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# Heart failure with preserved ejection fraction and obesity: emerging metabolic therapeutic strategies

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**Abstract**
The global prevalence of obesity is rapidly in creasing, significantly increasing the incidence of heart failure with preserved ejection fraction (HFpEF). Obesity, one of the most common clinical phenotypes of HFpEF, facilitates the onset and progression of HFpEF via multiple pathophysiological mechanisms. Lifestyle intervention, which serves as the cornerstone of weight loss, plays a crucial role in the management of HFpEF. Novel antidiabetic therapies, including sodium glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and glucose–dependent insulinotropic polypeptide (GIP)/glucagon–like peptide-1 (GLP-1) dual receptor agonists, have favourable effects on clinical outcomes in obese HFpEF patients. For patients with heart failure (HF) prior to bariatric surgery (BSx), there is moderate evidence supporting the efficacy and safety of the procedure. This review systematically summarizes the clinical evidence related to metabolic therapy treatment strategies for obese HFpEF patients and discusses the potential advantages of such therapy.

**Keywords** HFpEF, Obesity, Lifestyle intervention, SGLT2i, GLP-1 RA, GIP/GLP-1 dual receptor agonists, Bariatric surgery

## Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for more than 50% of all cases of heart failure (HF), and its prevalence is increasing due to population ageing and the global epidemic of metabolic disorders. However, mortality rates and clinical outcomes for individuals with HFpEF have shown limited improvement over time [1]. Despite advances in cardiovascular medicine, the management of HFpEF remains a significant therapeutic challenge [2]. Although HFpEF shares symptomatic similarities with heart failure with reduced ejection fraction (HFrEF), it is characterized by distinct pathophysiological mechanisms, and transition from HFpEF to HFrEF is exceedingly rare [3]. The heterogeneous, multisystemic nature of HFpEF pathophysiology likely underlies the current absence of consensus guidelines for standardized treatment [4]. Consequently, phenotyping HFpEF patients on the basis of their clinical profiles is critical for guiding personalized therapeutic approaches.

According to the World Obesity Atlas 2025 Report, the global prevalence of overweight and obesity among adults is projected to increase from 36% in 2000 to 50% by 2030 [5]. Obesity, one of the most common clinical phenotypes of HFpEF, is specifically and independently associated with the disease, and it often manifests unique clinical and haemodynamic features in individuals [6]. Studies have demonstrated that approximately 80% of HFpEF patients are overweight or obese and exhibit

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manifestations of metabolic syndrome (MetS), including type 2 diabetes mellitus (T2DM), hypertension, and dyslipidaemia, collectively defining the cardiometabolic phenotype of HFpEF [7, 8]. Novel antidiabetic therapies, including sodium glucose cotransporter 2 inhibitors (SGLT2i), glucagon–like peptide-1 receptor agonists (GLP-1 RA), and glucose–dependent insulinotropic polypeptide (GIP)/glucagon–like peptide-1 (GLP-1) dual receptor agonists, have demonstrated clear efficacy in the management of MetS [9–11]. Recent clinical trials further suggest that these agents may also have favourable effects on clinical outcomes in obese HFpEF patients. Moreover, the evidence supporting lifestyle intervention has become increasingly robust, and clinical experience with bariatric surgery (BSx) continues to accumulate. On this basis, the treatment options for obese HFpEF patients have transitioned towards metabolism-focused therapeutic strategies.

This review synthesizes current evidence on the clinical benefits and the pathophysiological mechanisms underlying the effects of lifestyle intervention, pharmacological therapies, and BSx in obese HFpEF patients and offers insights into optimizing the management of this patient population.

## Relationship between obesity and HFpEF

### *Challenges related to diagnosing HFpEF in people with obesity*

Due to the lack of definitive testing for HFpEF diagnosis, clinical scoring systems may be useful to aid diagnosis [12]. Currently, diagnosis of HFpEF in clinical practicerequires objective evidence of congestion, which is typically evaluated through clinical examination, echocardiography, and testing of natriuretic peptide (NP) levels [13, 14]. Nonetheless, these diagnostic tools have significant limitations in Severe obesity. Clinically, severe obesity can manifest with symptoms overlapping with HFpEF, such as dyspnea, fatigue, and reduced exercise tolerance. Furthermore, It complicates the physical assessment of HFpEF indicators: evaluation of jugular venous pressure, auscultation for lung rales, and assessment of peripheral edema. Additionally, assessment of NP can be challenging in the context of obesity. NP levels in obese HFpEF patients are often attenuated and may fall within the "normal" range [15]. Research has found that the currently recommended N-terminal pro–B-type natriuretic peptid (NT-proBNP) threshold of < 125 ng/L demonstrated only 67% sensitivity in individuals with body mass index (BMI) > 35 kg/m$^2$ [16]. Notably, even echocardiographic Doppler parameters such as the E/e' ratio may underestimate the severity of systemic congestion in this population [17]. Therefore, the American College of Cardiology (ACC) guidelines recommends using lower NP thresholds for individuals with obesity and exertional dyspnea to avoid missed HFpEF diagnoses in this population [18]. However, further research is needed to establish specific cutoff values. Consequently, in cases in which the diagnosis is unclear, invasive haemodynamic exercise testing is typically required to confirm the diagnosis [13, 14].

### *Obesity paradox in HF*

The 'obesity paradox' describes a puzzling phenomenon. Although obese patients have a higher risk of developing HF, they tend to show better short- and intermediate-term survival rates than leaner patients after an HF diagnosis [19]. This phenomenon has also been observed in individuals with other conditions, including coronary artery disease, chronic kidney disease, and chronic obstructive pulmonary disease. Body composition analyses also reveal this paradoxical relationship, with both higher fat mass and greater lean body mass being associated with improved survival outcomes [20]. Notably, overweight and Class I obese HF patients tend to have better survival rates than HF patients with normal or underweight BMI, whereas more severe obesity (Classes II and III) is correlated with increased mortality risk. Consequently, the relationship between body weight and mortality due to cardiovascular disease follows a U-shaped curve, with the highest mortality observed at the extremes of BMI (i.e., underweight and severe obesity) [21, 22]. The reasons for the obesity paradox remain incompletely understood. Potential protective effects of obesity may stem from several mechanisms. First, individuals with excess adiposity may possess enhanced metabolic reserve capacity. Second, they might exhibit greater tolerance to cardioprotective vasoactive medications, particularly under conditions of elevated vascular resistance and blood pressure. Third, other speculative pathophysiological mechanisms could also play a role [23].

### *Pathophysiology of obesity and HFpEF*

Patients with HFpEF exhibit an increase in overall cardiac volume, and this is more pronounced in obese individuals, manifesting as ventricular dilatation, ventricular wall thickening, and increases in the amount of epicardial adipose tissue (EAT) [24, 25]. In HFpEF, progressive left ventricular (LV) wall thickening drives concentric remodelling that is accompanied by impaired myocardial diastolic function and increased stiffness and ultimately leads to LV diastolic dysfunction. Concentric remodelling appears to be closely associated with insulin resistance [26], diabetes [26], hyperleptinemia [27], myocardial steatosis [28], and expansion of visceral adipose tissue (VAT) [29]. Compared with nonobese patients, obese HFpEF patients demonstrate more pronounced LV concentric remodelling and an elevated LV mass–volume ratio

[24]. As is true for the LV, obesity is also linked to right ventricular remodelling. Additionally, HFpEF patients exhibit mildly impaired LV contractility at rest and severely compromised systolic reserve during exercise, and these conditions further exacerbate diastolic reserve impairment [30, 31]. The expansion of EAT enhances pericardial mechanical constraints on the heart, increasing ventricular interdependence and increasing intracavitary pressure under equivalent filling pressures [32]. This external constraint explains the lower NP levels and echocardiographic filling pressure estimates observed in obese HFpEF patients than in nonobese individuals. In addition to its mechanical effects, EAT directly damages the myocardium through the secretion of proinflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) and thereby inducing mitochondrial dysfunction and capillary rarefaction [33–36]. Recent studies [25, 37–39] demonstrate that increased epicardial EAT in HFpEF patients is closely linked to several adverse conditions: severe haemodynamic derangements, right ventricular–pulmonary arterial uncoupling, LV fibrosis, and reduced exercise tolerance. Moreover, elevated EAT levels are significantly correlated with increased risks of heart failure hospitalization and mortality. In obese HFpEF, inflammation and oxidative stress are not merely secondary phenomena accompanying heart failure progression, but rather constitute core pathological mechanisms driven by obesity itself. These mechanisms act on cardiomyocytes and the coronary microvascular system, ultimately leading to diastolic dysfunction and ventricular stiffness. This contrasts with HFrEF, which primarily originates from myocardial injury (resulting from ischemia, infection, or toxicity) and neurohormonal activation, triggering cardiomyocyte apoptosis, necrosis, fibrosis, and ventricular remodeling, dominated by systolic dysfunction [40].

The pathophysiological abnormalities observed in obese HFpEF patients include sodium retention, neurohormonal dysregulation, altered energy metabolism, cardiac lipotoxicity, VAT expansion, and systemic low-grade inflammation [41]. In obesity, renal tubular sodium retention and plasma volume expansion result from aldosterone overproduction and enhanced NP degradation [42]. Adipocytes directly synthesize aldosterone and indirectly promote adrenal aldosterone secretion via leptin and catecholamine release [43]. Obesity also induces metabolic alterations, including hyperleptinemia, hypoadiponectinemia, and insulin resistance, all of which are closely implicated in the pathogenesis and progression of HFpEF [44–47]. Furthermore, obesity contributes to myocardial dysfunction and apoptotic injury through excessive accumulation of metabolites, including triglycerides and free fatty acids, a process termed cardiac lipotoxicity [44, 48, 49]. Weight gain promotes adipocyte hypertrophy or hyperplasia, driving visceral fat deposition and shifting adipose tissue from an anti-inflammatory, angiogenesis- and lipid storage-favourable state to a proinflammatory phenotype [50]. Inflammatory VAT, particularly perivascular and pericardial fat, exerts detrimental effects via the secretion of proinflammatory adipokines [51, 52].

## Therapeutic approaches

### *Lifestyle intervention for patients with obesity and HFpEF*

Lifestyle interventions, including dietary therapy and exercise therapy, play pivotal roles in the prevention and management of cardiovascular disease. However, no specific dietary or exercise guidelines have been established for obese HFpEF patients.

### *Dietary management of HFpEF*

Emerging evidence suggests that dietary patterns are linked to the pathogenesis [53–55], prognosis [56–58], and potential reversibility [59] of HFpEF. Clinical studies are actively investigating the effects of various dietary regimens on HFpEF, necessitating careful evaluation of their benefits and risks (Table 1). The GOURMET-HF trial, which included patients with both HFrEF and HFpEF, demonstrated that the Dietary Approaches to Stop Hypertension (DASH)/sodium-restricted (SDR) diet modestly reduced 30-day hospital readmission rates [60]. Additional studies have confirmed the efficacy of the DASH/SDR diet in managing hypertension, lowering 24-hour ambulatory systolic and diastolic blood pressure, and improving LV diastolic function, arterial elasticity, and ventricular–arterial coupling in HFpEF patients [61, 62]. A low-energy diet (LED) has been shown to reduce myocardial steatosis and enhance diastolic filling in patients with T2DM [63]. Meal replacement plans (MRPs) involving LEDs are currently proposed as alternative strategies for achieving weight loss and improving cardiovascular outcomes. Low-energy MRPs promote weight reduction, ameliorate cardiometabolic risks associated with diabetes [64], and reverse cardiovascular remodelling in obese T2DM patients [65]. Following a ketogenic diet promotes weight loss via increased lipolysis [66]. A recent animal study reported that ketone supplementation ameliorated HFpEF phenotypes in mice [67]. Beneficial haemodynamic effects were also observed in HFrEF patients treated with ketone bodies [68]. However, evidence suggests that following a ketogenic diet may increase circulating free fatty acid levels, exacerbating cardiac lipotoxicity and altering myocardial energy metabolism and thereby posing potential risks to cardiovascular health [69]. The Mediterranean diet (MedDiet) is recognized for its cardioprotective properties [70]. The MEDIT-AHF trial revealed that while stricter adherence to the MedDiet correlated with reduced HF rehospitalization rates in patients who had been hospitalized for

**Table 1** Evidence on the cardiovascular benefits of dietary regimens

| Dietary regimens | Intervention | Trial population/animal model | Follow-up period | Evidence | References |
|---|---|---|---|---|---|
| DASH/SDR diet | DASH/SRD vs. usual care | 66 HF patients (Including HFpEF and HFrEF) | 12 weeks | 1 The the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) increased similarly between groups<br>2 30-day HF readmissions trended lower in DASH/SRD participants | Hummel et al. [60] |
| | DASH/SRD | 13 hypertensive HFPEF patients | 21 days | Reduce systemic blood pressure, arterial stiffness, and oxidative stress | Hummel et al. [61] |
| | DASH/SRD | 13 hypertensive HFPEF patients | 21 days | Benefits in ventricular diastolic function, arterial elastance, and ventricular–arterial coupling | Hummel et al. [62] |
| LED | very-low-calorie diet (450 kcal/day) | 12 obese, insulin-treated T2DM patients | 16 weeks | Reduce of myocardial steatosis and enhance diastolic filling in patients with T2DM | Hummel et al. [63] |
| | Low-energy MRPs vs. Regular diet | 306 obese T2DM patients | 2 years | Weight loss and improvement of diabetes-related cardiometabolic risk | Lean et al. [64] |
| | low-energy MRPs | 87 obese T2DM patients vs. 36 healthy control participants | 12 weeks | Reverse of cardiovascular remodeling in obese T2DM patients | Gulsin et al. [65] |
| Ketogenic diet | low-carbohydrate diets vs. low-fat diets | 447 overweight patients | 12 months | Benefits in weight loss | Nordmann et al. [66] |
| | long-term high-fat diet, and desoxycorticosterone pivalate challenge | HFpEF mice | - | Ameliorate of HFpEF phenotypes in mice | Deng et al. [67] |
| | 3-hydroxybutyrate infusion | 24 HFrEF patients vs. 10 age-matched volunteers | - | Benefits in hemodynamic effects in HFrEF patients | Nielsen et al. [68] |
| MedDiet | adherent to the MedDiet vs. nonadherent | 991 acute heart failure | 2.1 years | Reduce of HF hospitalizations | Miró et al. [71] |
| | MedDiet supplemented with 50mL/d of extra virgin olive oil vs. MedDiet supplemented 30 g/d of nuts vs. a low-fat diet | 164 participants at high risk for cardiovascular disease | 12 months | Increase in serum markers of atheroma plaque stability and benefits in systemic infammation in patients with HF | Casas et al. [72] |
| | a low-fat diet vs. one of two MedDiet [MedDiet + virgin olive oil vs. MedDiet + nuts] | 930 subjects at high cardiovascular risk | 1 year | 1 Reduce of NT-proBNP, vivo oxidized low-density lipoprotein and lipoprotein(a) plasma<br>2 Reduce of against risk factors for HF | Fitó et al. [73] |
| | MedDiet | 690 first-diagnosed acute coronary syndrome patients | 10 years | Benefits of preventing recurrent cardiac episodes in coronary patients with major acute coronary syndrome complications | Kouvari et al. [74] |

HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; HF, Heart failure; DASH, Dietary approaches to stop hypertension; SDR, Sodium-restricted; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LED, Low-energy diet; MRP, Meal replacement plans; T2DM, Type 2 diabetes mellitus; MedDiet, Mediterranean diet; NT-proBNP, N-terminal pro–B-type natriuretic peptid

acute HF, it did not improve long-term mortality [71]. The PREDIMED trial demonstrated that the MedDiet improves systemic inflammatory markers in subjects at high cardiovascular risk and contributes to reducing risk factors for HF [72, 73]. These findings were corroborated in a Greek heart failure cohort comprising 38% HFpEF patients, suggesting that this diet may have broader therapeutic potential [74]. Other dietary approaches may also confer benefits in HFpEF patients. For example, plant-based diets—such as vegan, lacto-ovo vegetarian, and pesco-vegetarian regimens—have been shown to have favourable effects on cardiometabolic health, including reductions in blood pressure, glucose, and lipid levels as well as anti-inflammatory and weight-modulating properties [75].

#### *Physical activity in HFpEF*

The ACC guidelines recommends that exercise training (ET) can improve functional status in individuals with HFpEF [18]. Accumulating evidence indicates that ET improves diastolic function, cardiorespiratory fitness, exercise capacity, and quality of life (QoL) in HFpEF patients [76–78]. Several studies further reported reduced hospitalization rates and/or fewer cardiac events following ET in this population [79, 80]. Although these prospective clinical studies were specifically designed for HFpEF patients, they were limited by relatively small sample sizes and mostly short-term follow-up periods. Nevertheless, the available data preliminarily demonstrate the potential benefits of ET for HFpEF management. Furthermore, a recent ACC/American Heart Association (AHA) scientific statement systematically analysed data from 11 randomized controlled trials (RCTs) in which supervised exercise training (SET) in chronic HFpEF patients was evaluated; these trials incorporated modalities such as walking, stationary cycling, high-intensity interval training (HIIT), resistance training, and dance [81]. Compared with controls, SET significantly increased the 6-minute walk distance (6MWD), whereas peak oxygen consumption ($VO_2$ peak) increased by 14% from baseline, in contrast with a 0.2% decrease in the control group. HIIT has emerged as an alternative to moderate-intensity continuous training in cardiac rehabilitation [82]. Over approximately 16 weeks, HIIT followed by low-intensity training (LIT) combined with LED demonstrated superior efficacy in improving the $VO_2$ peak and the participants' QoL [83]. HIIT protocols often achieve ≥ 85% of the $VO_2$ peak [84, 85], whereas LIT with LEDs yields the greatest improvement in the 6MWD [83]. Importantly, a meta-analysis of six RCTs reported no major exercise-related adverse events, reinforcing the safety of ET in HFpEF patients [86].

Smaller trials have explored combined LED and ET interventions in obese HFpEF patients (Table 2). The SECRET trial evaluated 20-week LED and/or ET interventions and revealed that significant increases in the $VO_2$ peak could be achieved using either of these approaches, although neither improved the total score on the Minnesota Living with Heart Failure (MLHF) questionnaire. Notably, changes in the $VO_2$ peak correlated positively with the percentage of lean body mass [87]. In a study of 40 patients with MetS and HFpEF, a 3-month intervention involving dietary control and 3 h of moderate-intensity exercise over 3 weeks led to marked $VO_2$ peak improvements in the successful weight loss group. At the 1-year follow-up, this group also exhibited better New York Heart Association functional class outcomes and lower hospitalization risk [88]. Another trial investigating 15 weeks of LED and ET supplemented with weekly 30- to 60-minute multidisciplinary sessions (exercise, nutrition, and behavioural counselling) and wrist-worn activity monitoring reported significant

**Table 2** Evidence of exercise training in obese HFpEF patients

| Interventions | Trial population | Follow-up period | Primary endpoints | References |
|---|---|---|---|---|
| LED and/or ET | 100 old obese HFpEF patients | 20 weeks | 1. Increase of $VO_2$ peak<br>2. No significant change in MLHF total score<br>3. Changes in $VO_2$ peak correlated positively with the percentage of lean body mass | Kitzman et al. [87] |
| Dietary control and moderate-intensity exercise | 40 MetS and obese HFpEF patients | 1 years | 1. $VO_2$ peak improvements in the successful weight loss group after 3 momths<br>2. At 1-year follow-up, the successful weight loss group exhibited better New York Heart Association functional class outcomes and lower hospitalization risk | Ritzel et al. [88] |
| LED and ET (supplemented with weekly 30- to 60-minute multidisciplinary sessions and wrist-worn activity monitoring) | 40 obese HFpEF patients | 26 weeks | 1. Improvements in 6MWD and reductions in MLHF scores<br>2. Changes in 6MWD and MLHF scores moderate correlations with weight loss | El et al. [89] |

HFpEF, Heart failure with preserved ejection fraction; ET, Exercise training; LED, Low-energy diet; $VO_2$ peak, Peak oxygen consumption; MLHF, Minnesota living with heart failure; MetS, Metabolic syndrome; 6MWD, 6-minute walk distance

improvements in the 6MWD and reductions in MLHF scores, with moderate correlations with weight loss [89]. These findings suggest that the benefits of ET in obese HFpEF patients may stem partially from weight reduction. However, further research designed to elucidate the mechanistic pathways underlying these improvements is warranted.

### New antidiabetic medications for patients with obesity and HFpEF

Emerging studies indicated that the new antidiabetic medications, including SGLT2i, GLP-1 RA and GIP/GLP-1 dual receptor agonists, provided the cardiovascular benefits in obese HFpEF patients. Notably, there were several clinical trials that supported this point (Table 3).

### Clinical evidence regarding the effects of SGLT2i in HFpEF patients

SGLT2i, while primarily used to treat T2DM, have demonstrated weight loss effects in both diabetic and non-diabetic obese populations [90–93]. The 2022 ACC/AHA/Heart Failure Society of America (HFSA) guidelines now recommend the use of SGLT2i for HF management across the full ejection fraction spectrum [94]. The EMPEROR-Preserved and DELIVER trials established foundational evidence that SGLT2is improve outcomes in HFpEF patients. The EMPEROR-Preserved trial randomized 5,988 HFpEF patients (with or without T2DM) 1:1 to empagliflozin or placebo [95]. Compared with placebo, empagliflozin significantly reduced the composite endpoint risk of cardiovascular death or HF hospitalization. At 52 weeks, empagliflozin also decreased total HF hospitalizations and modestly improved QoL, as assessed by the KCCQ-CSS. Similarly, the DELIVER trial enrolled 6,263 HFpEF patients (with or without T2DM) randomized 1:1 to dapagliflozin or placebo [96]. Dapagliflozin demonstrated superiority over placebo in improving HF-related outcomes, reducing the composite endpoint of worsening HF or cardiovascular death, lowering HF hospitalization rates, and alleviating symptom burden. A meta-analysis further confirmed that SGLT2i reduce the composite of cardiovascular death or first HF hospitalization as well as recurrent HF hospitalizations in HFpEF patients [97]. Thus, the efficacy of SGLT2i in HFpEF patients has been validated. Notably, no dedicated clinical trials have yet evaluated the effectiveness of SGLT2i in obese HFpEF populations. Further RCTs are warranted to assess their efficacy in this subgroup and to explore potential unique mechanistic pathways linking weight loss, metabolic modulation, and HFpEF-related pathophysiology.

### Clinical evidence regarding the benefits of GLP-1 RA in HFpEF patients

While GLP-1 RA demonstrate protective effects against atherosclerotic cardiovascular disease (ASCVD), their role in HF remains uncertain [98]. Although most cardiovascular outcome trials (CVOTs) of GLP-1 RA have shown significant reductions in 3-point major adverse cardiovascular events (MACE), findings on hospitalization for HF—a key secondary endpoint—exhibit heterogeneity across studies. For example, The SELECT trial enrolled more than 4,000 HF patients and demonstrated that semaglutide reduced the risk of composite HF endpoints by 18%, with a significant decrease in the absolute number of hospitalizations or urgent care visits for HF [10]. In the EXSCEL trial including 14,752 T2DM patients, exenatide showed no significant effect on the composite endpoint of all-cause mortality and HF hospitalization in the HF subgroup. In contrast, exenatide significantly reduced the risk of these endpoints in participants without HF [99]. In the LEADER trial involving 9340 T2DM patients, liraglutide significantly reduced the risk of 3-point MACE, but no significant difference was observed in HF hospitalization [100]. Notably, current evidence regarding the impact of GLP-1 RA on HF primarily originates from placebo-controlled CVOTs conducted in populations with T2DM or obesity characterized by significant cardiovascular risk factors or established cardiovascular disease. None of the trials considered HF as the primary composite endpoint. Instead, most of them treated it as a secondary endpoint. Furthermore, the trials lacked a standardized evaluation of HF characteristics and did not differentiate among various HF phenotypes. Thus, while CVOTs provide critical insights into the potential benefits of GLP-1 RA in T2DM patients with comorbid HF, dedicated RCTs are warranted to precisely delineate the magnitude and mechanistic characteristics of the therapeutic effects of these drugs.

The STEP-HFpEF trial was the first RCT to specifically target obese HFpEF patients [101]. This study enrolled 529 symptomatic, physically limited obese HFpEF patients who were randomized 1:1 to receive either placebo or once-weekly semaglutide 2.4 mg. At 52 weeks, semaglutide treatment resulted in a mean improvement of 16.6 points in the KCCQ-CSS, significantly surpassing the 8.7-point improvement observed with the placebo. Additionally, compared with the placebo, semaglutide induced a 13.3% reduction in body weight. This study demonstrated that obese HFpEF patients who received 2.4 mg of semaglutide once weekly for one year experienced significant weight reduction and improvement in HF-related symptoms, as well as decreased physical limitations and increased exercise capacity. Exploratory analyses further revealed significant reductions in

**Table 3** Novel antidiabetic therapy and clinical outcomes in patients with HFpEF

| Study of trial | Medication | Trial population | Follow-up period | Primary endpoints | number needed to treat (NNT) for primary endpoints(95%CI) | Key safety outcomes |
|---|---|---|---|---|---|---|
| EMPER-OR-Pre-served [95] | Empagliflozin 10 mg po once per day vs. placebo | 5988 HFpEF patients (with or without T2DM) | 26.2 months | the composite endpoint risk of cardiovascular death or HF hospitalization significantly reduced from baseline to a median of 26.2 months | 31 (20 to 69) | 1 serious adverse events (SAE) : 47.9% (empagliflozin group) vs. 51.6% (placebo group)<br>2 discontinuations due to adverse events (AE): 19.1% (empagliflozin group) vs. 18.4% (placebo group) |
| DELIVER [96] | Dapagliflozin 10 mg po once per day vs. placebo | 6263 HFpEF patients (with or without T2DM) | 2.3 years | the composite endpoint of HF worsening or cardiovascular death significantly reduced from baseline to a median of 2.3 years | 32 (20 to 82) | 1 SAE: 43.5% (dapagliflozin group) vs. 45.5% (placebo group)<br>2 discontinuations due to AE: 5.8% (dapagliflozin group) vs. 5.8% (placebo group) |
| STEP-HFpEF [101] | Semaglutide 2.4 mg sc once per week vs. placebo | 529 obese-HFpEF patients (with or without T2DM) | 52 weeks | 1 7.8 points estimated difference in KCCQ from baseline to Week 52<br>2 10.7 estimated difference in body weight from baseline to Week 52 | - | 1 SAE: 13.3% (semaglutide group) vs. 26.7% (placebo group)<br>2 discontinuations due to AE: 13.3% (semaglutide group) vs. 5.2% (placebo group) |
| STEP-HFpEF DM [103] | Semaglutide 2.4 mg sc once per week vs. placebo | 616 obese-HFpEF patients with T2DM | 52 weeks | 1 7.3 points estimated difference in KCCQ from baseline to Week 52<br>2 6.4 estimated difference in body weight from baseline to Week 52 | - | 1 SAE: 17.7% (semaglutide group) vs. 28.8% (placebo group)<br>2 discontinuations due to AE: 10.6% (semaglutide group) vs. 8.2% (placebo group) |
| SUMMIT [108] | Tirzepatide up to 15 mg sc once per week vs. placebo | 731 obese-HFpEF patients (with or without T2DM) | 52 weeks | 1 the composite endpoint of HF worsening or cardiovascular death significantly significantly improved from baseline to a median of 104 weeks<br>2 6.9 points estimated difference in KCCQ from baseline to Week 52 | 19 (10 to 173) | 1 SAE: to be similar in the tirzepatide group and placebo group<br>2 discontinuations due to AE: 6.3% (tirzepatide group) vs. 1.4% (placebo group) |

HFpEF, Heart failure with preserved ejection fraction; HF, Heart failure; T2DM, Type 2 diabetes mellitus; KCCQ, Kansas city cardiomyopathy questionnaire

NT-proBNP levels and HF event risk with semaglutide. Importantly, this trial positioned obesity-targeted therapy as a disease-specific intervention for HFpEF, with treatment benefits exceeding those provided by currently approved HFpEF therapies [102]. Similarly, in the STEP-HFpEF DM trial, which included 616 obese HFpEF patients with comorbid T2DM, once-weekly semaglutide 2.4 mg improved the KCCQ-CSS by 13.7 points versus 6.4 points with placebo at 52 weeks [103]. Body weight was reduced by 9.8% in the semaglutide group compared with 3.4% in the placebo group.

Intriguingly, despite a 40% smaller between-group difference in weight loss (6.4% vs. 10.7% in STEP-HFpEF), the magnitude of HFpEF symptom improvement was comparable in the two trials [104]. Further analysis revealed that patients with a more severe HFpEF phenotype—characterized by high NT-proBNP concentrations, a history of atrial fibrillation, or loop diuretic use—demonstrated greater improvements in KCCQ-CSS with semaglutide treatment than those with less severe disease [104]. This occurred despite similar weight loss between groups. These observation suggests that the clinical benefits of semaglutide in HFpEF may extend beyond weight loss, potentially involving direct cardioprotective mechanisms [105]. Collectively, the results of the STEP-HFpEF trials establish semaglutide as a novel therapeutic option for HFpEF and emphasize obesity not only as a comorbidity but also as a pivotal contributor to HFpEF pathogenesis and a viable treatment target [106]. Nevertheless, future CVOTs with hard clinical endpoints are essential to confirm the cardiovascular benefits of semaglutide in HFpEF patients and elucidate its underlying mechanisms of action.

### Clinical evidence regarding the benefits of tirzepatide in HFpEF patients

The GIP/GLP-1 dual receptor agonist tirzepatide has been approved for the treatment of obesity and T2DM. In the SURMOUNT-1 trial, overweight and obese subjects receiving once-weekly tirzepatide (5–15 mg) for 72 weeks demonstrated mean body weight reductions ranging from 13.7 kg to 21.2 kg [107]. The recently published SUMMIT study enrolled 731 obese HFpEF patients with or without concomitant T2DM; these patients were randomly assigned in a 1:1 ratio to receive tirzepatide or placebo for 52 weeks [108]. Compared with the placebo group, the tirzepatide group exhibited significantly greater improvement in KCCQ-CSS scores (mean improvement of 19.5 vs. 12.7 points, respectively). With respect to weight reduction, tirzepatide treatment resulted in a decrease of 13.9% in mean body weight, substantially exceeding the 2.2% reduction observed in the placebo group. Additionally, in the tirzepatide group, the mean increase in the 6MWD was 26.0 m, significantly greater than the 10.1-metre increase observed in the placebo group. Most notably, after a median follow-up of 104 weeks, significantly fewer patients in the tirzepatide group than in the placebo group experienced worsening HF events or died from cardiovascular causes (36 patients [9.9%] vs. 56 patients [15.3%], respectively). These findings suggest that tirzepatide reduces the risk of death from cardiovascular causes or worsening HF in obese HFpEF patients while alleviating the severity of HF symptoms and enhancing exercise tolerance. Further analysis revealed that, in obese HFpEF patients with worse baseline health status (KCCQ-CSS < 53.5), tirzepatide significantly improved health status (between-group ΔKCCQ-CSS, 9.07; 95% CI, 3.71 to14.43) and reduced the composite risk of cardiovascular death or worsening heart failure by 48% (hazard ratio, 0.52; 95% CI, 0.30 to 0.90) compared to those with better baseline status (KCCQ-CSS ≥ 53.5). These findings indicate that obese HFpEF patients with greater symptom burden at baseline achieve enhanced prognostic improvement with tirzepatide therapy.

Both the SUMMIT and STEP-HFpEF trials are randomized, double-blind, placebo-controlled studies conducted in obese HFpEF populations. However, the SUMMIT trial implemented stricter inclusion criteria (left ventricular ejection fraction (LVEF) ≥ 50%, age ≥ 40), resulting in closer alignment with the specific characteristics of the HFpEF population. In contrast, the STEP-HFpEF trial employed broader inclusion criteria (LVEF ≥ 45%, age ≥ 18 ). This may explain SUMMIT's more substantial effect on hard endpoints (38% risk reduction in heart-related outcomes).

### Potential cardioprotective mechanisms of new antidiabetic medications

#### *SGLT2i for HFpEF patients*

The effects of SGLT2i on cardiac structure and function are mediated primarily through improvements in systemic haemodynamics and metabolic effects (Fig. 1).

In terms of ventricular load, SGLT2i reduce cardiac load via osmotic diuresis and enhance urinary sodium excretion while also decreasing arterial stiffness and improving endothelial function [109]. Additionally, SGLT2i lower body weight and blood pressure by inhibiting glucose and sodium reabsorption in the proximal renal tubules. They also increase plasma erythropoietin levels, thereby increasing haematocrit and improving cardiac output [110, 111]. SGLT2i further enhance diastolic function, potentially by reducing sarcoplasmic reticulum calcium release during diastole [112]. The mechanisms underlying the protective effects of SGLT2i on cardiac structure and function are also closely linked to ion channel regulation. Studies indicate that SGLT2i modulate the activity of the myocardial-specific sodium-hydrogen

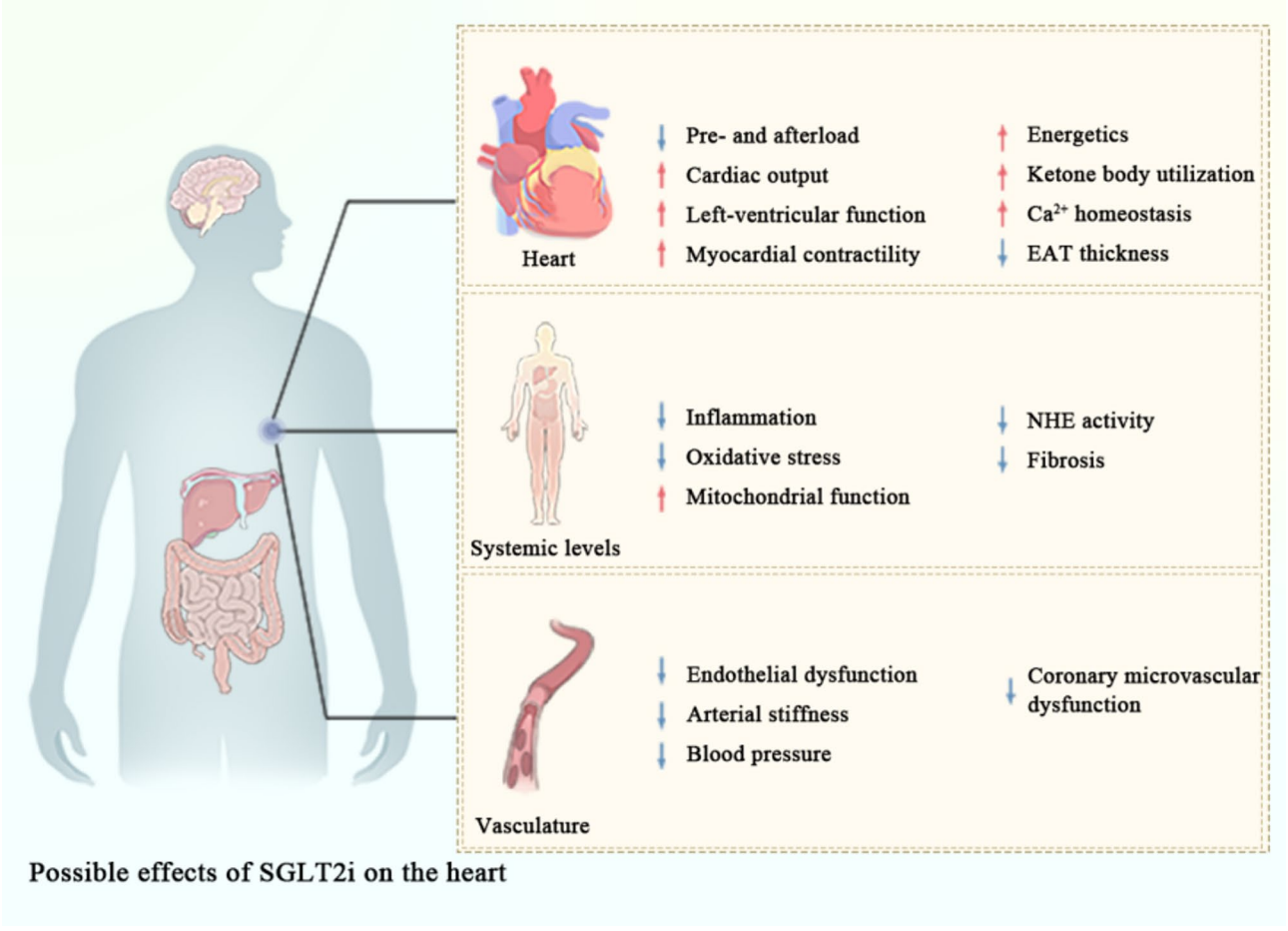


**Fig. 1** Mechanistic insights into the role of SGLT2i at cardiac, systemic, vascular levels. SGLT2i exert multiple mechanisms independent of their hypoglycemic effects, including the improvement of hemodynamics, inhibition of inflammatory responses, reduction of oxidative stress, and enhancement of mitochondrial function

exchanger 1 (NHE1), thereby improving mitochondrial respiratory function, maintaining myocardial $Ca^{2+}$ homeostasis, and delaying the decline in contractile function [113–115]. Moreover, in cardiomyocytes, SGLT2i inhibit late sodium current and calcium/calmodulin-dependent protein kinase II activity, promoting the contraction–relaxation cycle [114]. Overall, SGLT2i reduce ventricular load through diuresis and afterload reduction, enhance output by increasing hemoglobin concentration, and directly modulate ion channels to improve cardiac function.

Metabolically, inflammation and oxidative stress contribute significantly to cardiac structural and diastolic dysfunction and play a central role in the initiation and progression of HF [116]. Cardiac inflammation is closely associated with macrophage infiltration. Lin et al. [117] demonstrated that dapagliflozin provides direct cardiac protection by suppressing the NHE1/mitogen-activated protein kinase/activator protein-1 pathway-mediated inflammatory response in cardiomyocytes, reducing proinflammatory macrophage infiltration in the cardiac tissue of HF mice. Ye et al. [118] confirmed that dapagliflozin decreases activation of nucleotide-binding oligomerization domain-like receptor protein 3 inflammasomes and reduces the levels of IL-1β, IL-6, TNF-α, and caspase-1 in an adenosine monophosphate (AMP)-activated protein kinase (AMPK)-dependent manner, thereby ameliorating myocardial fibrosis and reshaping left ventricular function. Another study demonstrated that empagliflozin appears to primarily reduce oxidative stress in cardiomyocytes by inhibiting NHE1, consequently enhancing cardiomyocyte stiffness, promoting extracellular matrix remodelling, mitigating centripetal hypertrophy of the heart, and alleviating systemic inflammation [119]. Other anti-inflammatory effects of SGLT2i may involve reduction of the amount of epicardial adipose tissue [120], modification of apolipoprotein profiles (e.g., decreasing the levels of low-density lipoprotein and triglycerides while increasing the level of high-density lipoprotein) [121], and improvement of hepatic steatosis [122]. SGLT2i exert cardioprotective effects by suppressing key inflammatory pathways and oxidative

stress, thereby reducing macrophage infiltration, cytokine release, myocardial fibrosis, and adverse remodeling.

SGLT2i also enhance cardiac energy metabolism. By restoring the intracellular AMP/adenosine triphosphate (ATP) ratio, AMPK is activated, dynamin-related protein 1 phosphorylation is inhibited, and mitochondrial fission is regulated, thereby reducing mitochondrial deoxyribonucleic acid (DNA) damage [123]. Furthermore, SGLT2i improve energy metabolism by maintaining respiratory chain function, stabilizing the mitochondrial membrane potential, decreasing reactive oxygen species (ROS) production, and inhibiting mitochondrial permeability transition pore opening, ultimately promoting cell survival [124]. SGLT2i increase the levels of myocardial ketone bodies, which serve as alternative fuel sources in HF. Although increased ketone oxidation increases total cardiac energy expenditure, it does not improve cardiac efficiency [125]. Empagliflozin is also capable of improving the lipopolysaccharide-induced inflammatory response in cardiomyocytes, activating AMPK phosphorylation, modulating inflammatory pathways, and maintaining cellular energy homeostasis [126]. Collectively, these actions enable SGLT2i to improve cardiac energy metabolism by enhancing mitochondrial function, promoting ketone oxidation for energy, and regulating cellular energy homeostasis.

Coronary microvascular dysfunction also plays a critical role in the pathogenesis of HFpEF [127]. Multiple studies have suggested that SGLT2i significantly improve microvascular dysfunction. In an ob/ob−/− mouse model, 10 weeks of empagliflozin treatment markedly enhanced coronary microvascular function by inhibiting SGLT2 activity, thereby improving cardiac contractility [128]. Similarly, Juni et al. [129] reported that empagliflozin restored endothelial-derived nitric oxide release by suppressing TNF-α-induced ROS accumulation, thereby improving myocardial contraction and relaxation. These findings collectively suggest that the beneficial effects of SGLT2i on cardiac function may be partly mediated through endothelium-dependent mechanisms, highlighting the pathophysiological importance of endothelial–myocardial crosstalk.

#### *GLP-1 RA for HFpEF patients*

Preclinical and clinical studies indicate that GLP-1 RA exert potent cardioprotective effects via multiple mechanisms. Additionally, GLP-1 RA facilitate the mediation of biological effects associated with hormones that influence not only cardiac function but also other organs and tissues (Fig. 2).

Emerging evidence indicates that HFpEF patients face a significantly elevated risk of ASCVD [130]. Consequently, ASCVD prevention may improve outcomes in this population. However, the precise pathophysiological interplay between atherosclerotic progression and HFpEF remains incompletely understood. Current studies attribute the cardiovascular benefits of GLP-1 RA in reducing MACE predominantly to their anti-atherosclerotic properties [131]. The LEADER trial demonstrated that liraglutide significantly decreased 3-point MACE risk [100], with divergence in Kaplan-Meier cumulative event curves emerging 12–18 months postrandomization, suggesting that its cardiovascular benefits likely stem from attenuation of atherosclerotic progression [132]. Similarly, Sun et al. [133] reported that liraglutide treatment markedly reduced the levels of inflammatory biomarkers and carotid intima–media thickness in individuals with impaired glucose tolerance. Another clinical study revealed that liraglutide suppressed monocyte chemoattractant protein-1 (MCP-1) secretion in human carotid endarterectomy specimens [134]. In ApoE−/−mice, four-week liraglutide infusion significantly reduced aortic root atherosclerotic lesion size and monocyte/macrophage accumulation [134]. An ex vivo study of isolated aortic rings from high-fat diet-fed ApoE−/−mice revealed that liraglutide upregulated endothelial nitric oxide synthase expression and reduced intercellular adhesion molecule-1 levels, indicating GLP-1 receptor-dependent reversal of endothelial dysfunction [135]. Chang et al. [136] demonstrated that dulaglutide mitigates the proatherogenic effects of oxidized low-density lipoprotein by blocking p53-mediated suppression of Kruppel-like factor 2, a transcription factor critical for vascular homeostasis. Therefore, the aforementioned studies demonstrate that GLP-1 RA exert anti-atherosclerotic effects through reducing inflammatory responses, improving endothelial function, and inhibiting plaque formation.

GLP-1 RA have also been demonstrated to reduce EAT thickness, suppress RAAS activation, improve myocardial energy metabolism, and attenuate systemic inflammation and cardiac oxidative stress [137–139]. These direct cardioprotective mechanisms may underlie their therapeutic potential in obese HFpEF patients. Increased EAT thickness is strongly associated with cardiac structural and functional abnormalities, reduced exercise capacity, and elevated risks of hospitalization and mortality in HFpEF patients. Multiple studies have shown that GLP-1 RA reduce EAT thickness. In a 24-week case–control study of obese patients with T2DM, the liraglutide plus metformin group exhibited reductions in EAT thickness from 9.6 ± 2.0 mm to 6.8 ± 1.5 mm at 12 weeks and 6.2 ± 1.5 mm at 24 weeks, whereas no significant reduction was observed in the metformin-only group [140]. Similarly, Iacobellis et al. reported significant reductions in EAT thickness in obese T2DM patients after 12 weeks of treatment with semaglutide or dulaglutide, with the extent of reduction showing dose dependency [141]. Notably, human EAT expresses GLP-1R, and GLP-1R

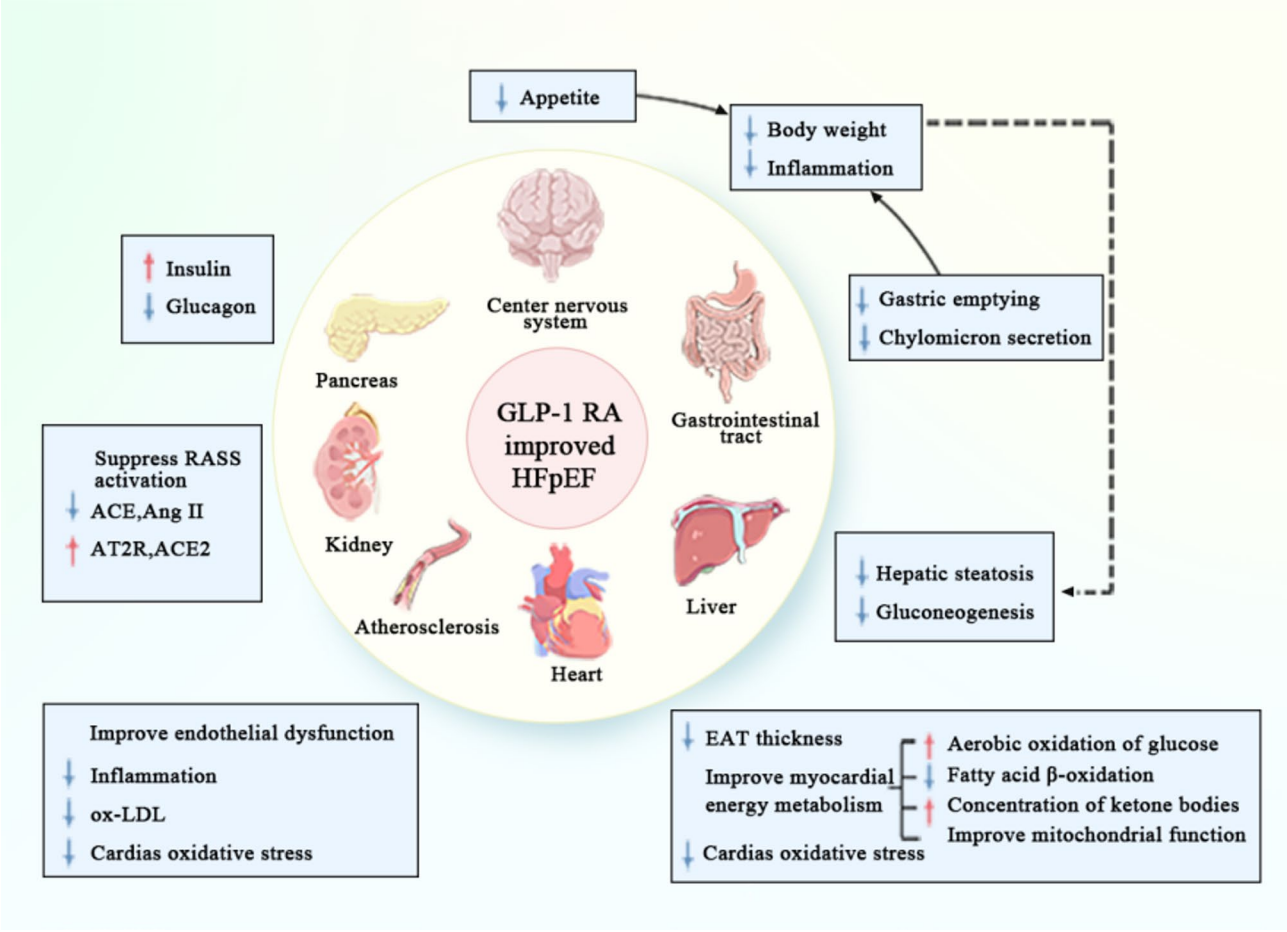


**Fig. 2** The effects of cardiac protection mediated by GLP-1 RA include multiple physiological mechanisms. GLP-1 RA enhance glucose homeostasis by acting on pancreatic islet cells, while their action on the central nervous system and gastrointestinal tract reduces appetite and body weight; decreases hepatic gluconeogenesis and steatosis, indirectly contributing to improved glycemic control and lipid profiles; inhibit the activation of the RAAS; delay the progression of atherosclerosis; GLP-1 RA exert both direct and indirect protective effects on the heart, reduced epicardial fat thickness, optimized myocardial energy metabolism, diminished cardiac oxidative stress, and ultimately improved prognosis in HFpEF

expression is positively correlated with the expression of genes involved in fatty acid β-oxidation and browning of white adipose tissue but negatively correlated with the expression of adipogenesis-related genes. This molecular interplay may explain the preferential benefits of GLP-1 RA in obese HFpEF patients [142]. However, whether the EAT-reducing effects of GLP-1 RA are independent of their weight loss-inducing properties continues to be debated.

Chronic activation of the RAAS can cause significant structural alterations in multiple components of the cardiovascular system [143]. Angiotensin II (Ang II), the primary bioactive peptide in the RAAS, plays a pivotal role in cardiac remodelling and in the development of hypertension [144]. The study demonstrated that in spontaneously hypertensive rats, liraglutide reduced circulating Ang II levels, upregulated cardiac angiotensin II type 2 receptor (AT2R) and angiotensin-converting enzyme-2 (ACE2) expression, and attenuated myocardial hypertrophy [145]. In a murine model of cardiometabolic HFpEF, liraglutide alleviated myocardial hypertrophy, fibrosis, and inflammation; reduced NP levels; and mitigated pulmonary congestion [146]. A clinical trial involving 12 healthy young males demonstrated that a 2-hour infusion of synthetic human GLP-1 decreased circulating Ang II by 19% and induced diuresis [147]. Furthermore, GLP-1 inhibits ACE activity while stimulating ACE2, thereby promoting the conversion of Ang II to angiotensin (1–7), a hormone that exerts vasodilatory and antifibrotic effects [148]. Ang II also enhances sodium-hydrogen exchanger isoform 3 activity, thereby increasing proximal tubular sodium and water reabsorption [149]. Thereby, these evidence suggests that GLP-1 RA counteract the action of Ang II through multiple pathways.

In HF, metabolic derangements in cardiac substrates—including fatty acids, glucose, ketones, lactate, and amino acids—contribute to myocardial metabolic remodelling

and ultimately lead to structural and functional impairments [150]. Importantly, GLP-1 RA can exert beneficial effects on myocardial energy metabolism. Aoi et al. [151] demonstrated that exenatide enhances glucose uptake, activates phosphofructokinase-1, and suppresses carnitine palmitoyltransferase 1 activity in H9c2 cells, thereby optimizing energy substrate utilization. The shift towards increased myocardial glucose oxidation and reduced fatty acid oxidation mediated by GLP-1 RA improves cardiac metabolic efficiency and function [152]. In a hypoxia/reoxygenation model, exenatide preserved mitochondrial function by reducing reactive ROS generation, mitigating calcium overload, and stabilizing the mitochondrial membrane potential [153]. Similarly, exenatide restored mitochondrial morphology in db/db mice by reducing ROS accumulation and enhancing mitophagy [154]. GLP-1 also upregulates the expression of adiponectin, a hormone that modulates mitochondrial dynamics via AMPK and sirtuin 1 phosphorylation [155]. These evidence indicates that GLP-1 RA protect cardiomyocytes from metabolic dysfunction by optimizing energy metabolism and enhancing mitochondrial function.

Recent animal and human studies highlight the critical role of systemic inflammation—driven by comorbidities such as obesity, T2DM, hypertension, and ageing—in the pathogenesis of HFpEF, with obesity recognized as a key driver of this proinflammatory state [156]. The anti-inflammatory properties of GLP-1 RA are well documented. Compared with insulin monotherapy, liraglutide combined with insulin significantly reduced MCP-1 and nuclear factor-κB (NF-κB) levels in T2DM patients [157]. Another clinical trial reported that liraglutide combined with moderate exercise effectively lowered high-sensitivity C-reactive protein levels [158]. In rodent studies, semaglutide attenuated exercise-induced myocardial injury by suppressing inflammation and oxidative stress [159], whereas dulaglutide reduced the levels of proinflammatory cytokines (e.g., IL-1β, IL-6, and MCP-1) in human fibroblast-like synoviocytes via inhibition of c-Jun N-terminal kinase/NF-κB signalling [160]. Liraglutide increases superoxide dismutase activity while reducing plasma malondialdehyde and oxidized low-density lipoprotein levels [161–163]. Exenatide pretreatment of H9c2 cardiomyocytes diminishes H2O2-induced ROS production and upregulates the expression of antioxidant enzymes such as glutathione peroxidase-1 and manganese superoxide dismutase [164]. Collectively, these findings demonstrate that GLP-1 RA mitigate systemic inflammation through multi-targeted suppression of proinflammatory cytokines and enhancement of endogenous antioxidant defenses.

#### *Tirzepatide for HFpEF patients*

Current evidence regarding the cardioprotective mechanisms of tirzepatide remains limited. Mechanistic analyses from the SUMMIT trial [165] demonstrated that, compared with placebo, tirzepatide reduced blood pressure and attenuated circulatory volume expansion in obese HFpEF patients. Tirzepatide also alleviated systemic inflammation, improved the estimated glomerular filtration rate, and reduced microalbuminuria. Furthermore, tirzepatide significantly lowered cardiac troponin T levels compared with placebo, indicating reduced myocardial injury, along with a concurrent decline in NT-proBNP levels. Tirzepatide reduced estimated blood volume, and this reduction was linked to: lower systolic blood pressure, an improved urinary albumin-to-creatinine ratio, higher KCCQ-CSS scores, and greater 6MWD distances. Together, these associations suggest that alleviating circulatory volume overload (or removing volume-related stressors) is a key mechanism for tirzepatide's clinical benefits. Furthermore, tirzepatide-mediated attenuation of systemic inflammation was significantly associated with reductions in myocardial injury biomarkers and modestly correlated with improvements in the 6MWD. Additionally, the cardiac magnetic resonance substudy of the SUMMIT trial revealed that compared with placebo, tirzepatide treatment of obese HFpEF patients reduced the LV mass and paracardial adipose tissue volume, with the changes in the LV mass paralleling the degree of weight loss [166]. These physiological adaptations likely underlie the observed reduction in heart failure events in the main SUMMIT study. Collectively, these findings provide novel insights into the mechanisms by which tirzepatide improves clinical outcomes in obese HFpEF patients. However, whether the benefits of tirzepatide in this population are independent of its weight-reducing effects requires further validation through clinical and preclinical studies.

### BSx for patients with obesity and HFpEF

BSx, primarily laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy, delivers effective and sustained weight loss for patients with BMI ≥ 35 kg/m² or ≥ 30 kg/m² with metabolic comorbidities [167, 168]. Although RCTs evaluating BSx in patients with confirmed HF are currently lacking, the ACC guidelines recommend that for individuals with HF and obesity, BSx appears effective for intentional weight loss and potentially reduces the risk of HF events, including hospitalization for HF and death [18]. A self-controlled case study of 524 HF patients demonstrated significantly lower rates of emergency visits and hospitalizations for acute HF exacerbations during postoperative months 13–24 than during the preoperative 13-24-month period [169]. Additional evidence derives from retrospective cohort studies

reporting intermediate-term mortality outcomes in patients with baseline HF (without detailed phenotyping). Two U.S. administrative database analyses revealed lower in-hospital mortality among obese HF patients with prior BSx than among their nonsurgical counterparts [170, 171]. Swedish registry data indicated a 77% reduction in mortality risk in the BSx subgroup with preoperative HF versus the nonsurgical control group [172]. A Canadian study of 274 patients with baseline HF similarly reported significantly reduced cardiovascular and all-cause mortality at a median follow-up of 4.6 years, along with decreased subsequent HF hospitalization risk in the BSx group [173]. Data on preoperative patients with HFpEF remain substantially limited. This gap primarily stems from the inadequate sensitivity of current HFpEF diagnostic criteria in severely obese populations. Future efforts should focus on developing dedicated diagnostic scoring systems for HFpEF tailored to individuals with severe obesity. Subsequently, randomized trials in obese HFpEF population will be essential to establish the efficacy and safety of BSx, thereby providing an evidence-based foundation for BSx in HFpEF management.

## Conclusion and future directions

The increasing prevalence of obesity is closely linked to the increasing incidence of HFpEF. The association between obesity and HFpEF is largely independent of traditional risk factors, underscoring the importance of elucidating the nontraditional mechanistic pathways that connect these conditions and in that way to identify novel targets for HFpEF prevention and treatment. Current evidence indicates that lifestyle interventions significantly improve clinical outcomes in obese HFpEF patients. Emerging therapies, including SGLT2i, GLP-1 RA, and tirzepatide, offer promising options for ameliorating metabolic derangements, alleviating symptoms, and improving prognosis in this population. Additionally, accumulating experience with BSx further supports the substantial benefits of metabolism-targeted therapeutic strategies in obese HFpEF patients.

It remains unclear whether the benefits of pharmacological or non-pharmacological therapies in obese HFpEF patients are attributable solely to weight loss or are also directly mediated by weight loss-independent effects on cardiovascular structure, function, and hemodynamics. Therefore, future studies are needed to elucidate the weight loss-dependent and -independent mechanisms of benefit in obese HFpEF treatment, utilizing both preclinical and clinical investigations. Furthermore, RCTs should explore optimal combination strategies—including lifestyle interventions, pharmacotherapy, and surgical procedures—tailored to patients stratified by BMI. The goal is to comprehensively improve patients' clinical symptoms, functional status, metabolic parameters, heart failure hospitalization rates, and long-term survival.

**Abbreviations**

| | |
|---|---|
| HFpEF | Heart failure with preserved ejection fraction |
| HF | Heart failure |
| HFrEF | Heart failure with reduced ejection fraction |
| MetS | Metabolic syndrome |
| T2DM | Type 2 diabetes mellitus |
| SGLT2i | Sodium glucose cotransporter 2 inhibitors |
| GLP-1 | RA Glucagon-like peptide-1 receptor agonists |
| GIP | Glucose–dependent insulinotropic polypeptide |
| GLP-1 | Glucagon-like peptide-1 |
| BSx | Bariatric surgery |
| NP | Natriuretic peptide |
| NT-proBNP | N-terminal pro–B-type natriuretic peptid |
| BMI | Body mass index |
| ACC | American College of Cardiology |
| EAT | Epicardial adipose tissue |
| LV | Left ventricular |
| VAT | Visceral adipose tissue |
| IL-1β | Interleukin-1β |
| IL-6 | Interleukin-6 |
| TNF-α | Tumour necrosis factor-α |
| DASH | Dietary approaches to stop hypertension |
| SDR | Sodium-restricted |
| LED | Low-energy diet |
| MRPs | Meal replacement plans |
| MedDiet | Mediterranean diet |
| KCCQ-CSS | Kansas city cardiomyopathy questionnaire clinical summary score |
| ET | Exercise training |
| QoL | Quality of life |
| AHA | American heart association |
| RCTs | Randomized controlled trials |
| SET | Supervised exercise training |
| HIIT | High-intensity interval training |
| 6MWD | 6-minute walk distance |
| $VO_2$ peak | Peak oxygen consumption |
| LIT | Low-intensity training |
| MLHF | Minnesota living with heart failure |
| NNT | Number needed to treat |
| SAE | Serious adverse events |
| AE | Adverse events |
| HFSA | Heart failure society of America |
| ASCVD | Atherosclerotic cardiovascular disease |
| CVOTs | Cardiovascular outcome trials |
| MACE | Major adverse cardiovascular events |
| LVEF | Left ventricular ejection fraction |
| NHE1 | Myocardial-specific sodium-hydrogen exchanger 1 |
| AMP | Adenosine monophosphate |
| AMPK | AMP-activated protein kinase |
| ATP | Adenosine triphosphate |
| DNA | Deoxyribonucleic acid |
| ROS | Reactive oxygen species |
| MCP-1 | Monocyte chemoattractant protein-1 |
| Ang II | Angiotensin II |
| AT2R | Angiotensin II type 2 receptor |
| ACE2 | Angiotensin-converting enzyme-2 |
| NF-κB | Nuclear factor-κB |

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**Author contributions**

WWZ and QXQ wrote the manuscript draft. JL designed the figures. CJH searched the literature. HYF revised the manuscript. All authors approved the final version of the manuscript.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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