell cultures (43). The lipid profile of these patients appears to worsen on HEMT regardless of glucose tolerance status (44), raising the question of whether to initiate lipid-lowering treatment in clinical practice.

This review focuses on clinical studies investigating lipid profile components. We found seven retrospective studies and three observational prospective studies exploring lipid changes after HEMT (Table 1) (40, 44, 45, 46, 47, 48, 49, 50, 51, 52), one of which examined lipid changes after ETI and showed a significant 20% increase in LDL-C 1 year after starting HEMT (47). Most studies reported an increase in total cholesterol (TC), LDL-C, and triglycerides. HDL-cholesterol (HDL-C) also increased, although data on HDL functionality are currently unavailable.

LDL-C levels are independently associated with BMI in CF patients (53, 54) and a recent study explored the correlation between weight status at baseline, weight gain, and changes in metabolic biomarkers after a median follow-up of 3.5 years on HEMT. The authors concluded that increased weight or weight gain over time was associated with improved FEV1 (forced expiratory volume in 1 s) and with some unfavorable cardiometabolic trends, including raised LDL-C, insulin resistance, elevated triglycerides, and blood pressure (42). In addition, a family history of CV RFs and exocrine pancreatic insufficiency was associated with more adverse changes in lipid profile following initiation of CFTR modulator therapy (45, 46, 48). Raised endogenous insulin levels are linked to increased adipose tissue and elevated triglycerides, suggesting that the metabolic health of patients who become overweight or obese while on CFTR modulators may further deteriorate as a result of adaptive hyperinsulinemia in response to weight gain (53, 55).

The underlying mechanisms have not yet been fully elucidated. An increase in intestinal absorption and an improvement in intracellular lipid metabolism by enterocytes are suggested explanations. Some studies have reported an increase in fat-soluble vitamins, specifically vitamins A and D, while vitamin E showed no change, and vitamin K was not examined (44, 47, 49).

Table 1 Lipid profile changes in patients following initiation of HEMT.

Author	Design	TC	LDL-C	HDL-C	Triglycerides	Other lipid related biomarkers	Conclusion
Petersen *et al.* (45)	Retrospective, before-after HEMT, *n* = 134, 34 y	Δ 25 mg/dL/y *P* < 0.0005	Δ 18 mg/dL/y *P* < 0.0005	Δ 9 mg/dL/y *P* < 0.05	-	-	Significant increases in TC, LDL-C and HDL-C
Carnovale *et al.* (49)	Retrospective, before-after HEMT, *n* = 20, 32 y	134 vs 157 mg/dL *P* = 0.035	47 vs 91 mg/dL *P* = 0.0001	56 vs 49 mg/dL NS	80 vs 79 mg/dL NS	Non-HDL-C 63.5 vs 97 mg/dL *P* = 0.004	Significant increases in TC, LDL-C, non-HDL-C and vitamin A
Despotes *et al.* (48)	Retrospective, before-after HEMT, *n* = 41, 40 y	152.5 vs 168.8 Δ 16 mg/dL *P* = 0.007	73.5 vs 90.6 Δ 17 mg/dL *P* < 0.001	53.2 vs 52.2 Δ −1 mg/dL NS	-	TC/HDL 3.07 vs 3.49 *P* = 0.014	Significant increases in TC and LDL-C
Castaldo *et al.* (51)	Retrospective, before-after HEMT, *n* = 63, F508del/F508del	129 vs 144 mg/dL *P* < 0.005	61 vs 86 mg/dL *P* < 0.005	50 vs 53 mg/dL NS	75 vs 95 mg/dL NS	-	Significant increases in TC and LDL-C
Castaldo *et al.* (52)	Retrospective, before-after HEMT, *n* = 105 F508del/CFTR variant	140 vs 156 mg/dL *P* < 0.001	74 vs 88 mg/dL *P* < 0.001	53 vs 51 mg/dL *P* = 0.087	76 vs 75 mg/dL NS	-	Significant increases in TC and LDL-C
Patel *et al.* (44)	Retrospective, before-after HEMT, *n* = 137	126 vs 154 mg/dL *P* < 0.0001	63 vs 78 mg/dL *P* = 0.0025	43 vs 49 mg/dL *P* = 0.0013	96 vs 100 mg/dL NS	-	Serum lipids, vitamins A and D increased
Lonabaugh *et al.* (46)	Retrospective before-after HEMT, *n* = 128 patients, 33 y	Δ 15 mg/dL *P* < 0.001	Δ 9.3 mg/dL *P* < 0.001	Δ 3.8 mg/dL *P* < 0.001	Δ 8.66 mg/dL *P* = 0.022	-	Significant increases in TC, LDL-C, HDL-C and triglycerides
Hevilla *et al.* (47)	Observational prospective study, changes in biomarkers 1 year after HEMT, *n* = 31	146.1 vs 158.3 mg/dL Δ 12.2 mg/dL *P* = 0.098	84.7 vs 101.7 mg/dL Δ 17 mg/dL *P* = 0.023	54.1 vs 52.8 mg/dL Δ 1.3 mg/dL *P* = 0.639	77.2 vs 89.9 mg/dL Δ 12.7 mg/dL *P* = 0.192	-	Significant increase in LDL-C
Gramegna *et al.* (50)	Observational prospective study, changes in biomarkers 6 months after HEMT, *n* = 58	-	-	-	-	-	Significant increases in TC, LDL-C, HDL-C, non-HDL-C, Apo-B, remnant cholesterol and triglycerides
Ratti *et al.* (40)	Prospective cohort study, 1 year after HEMT *n* = 186, ≥18 y	-	-	47.3 vs 47.7 mg/dL *P* = 0.25	90.5 vs 111.1 mg/dL *P* = 0.20	-	No significant increases in triglycerides and HDL-c but significant increase in patients meeting the triglycerides criteria for MetS

Results expressed as paired mean (mg/dL) or mean absolute difference, annualized or over the study observation period.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HEMT, highly effective modulator therapy; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; NS, not significant; y, years.

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An increase in hepatic production, possibly secondary to improved portal insulin levels, is another plausible explanation. Hyperinsulinemia promotes the production of VLDL. However, a closer examination of Patel *et al.*'s results reveals that while VLDL-C remained unchanged, non-HDL-C increased (44), suggesting either enhanced intestinal absorption of lymphatically transported cholesterol in chylomicrons or increased conversion of TG-rich lipoproteins into LDLs. These findings are in contrast with Gramegna *et al.*, who reported an increase in remnant cholesterol in patients treated with HEMT for 6 months (50).

A group of authors showed that *de novo* cholesterol synthesis was stimulated to compensate for impaired intestinal absorption in CF patients, especially in pancreatic-insufficient patients; however, this cholesterol cannot be effectively released into the bloodstream to correct hypocholesterolemia, possibly due to CFTR channel dysfunction, contributing, among other factors, to CF liver disease (56, 57). The same investigators examined cholesterol synthesis and intestinal absorption in 63 homozygous and 105 heterozygous patients for the F508del mutation, both before and 1 year after initiating ETI therapy. The results showed that homozygous patients exhibited increased cholesterol synthesis with, as a consequence, increased serum cholesterol level, whereas heterozygous patients demonstrated improved intestinal absorption and reduced *de novo* synthesis (51, 52).

In conclusion, although non-HDL-C increases, primarily driven by LDL-C, the data suggest no heightened risk of incident atherogenic dyslipidemia (i.e., low HDL-C, raised triglycerides, and elevated remnant cholesterol) on HEMT. Further studies are needed to determine whether this modest increase in LDL-C can lead to a higher incidence of CV events.

Glycemic effects of HEMT

One of the most common CF complications is CFRD, which results from a complex pathophysiological process. It is caused by a combination of β-cell dysfunction, islet mass loss, and systemic insulin resistance due to acute and chronic inflammation, visceral fat, and a high-calorie fat diet, among others (58, 59). The primary mechanism leading to long-term insulin secretion deficit is a 'crosstalk' between the exocrine and endocrine pancreas, where inflammatory cells migrate from the exocrine tissue to the islets of Langerhans, ultimately causing their destruction. Although the depletion of endocrine pancreatic mass can occur early and hyperglycemic excursions may be observed from a young age, it has been shown that the islets survive for a long time despite the destruction of exocrine tissue in patients with an exocrine insufficiency phenotype, which is why other mechanisms have also been proposed and described, such as defects in incretin regulation. The involvement of the CFTR channel in glucose homeostasis has also been mentioned, with its dysfunction or total absence possibly contributing to CFRD (60).

It appears that HEMTs are associated with improvements in glycemic balance markers (HbA1c, continuous interstitial glucose monitoring, oral glucose tolerance test (OGTT), and daily insulin requirement) (61, 62, 63, 64, 65, 66). This effect may be linked to a potential preservation of β-cell function, which could result from reduced pancreatic inflammation and possible restoration of CFTR function. In addition, it may be explained by improved insulin sensitivity resulting from increased skeletal muscle mass, enhanced exercise tolerance, and decreased chronic systemic inflammation. These beneficial effects have led some to suggest direct involvement of CFTR channels in insulin secretion, despite it being almost absent from β-cells and insulin sensitivity.

However, studies examining β-cell function and insulin sensitivity before and after HEMT show heterogeneous results, likely due to small sample sizes and varying study designs (Table 2) (29, 61, 62, 67). Various methods to assess insulin secretion and resistance, which have not been validated in CF populations, were used to assess the effects of modulators on determinants of glucose homeostasis, leading to inconsistent results. The insulinogenic index (IGI), computed to estimate the early phase of insulin secretion during an OGTT, is well correlated with the risk of developing CFRD but lacks prospective validation (68). Two studies examined insulin secretion using the IGI before and after ETI but found no improvement in this index (61, 69). The results of a prospective PROMISE endocrine substudy investigating the effects of 24 months of ETI therapy on HbA1c, OGTT, insulin sensitivity, and β-cell function indices were recently published. The study reported a significant improvement in HbA1c and fasting glucose levels. However, no significant changes were observed in OGTT-derived biomarkers of insulin sensitivity, insulin resistance, or computed β-cell function (70). The hyperinsulinemic-euglycemic clamp is the gold standard for measuring insulin sensitivity but is difficult to use in routine practice or even in clinical research.

It is too early to assert that these effects will lead to a decrease in the prevalence of CFRD, although analyses from American and British registries indicate a decline in its prevalence over recent years (71). This was observed despite the possible increase in insulin resistance among patients who became overweight or obese, in whom insulin resistance could play a greater role in the development of CFRD. Indeed, patients with CF who have preserved residual function of B-cells are not immune to developing or worsening underlying insulin resistance and, consequently, developing impaired glucose tolerance or type 2 diabetes mellitus (T2DM),

Table 2 Effect of HEMT on carbohydrate metabolism.

Author	Design	Conclusion(s)
Volkova *et al.* (71)	Observational longitudinal study, US register: 2,509 patients. UK register: 2,480 patients. Treated vs untreated. 5 years FU, IVA	Favorable trends in CFRD prevalence
Scully *et al.* (64)	Prospective observational study, 34 patients, with and without diabetes, 3–12 m FU, ETI	Improvement of CGM data with treatment, time in target range increased
Piona *et al.* (69)	Prospective, 21 non-diabetic patients, 12–18 m FU, LUMA/IVA or ETI, several fasting and OGTT-derived biomarkers of insulin sensitivity/resistance and beta-cell function computed	No improvement in insulin secretion and sensitivity
Crow *et al.* (66)	Retrospective single center study, 11 CFRD patients, 6 m FU, ETI	No improvement in CGM data and insulin requirements
Korten *et al.* (65)	Prospective, 12 patients, different glucose tolerance stages, ETI	Improvement of OGTT.
Chan *et al.* (62)	Prospective, 22 patients, different glucose tolerance stages, ETI, C-peptide index, HOMA2 IR and IS (OGTT Cpep), and C-peptide oral disposition index	No improvement of OGTT. Improving trends in CGM data. Improvement in insulin secretion but worsening insulin sensitivity. Improvement in HbA1c
Granados *et al.* (29)	Prospective, eight patients, ETI, C pep iAUC/Gluc iAUC), HOMA2 IR, matsuda index	Improvement in insulin secretion but worsening insulin sensitivity
Steinack *et al.* (61)	Single center observational study, 33 patients, different glucose tolerance stages, ETI, insulinogenic index, matsuda index, HOMA2-IR	Improvement of OGTT and HbA1c. No improvement in insulin sensitivity nor secretion
Lurquin *et al.* (63)	Single center retrospective study, 17 patients with CFRD, TEZE/IVA shift to ETI during study period	Reduction in daily insulin dose (weight based)
Flatt *et al.* (67)	Longitudinal, case–control study, nine patients treated vs eight untreated, ETI, glucose-potentiated arginine, and mixed-meal tolerance test measures	Preservation of β-cell function
Chan *et al.* (70)	Multicenter, prospective observational study. ETI, 58 to 68 patients, HbA1c, 3 h oral glucose tolerance tests (OGTTs), C-peptide deconvolution, and oral minimal model. Before ETI initiation and at 12–18 months and 24–30 months	Reduction in fasting glucose and HbA1c levels. Glucose tolerance showed variability. Overall measures of insulin secretion remained stable

Abbreviations: CFRD, cystic fibrosis-related diabetes; CGM, continuous glucose monitoring; ETI, elexacaftor-tezacaftor-ivacaftor; HbA1c, glycated hemoglobin, A1c; HEMT, highly effective modulator therapy; IVA, ivacaftor; LUMA, lumacaftor; OGTT, oral glucose tolerance test; TEZA, tezacaftor.

both of which contribute to add one score to the MetS. Worsening of insulin resistance could play an increasing role in the onset of diabetes in CF, especially since hyperinsulinemia in CF patients is independently associated with BMI.

Effect of HEMT on blood pressure

In addition, some studies have reported an increase in blood pressure, with an average rise in systolic blood pressure ranging from 4 to 12 mmHg, occasionally necessitating the initiation or intensification of antihypertensive treatment (Table 3) (6, 45, 72, 73).

According to the US Cystic Fibrosis Foundation Patient Registry, the prevalence of hypertension among adults with CF increased from 6.5 to 8% between 2020 and 2023, reaching 14% in those with advanced lung disease (20, 74). No corresponding data were identified from Australian, European, or Canadian registries for this review.

The mechanism of raised blood pressure is not fully understood, but HEMTs help restore a specific ionic balance in CF patients, who lose salt rapidly through perspiration due to impaired CFTR function. As a result, dietary recommendations will need to evolve, as these patients were previously advised to increase salt intake (23). It was demonstrated that, similar to the general population, obesity and overweight in individuals with CF are associated with a higher risk of arterial hypertension (42, 54). The rise in hypertension is likely attributable to the increased prevalence of obesity in the CF population but may also result from the direct effects of restoring CFTR channel function.

Cardiovascular risk assessment and perspectives

HEMTs clearly contribute to aligning CF patients with the general population in terms of cardiometabolic health and life expectancy. There is a growing occurrence of CF phenotypes that may predispose patients to CV disease. These new exposures to conventional RFs compound preclinical CV abnormalities already observed in CF, such as endothelial dysfunction, inflammation-mediated vascular damage, increased arterial stiffness, early carotid

Table 3 Changes in blood pressure following initiation of HEMT.

Author	Design	Conclusion(s)
Middleton *et al.* (6)	Randomized, double-blind, placebo-controlled trial, >12 years	Baseline mean SBP & DBP in the ETI group 113.4 and 69.4 mmHg, they increased by 3.1 and 1.9 mmHg, respectively, at week 24
Petersen *et al.* (45)	Retrospective, before-after HEMT, *n* = 134, 34 years	Number of patients meeting diagnostic criteria for either class 1 or class 2 hypertension was 47 (35%) at baseline and 85 (63%) at latest available follow-up. Distribution of blood pressure categories in the study cohort significantly altered on treatment ($P < 0.0001$)
Gramegna *et al.* (54)	Case series, before-after HEMT, *n* = 6	Increase in SBP & DBP pressure, although not clinically significant (respectively 116 vs 128 mmHg, $P = 0.0013$; and 71 vs 77 mmHg, $P = 0.0198$ between baseline and 6 months from ETI start)
Ross *et al.* (73)	Retrospective, before-after HEMT review, *n* = 237, ≥18 years	Mean SBP increased by 4.2 mmHg after ETI ($P < 0.001$). Mean DBP increased by 1.7 mmHg after ETI ($P = 0.02$). Percents of subjects with hypertension significantly increased after ETI (16.5–29.1%, $P < 0.001$). In total, 19.7% of patients without hypertension pre-ETI developed incident hypertension post-ETI; and 9.3% of all patients required a new start or an intensification of anti-hypertensive medications post-ETI.
Ratti *et al.* (40)	Prospective cohort study, before-after HEMT, *n* = 186, ≥18 years	A greater number of individuals met the criteria for class 1 hypertension or class 2 hypertension regardless of prior modulator exposure ($P < 0.0001$)

Results expressed as paired mean (mg/dL) or mean absolute difference, annualized or over the study observation period.
Abbreviations: DBP, diastolic blood pressure; ETI, elexacaftor-tezacaftor-ivacaftor; HEMT, highly effective modulator therapy; SBP, systolic blood pressure.
Class 1 hypertension: 130–139/80–89 mmHg.
Class 2 hypertension: ≥140/≥90 mmHg.

intima–media thickening, and microvascular complications, including chronic kidney disease (75).

These combined metabolic and secular effects necessitate a reevaluation of current approaches to CV risk management in CF patients (27, 45, 46, 48, 50). A study comparing the incidence of MetS in 152 patients treated with HEMT and 34 patients who had never received HEMT showed a significant increase in new-onset MetS 1 year after starting treatment, whereas no new cases were observed in the control group. However, this increase in the prevalence of MetS was not due to an increase in truncal obesity but was driven by hypertension and hypertriglyceridemia (40). MetS is associated with a threefold increase in CV risk in the general population, even when standard RFs are controlled. MetS also exposes patients to adverse pulmonary conditions, such as asthma and chronic obstructive pulmonary disease. More broadly, MetS can adversely affect lung physiology and disrupt surfactant production through lipotoxicity (76).

Patients with CF previously did not experience CV diseases as in the general population because they had different exposure to standard RFs and reduced longevity. However, with the increase in life expectancy, rising obesity rates, disruptions in lipid profiles, and the growing incidence of hypertension, the question arises: what is their overall CV risk?

Currently, there is no validated 10-year CV risk score specifically tailored for CF. The QRISK3 risk calculator may be the most relevant option, as it includes inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus as input variables, which are associated with increased risk of CV diseases.

A recent study used propensity score-matched analyses to compare the risk of major adverse cardiac events – including myocardial infarction, left-sided heart failure, and atrial fibrillation – in people with CF versus matched non-CF comparators from the general population and individuals with other inflammatory diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and HIV. It was shown that patients with CF may have a CV risk greater than that of the general population and similar to or even greater than that of patients with these aforementioned conditions (77).

Two studies, presented as posters at the 46th and 47th European Cystic Fibrosis Conferences, reported an increase in CV risk assessed using the QRISK3 score following the introduction of ETI. This heightened risk was primarily driven by an increase in BMI, with minimal or no contribution from circulating lipid levels or blood pressure (78, 79).

A recent prospective study of adults with CF and no prior CV history aimed to explore cardiometabolic risk exposure before and after HEMT initiation. They found that after 6 months of HEMT, the lipid profile worsened (including total cholesterol, LDL-C, HDL-C, Apo-B_{100}, non-HDL-C, RC, and triglycerides). Meanwhile, inflammatory markers such as hsCRP and interleukin-6 decreased, albeit without reaching statistical significance. In addition, levels of adiponectin and leptin, anti- and proatherogenic adipokines respectively, both involved in the pathophysiology of MetS (76), were reduced. The authors also observed an increase in the LIFE-CVD score,

a well-validated tool in young populations for primary CV prevention (50).

In addition to traditional risk calculators, a novel and opportunistic approach for risk stratification in the CF population could be the use of coronary artery calcium (CAC) scoring. CAC scoring is a robust and well-validated predictor of atherosclerotic CV disease events in the general population. Given that individuals with CF frequently undergo thoracic CT for pulmonary surveillance, CAC can often be quantified from these existing scans without requiring additional radiation exposure or cost. This approach would provide a direct measure of subclinical coronary atherosclerosis, potentially offering a more accurate assessment of individual risk than conventional scores that have not been validated in this unique patient cohort (80).

Awareness of the potential increase in CV risk is growing, prompting the issuance of new guidelines. The ESPEN-ESPGHAN-ECFS dietary recommendations have recently been updated, marking the first review since 2016. Authors recommend, at present, an annual lipid profile check for all patients on CFTR modulators, with no distinction specified in the text regarding the preservation of exocrine pancreatic function (81).

The ECFS recommends following the general population guidelines for lipid profile management in patients with CF (23). There are no clear recommendations regarding the interval between screenings for patients undergoing primary CV prevention. Risk assessment is an ongoing process and should be repeated periodically, such as every 5 years, despite the lack of empirical data to define optimal intervals (82).

The International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2022 recommended annual lipid profile screening for patients with CFRD who have preserved exocrine pancreatic function. For those with pancreatic insufficiency, lipid profile monitoring was advised every 5 years (14). Considering the recent literature, a reasonable and preliminary recommendation would be to extend this recommendation to all patients, especially those on CFTR modulators, irrespective of their exocrine status, until further data are available.

For patients taking CFTR modulators, blood pressure should be monitored 3 months after initiation of modulator therapy and at each routine visit, or at least annually during follow-up (23, 81, 83, 84).

Finally, closer monitoring of blood glucose levels is recommended to identify hypoglycemic events in patients receiving hypoglycemic medications (81).

The potential use of GLP-1 receptor agonists (GLP1-RA) in a subset of CF patients is also being contemplated, particularly in cases of obesity or CFRD. Originally developed as antihyperglycemic agents for T2DM, these molecules have demonstrated remarkable efficacy in promoting weight loss, primarily by lowering appetite, enhancing satiety, and slowing gastric emptying. They are also associated with many off-target beneficial metabolic effects, including increased lipolysis and natriuresis and improvements in lipid profile and blood pressure. These treatments are not approved for use in CFRD, despite evidence from several studies indicating incretin imbalance in CF patients. The reluctance stems from concerns about the risk of weight loss in an already catabolic state and the hypothesis that incretin-stimulated insulin secretion could accelerate the decline in β-cell function by overburdening the endocrine pancreas. Nonetheless, their selective use in CF could offer significant benefits, particularly in cases of obesity combined with diabetes and/or obesity in secondary CV prevention, since some GLP1-RAs have demonstrated CV risk reduction in patients with obesity and/or T2DM with a history of CVD or at high risk for atherosclerotic CVD (85, 86, 87). A recently published case series reported the use of GLP-1 RA in five CFRD patients with obesity. The treatment was well tolerated, resulting in significant weight loss in four patients, stable or improved pulmonary function, and either reduced or stable insulin requirements (88).

ETI was approved for patients with CF aged 12 and older, carrying at least one F508del mutation in the CFTR gene, by the Food and Drug Administration in October 2019, by the European Medicines Agency in August 2020, and by the Therapeutic Goods Administration in Australia in March 2021. The approval was later extended to children aged 6–11 in June 2021, January 2022, and February 2022 respectively, and then to children aged 2–5 in April 2023, September 2023, and May 2023 respectively. Regardless of this timeline, what it highlights is that we will first need to distinguish between two different phenotypes. Patients who experienced the pre-CFTR modulator era and were accustomed to historical dietary recommendations will, in principle, be at higher risk of developing CV RFs. On the other hand, patients born after the introduction of modulators, or those who were very young at the time and could benefit from them early, will be treated with standard-of-care modifications from the start (including a reduced focus on a high-fat, high-calorie diet) along with careful follow-up. As a result, they are generally expected to be at lower risk of developing metabolic syndrome features such as obesity. Of course, these allegations will have to be closely monitored.

We found no data on lipid profiles and very limited information on blood pressure in the various registries we reviewed. It is certain that these data will now be collected on a larger scale to address future challenges.

Conclusion

The management of CF has been fundamentally reshaped by HEMT, transforming a once-fatal disease into a

chronic, manageable condition. This review has synthesized the evidence demonstrating that this success brings with it new and complex cardiometabolic challenges. While HEMT may confer benefits to glucose homeostasis, the consistent observations of weight gain predominantly as fat mass, worsening atherogenic lipid profiles, and rising rates of hypertension signal a clear shift toward an increased prevalence of MetS. These are not isolated off-target effects but rather interconnected features of an emerging cardiometabolic phenotype in modern CF care. The critical uncertainty is whether these surrogate markers will translate into a higher burden of clinical CV events. Answering this question will require prospective monitoring and the validation of risk assessment tools specifically for this population. Consequently, the holistic multidisciplinary approach that has always been the hallmark of CF care must now evolve to integrate proactive CV risk stratification and management. The future of CF care will demand close collaboration between various stakeholders, such as pulmonologists, endocrinologists, and cardiologists, to ensure that the hard-won gains in longevity are not compromised by preventable CV disease.

Declaration of interest

FOL, MPH, and VP declare no commercial or financial relationships that could be perceived as potential conflicts of interest. SG is an advisory board member for Vertex and is a principal investigator of Vertex-sponsored studies.

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Author contribution statement

FL conceived the project. FL and SG conducted the literature review. FL, MPH, SG, and VP wrote the manuscript. FL prepared the tables. FL and MPH prepared the graphical abstract. All authors contributed to data interpretation. All authors contributed to the manuscript revision, read, and approved the final version.

Data availability

No datasets were generated or analyzed during the current study.

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