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Metabolic rewiring and inter-organ crosstalk in diabetic HFpEF

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Abstract

Heart failure with preserved ejection fraction (HFpEF) represents a significant and growing clinical challenge. Initially, for an extended period, HFpEF was simply considered as a subset of heart failure, manifesting as haemodynamic disorders such as hypertension, myocardial hypertrophy, and diastolic dysfunction. However, the rising prevalence of obesity and diabetes has reshaped the HFpEF phenotype, with nearly 45% of cases coexisting with diabetes. Currently, it is recognized as a multi-system disorder that involves the heart, liver, kidneys, skeletal muscle, adipose tissue, along with immune and inflammatory signaling pathways. In this review, we summarize the landscape of metabolic rewiring and the crosstalk between the heart and other organs/systems (e.g., adipose, gut, liver and hematopoiesis system) in diabetic HFpEF for the first instance. A diverse array of metabolites and cytokines play pivotal roles in this intricate crosstalk process, with metabolic rewiring, chronic inflammatory responses, immune dysregulation, endothelial dysfunction, and myocardial fibrosis identified as the central mechanisms at the heart of this complex interplay. The liver-heart axis links nonalcoholic steatohepatitis and HFpEF through shared lipid accumulation, inflammation, and fibrosis pathways, while the gut-heart axis involves dysbiosis-driven metabolites (e.g., trimethylamine N-oxide, indole-3-propionic acid and short-chain fatty acids) impacting cardiac function and inflammation. Adipose-heart crosstalk highlights epicardial adipose tissue as a source of local inflammation and mechanical stress, whereas the hematopoietic system contributes *via* immune cell activation and cytokine release. We contend that, based on the viewpoints expounded in this review, breaking this inter-organ/system vicious cycle is the linchpin of treating diabetic HFpEF.

Introduction

Heart failure (HF) remains a critical global health challenge, affecting over 64 million individuals worldwide. Among its subtypes, heart failure with preserved ejection fraction (HFpEF) has emerged as the predominant form [1–3]. This epidemiological shift correlates strongly with aging populations and escalating rates of hypertension, metabolic disorders, obesity, and diabetes [3–5]. Advanced phenotyping studies reveal that a substantial proportion of HFpEF patients exhibit a distinct "metabolic-obese" profile [6].

Diabetes coexists in nearly 45% of HFpEF cases [7]. Clinical evidence indicates that diabetic HFpEF patients exhibit greater comorbidity burdens, including severe hypertension, pulmonary complications, and renal dysfunction, alongside more pronounced cardiac structural changes such as elevated ventricular filling pressures and advanced diastolic dysfunction compared to non-diabetic HFpEF patients [8, 9]. Such pathophysiological distinctions suggest the necessity for tailored therapeutic strategies in this subpopulation.

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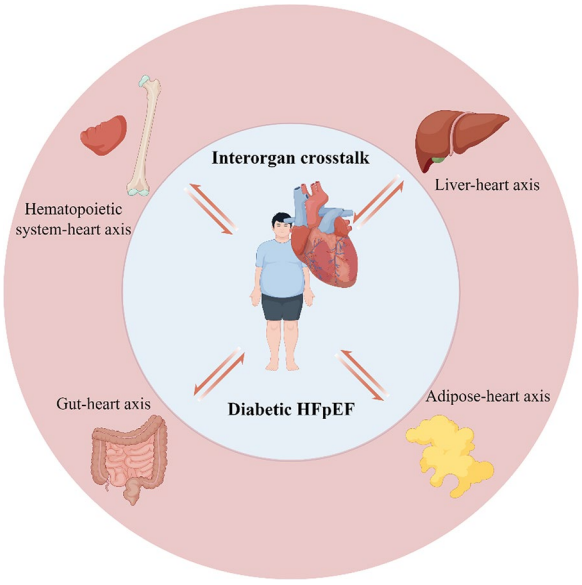
Graphical abstract



Research insights

What is currently known about this topic? Diabetic patients with HFpEF are younger and more obese than their non-diabetic counterparts, and often have a higher rate of hospitalization and poorer prognosis.

What is the key research question? What are the characteristics and mechanisms of diabetic HFpEF?

What is new? This study describes the key cellular mechanisms of this inter-organ crosstalk in diabetic HFpEF. We also discuss the mediators of this crosstalk, such as circulating metabolites, cytokines and other factors, which are either directly released into the circulation or transported by exosomes to their target tissue.

How might this study influence clinical practice? Findings could lead to personalized treatment strategies for diabetic HFpEF.

Keywords HFpEF, Diabetes, Metabolism, Inflammation, Inter-organ crosstalk

While some reviews have discussed the distinctive features of cardiometabolic HFpEF, the specific pathomechanisms underlying diabetic HFpEF remain inadequately defined [2, 10, 11]. In this review, we systematically describe four pivotal aspects of diabetic HFpEF: (1) biomarkers, (2) characteristic metabolic rewiring patterns, (3) inter-organ crosstalk networks, and (4) currently available therapeutic strategies. Particular emphasis is placed on delineating the mediators and molecular mechanisms underlying inter-organ crosstalk.

Diabetic HFpEF and biomarker

Diabetes mellitus, a multifactorial systemic disorder, exerts heterogeneous effects across multiple tissues yet remains diagnostically defined by hyperglycemia exceeding established thresholds. Notably, diabetic patients with HFpEF demonstrate distinct clinical characteristics-younger age, higher obesity prevalence, elevated hospitalization rates, and unfavorable prognoses compared to non-diabetic HFpEF cohorts [12–16]. Impairments in left ventricular (LV) global longitudinal strain are more pronounced in HFpEF with concurrent type 2 diabetes mellitus (T2DM) [17]. Furthermore, pre-diabetic states frequently coexist with HFpEF, correlating with aggravated clinical manifestations and increased HF-related hospital admissions [18]. Emerging evidence highlights long-term glycemic variability as an independent predictor of adverse outcomes in diabetic HFpEF populations [19], while the stress hyperglycemia ratio (derived from acute-to-chronic glycemic markers) serves as a prognostic indicator for long-term cardiovascular complications [20]. While the contribution of hyperglycemia to diabetes complications is well-documented, contemporary research imperatives demand comprehensive exploration of alternative inter-organ crosstalk in diabetic HFpEF (Fig. 1).

HFpEF harbors distinct plasma signatures linked to fluid retention, inflammatory activation, matrix remodeling, and cellular stress-injury axis [21, 22]. Based on the blood preparation and proteomic analysis of 545 diabetic

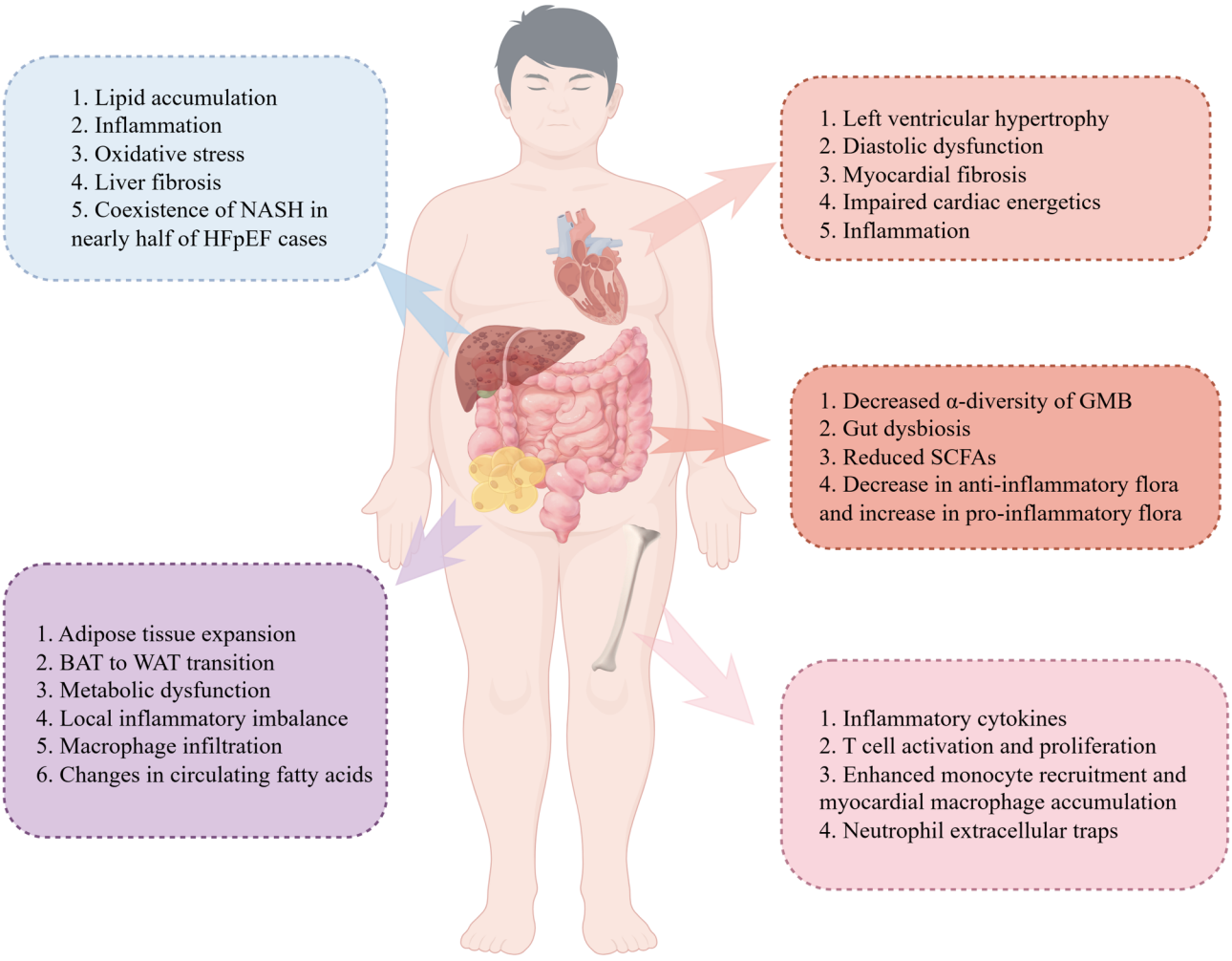


Fig. 1 Multisystemic changes in diabetic HFpEF. HFpEF is a multisystemic syndrome featuring prominent extracardiac involvement (e.g., liver, intestine, hematopoietic system and adipose tissue). Comprehensive treatment strategies targeting multiple systems may yield better outcomes. BAT, brown adipose tissue; GMB, gut microbiota; HFpEF, heart failure with preserved ejection fraction; NASH, nonalcoholic steatohepatitis; SCFAs, short-chain fatty acids; WAT, white adipose tissue

patients (244 with HFpEF and 301 without), Su et al. revealed that the plasma level of integrin subunit alpha 1 (ITGA1) was significantly elevated, which was an independent predictor of cardiac dysfunction in patients with T2DM. Further mechanistic studies demonstrated that an elevated ITGA1 level might affect the cardiac function of patients with diabetes complicated by HFpEF by promoting myocardial fibrosis [23]. Additionally, in a study involving 374 HFpEF patients, Alogna et al. found that high interleukin-6 (IL-6) levels were associated with more severe cardiometabolic disease, with a higher prevalence of obesity and diabetes, worse renal function, and anemia [24]. Distinct biomarker profiles further differentiate obese HFpEF phenotypes, characterized by elevated circulating markers of volume overload (adrenomedullin), fibrotic remodeling (thrombospondin-2), and systemic inflammation (galectin-9, CD4 + T-cell markers), underscoring the need for phenotype-specific therapeutic strategies [25].

The identification and application of biomarkers in HFpEF face significant challenges due to the syndrome's inherent heterogeneity, which encompasses diverse phenotypes (e.g., metabolic, hypertensive, or renal-driven subtypes) [26], complicating the discovery of universal biomarkers. Overlap with comorbidities such as obesity, diabetes, and chronic kidney disease further obscures biomarker specificity [27], as elevated levels (e.g., fibrosis markers) may reflect systemic dysfunction rather than HFpEF-specific pathophysiology. Addressing these limitations requires combining biomarkers with imaging, clinical context, and novel molecular tools to refine diagnosis and personalized management.

Cardiac substrate metabolism perturbations

HFpEF shares pathophysiological overlap with diabetes and obesity through disrupted energy metabolism, including defective fuel substrate utilization, lipotoxicity, and impaired cytoprotective signaling [5]. Transcriptomic analyses reveal HFpEF-specific upregulation of mitochondrial oxidative phosphorylation pathways-contrasting with downregulation patterns in heart failure with reduced ejection fraction (HFrEF)-while suppression of endoplasmic reticulum stress response, autophagy, and angiogenesis pathways occurs independently of comorbid conditions [28]. Paradoxically, despite prevalent obesity and insulin resistance, HFpEF myocardium demonstrates reduced fatty acid (FA) oxidation capacity and diminished tricarboxylic acid cycle intermediates compared to HFrEF, reflecting impaired metabolic flexibility that remains undetectable in systemic circulation [29]. Concomitant reductions in glycolytic intermediates and regulatory enzyme expression further characterize the metabolic landscape of HFpEF myocardium [30]. The current meta-analysis of metabolites found that higher plasma and serum levels of certain amino acids (branched-chain, aromatic, alanine, glutamate, lysine, and methionine), carbohydrates and energy-related metabolites (mannose, trehalose, and pyruvate), acylcarnitines (C4-DC, C4-OH, C5, C5-OH, and C8:1), the majority of glycerolipids (di- and triacylglycerols), (lyso)phosphatidylethanolamines, and ceramides included in meta-analysis were associated with higher risk of T2DM [31]. In individuals with cardiometabolic HFpEF, profound changes in cardiac metabolism have been identified (Fig. 2).

Clarifying the energy metabolic changes in HFpEF is hindered by the lack of animal models that can fully characterize the complex pathophysiology of HFpEF. Nowadays, metabolic syndrome-related models are established through methods such as a high-fat diet (HFD) combined with streptozotocin (STZ)-induced diabetes, or using leptin/leptin receptor-mutation mice (e.g., db/db or ob/ob strains) [32]. Lipoxin receptor-deficient mice ($ALX^{-/-}$) might serve as a new experimental model that defines multiple cellular and molecular mechanisms in HFpEF with profound age-associated endothelial dysfunction

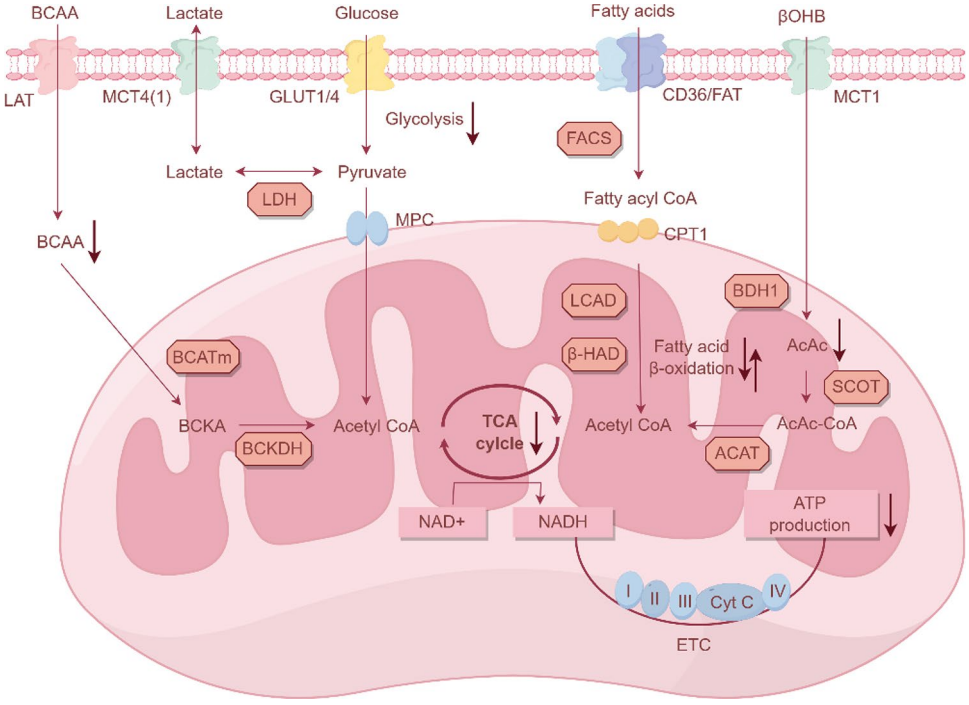


Fig. 2 Perturbations in cardiac substrate metabolism in diabetic HFpEF. Diabetic HFpEF exhibits impaired cardiac substrate metabolism, marked by reduced metabolic flexibility. Despite systemic insulin resistance, myocardial fatty acid oxidation decreases, contrasting with diabetes-related lipid overload, while glucose utilization is suppressed *via* GLUT4 downregulation and pyruvate dehydrogenase inhibition. Mitochondrial dysfunction and oxidative stress coexist with disrupted tricarboxylic acid cycle intermediates. Accumulated metabolites (e.g., acetyl-CoA, ceramides) drive lipotoxicity and epigenetic dysregulation. Concurrently, amino acid and ketone metabolism alterations exacerbate energetic inefficiency. AcAc, acetoacetate; ACAT, acetoacetyl CoA thiolase; ATP, adenosine triphosphate; BCAA, branched-chain amino acids; BCATm, mitochondrial BCAA amimotransferase; BCKA, branched-chain keto acids; BCKDH, branched-chain α-ketoacid dehydrogenase; BDH1, b-hydroxybutyrate dehydrogenase 1; CD36, the cluster of differentiation 36; CPT, carnitine palmitoyltransferase; Cyt C, cytochrome C; ETC, electron transport chain; FACS, fatty acid CoA synthetase; LAT, L-type amino acid transporters; LCAD, long-chain acyl-CoA dehydrogenase; LDH, lactate dehydrogenas; MCT1, monocarboxylate transporter 1; GLUT1/4, glucose transporter 1/4; MPC, mitochondrial pyruvate carrier; NAD, nicotinamide adenine dinucleotide; SCOT, succinyl-CoA:3-ketoacid CoA transferase; TCA, tricarboxylic acid; βHAD, 3-OH-acyl-CoA dehydrogenase; βOHB, b-hydroxybutyrate

and inflammation in the spleen, heart, and kidneys [33]. These models offer advantages in mimicking metabolic abnormalities (e.g., obesity, diabetes, dyslipidemia) commonly observed in HFpEF patients and allow for the study of systemic inflammation linked to adipose tissue dysfunction, endothelial dysfunction and myocardial fibrosis [34–36]. Limitations involve risks of progression to systolic dysfunction without strict intervention timing, rodent-specific metabolic discrepancies, and challenges in maintaining preserved ejection fraction (requiring precise stressor control) [37–39]. Despite these constraints, they remain pivotal for studying metabolic dysregulation's role in diabetic HFpEF pathophysiology.

In HFD/STZ-induced HFpEF mice, the impairment of endothelial SIRT6 expression links diabetic HFpEF by altering FA transport across the endothelial barrier. Pharmacological strategies to restore SIRT6 function in diabetic endothelium alleviate experimental HFpEF by limiting FA override and improving lipid accumulation [40]. Obesity in $ALX^{-/-}$ mice induce myocardium endothelial dysfunction with the alterations in cluster of differentiation 31/phosphorylated eNOS (CD31/peNOS) pathways [22]. Therapeutic modulation of nicotinamide adenine dinucleotide (NAD^+)-a critical cofactor in energy metabolism and cellular repair-through precursor supplementation represents a promising intervention avenue for HFpEF management [41–44].

Inter-organ crosstalk in diabetic HFpEF

HFpEF is increasingly recognized as a systemic disorder driven by intricate interactions between the heart and distant organs [45–48]. Emerging evidence highlights how metabolic dysfunction, chronic inflammation, and immune dysregulation propagate through circulating mediators-including metabolites, cytokines, and exosomes-to orchestrate cardiac remodeling and dysfunction. The liver, gut, adipose tissue, and hematopoietic system each contribute distinct yet interconnected mechanisms, forming a pathological network that perpetuates myocardial fibrosis, oxidative stress, and impaired energy metabolism (Fig. 3). This section delineates the critical axes of inter-organ crosstalk.

Liver-heart axis

The heart is a "catabolic" organ, and the liver is predominantly "anabolic" [46]. Multifaceted interactions exist between them [49], with heart diseases often affecting liver diseases and vice versa [50]. In the interplay between liver and heart diseases, nonalcoholic steatohepatitis (NASH) and HFpEF, considered the most common and related [46, 51], share similar risk factors like diabetes and obesity [52]. Up to half of HFpEF patients have NASH [53], and conversely, NASH also increases the risk of developing HFpEF [54]. Pathophysiologically, the combination of obesity and hypertension gives rise to the most common HFpEF phenotype, cardiometabolic HFpEF, characterized by lipid accumulation and abnormal activation of inflammatory pathways, jointly leading to cellular structural and functional damage, fibrosis progression, and organ dysfunction. This bears a striking resemblance to the pathophysiology of NASH, which involves lipid accumulation, inflammation, along with oxidative stress and fibrosis [46]. Additionally, the benefits of sodium-glucose co-transporter 2 inhibitor (SGLT2i), a clinical medication for HFpEF, on NASH have emerged in meta-analyses [55]. Moreover, pirfenidone, an anti-fibrotic drug, is currently undergoing clinical trials in HFpEF patients [56]. All of these similarities sparked significant interest among researchers in the potential liver-heart interactions between HFpEF and NASH. Many studies have been dedicated to this area, uncovering several metabolites involved in such interactions, which we will elaborate on in the subsequent sections.

Through multi-omics integrated analysis, Strocchi et al. for the first time revealed that serum amyloid A1/A4 (Saa1/4) are key candidate mediators of inter-organ crosstalk between the liver and the heart in HFpEF, and they exhibit cross-species conservation characteristics. They indicated that Saa1/4 may exert their functions through metabolic inflammation and myocardial fibrosis [57]. Wegermann et al. analyzed serum metabolites in NASH patients and found 53 related to HFpEF. Lipid metabolites were predominant (73.6%), like glycerophosphocholine and glycerophosphoethanolamine. Fifteen metabolites were significantly linked across different HFpEF phenotypes, mainly lipids and cysteine-related ones. These indicated lipid metabolism disorders as a shared mechanism for NASH and HFpEF [51]. In 2022, Science reported that coagulation factor 11, a protein synthesized and secreted solely by the liver, can activate the bone morphogenetic protein (BMP)-SMAD1/5 pathway in the heart, thereby suppressing inflammation and fibrosis and protecting diastolic cardiac function [58]. The latest study showed that secreted Fibroblast growth factor 21 (FGF21) from the live enhances the production of adiponectin in adipocytes, which in turn indirectly acts on cardiomyocytes, or FGF21 directly targets cardiomyocytes, to negatively regulate pyruvate dehydrogenase kinase 4 production by activating phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signals, then promoting mitochondrial bioenergetics [59]. Therefore, FGF21 protects against HFpEF *via* fine-tuning the multiorgan crosstalk among the adipose, liver, and heart [59]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is mainly synthesized and secreted by the liver. Da Dalt et al. discovered that systemic Pcsk9 knockout mice lead to the development of HFpEF and the accumulation of cardiac

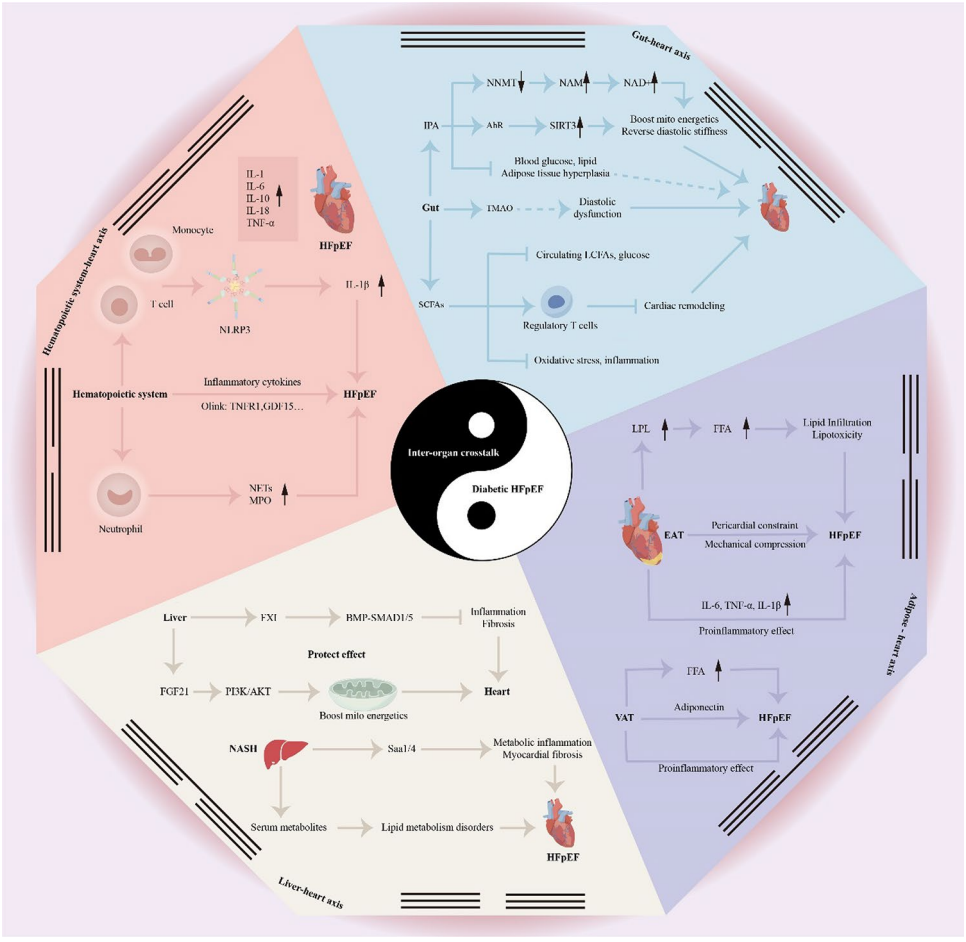


Fig. 3 The inter-organ crosstalk in diabetic HFpEF. In diabetic HFpEF, gut microbiota dysbiosis and metabolites like IPA, TMAO, SCFAs engage in the gut - heart axis. NASH and HFpEF share lipid-accumulation, inflammation, fibrosis mechanisms. Abnormal liver metabolites (Saa1/4, lipid metabolites) and liver-secreted FXI and FGF21 link liver and heart *via* metabolic inflammation and fibrosis pathways. EAT, near the heart, directly drives HFpEF pathology through local inflammation, lipotoxicity, and mechanical compression. VAT are indirectly involved *via* systemic metabolic disorders and inflammation. The hematopoietic system contributes through immune cell activation (macrophages, T-cells) and inflammatory cytokines, perpetuating myocardial injury. AhR, aryl hydrocarbon receptor; BMP, bone morphogenetic protein; EAT, epicardial adipose tissue; FGF21, fibroblast growth factor 21; FFA, free fatty acid; FXI, factor XI; GDF15, growth differentiation factor 15; HFpEF, heart failure with preserved ejection fraction; IL, interleukin; IPA, indole-3-propionic acid; LCFAs, long-chain fatty acids; LPL, lipoprotein lipase; MPO, myeloperoxidase; NAD, nicotinamide adenine dinucleotide; NAM, nicotinamide; NASH, nonalcoholic steatohepatitis; NETs, neutrophil extracellular traps; NLRP3, NOD-like receptor family pyrin domain-containing 3; NNMT, nicotinamide N-methyltransferase; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; Saa1/4, serum amyloid A1/A4; SCFAs, short-chain fatty acids; SIRT3, sirtuin 3; SMAD1/5, SMAD family member 1/5; TGF-β, transforming growth factor-β; TMAO, trimethylamine N-oxide; TNF-α, tumor necrosis factor-α; TNFR1, tumor necrosis factor receptor 1; VAT, visceral adipose tissue

lipids, especially cholesterol. Subsequent studies indicated that this is not caused by a reduction in circulating PCSK9, but rather driven by a decrease in cardiac PCSK9 [60]. In addition, myocardial infarction promotes hepatic fibrosis in mice with metabolic dysfunction-associated steatotic liver disease, accompanied by elevated circulating Ly6C^{hi} monocytes and their recruitment to damaged liver tissues [61]. Another study has found the ischemic heart sends signals to the liver through the acute inflammatory IL-6/signal transducer and activator of transcription 3 (STAT3) pathway and that the liver responds by down-regulating mineralocorticoid receptors to promote FGF21 production and to alleviate ischemic injury [62].

Overall, there are numerous interactions between liver and heart diseases, with NASH and HFpEF being the most classic examples. Many metabolites are involved in the interaction process between them. The commonalities and interactions between these two diseases offer new perspectives for disease management. Addressing lipid accumulation and inflammation may be a win-win strategy.

Gut-heart axis

In cardiometabolic HFpEF, the interplay between the heart and the gut is intricate yet crucial. Cardiac low-output, for one, can induce intestinal ischemia and intestinal

barrier damage [63]. Gut microbiota (GMB)-induced metabolite changes, for another, can affect cardiac function and structure [64–66]. This forms a vicious cycle. This interaction process will be expounded in detail hereinafter.

The alterations in GMB serve as the cornerstone of the gut-heart axis. Beale et al. discovered that in patients with HFpEF, the α-diversity of GMB decreased, manifested as a decline of the richness. β-diversity analysis indicated that the ratio of Firmicutes to Bacteroidetes (a commonly used biomarker of gut dysbiosis) showed a decreasing trend, and Ruminococcus (which produces short-chain fatty acids (SCFAs)) significantly decreased [45]. There are significant differences in the microbial abundances of Lactobacillaceae, Ruminococcaceae, Erysipelotrichaceae, and Lachnospiraceae between the obesity-related HFpEF rat model and control [67]. Huang et al. elucidated the bridging role of inflammation in the gut - heart axis. They found that in HFpEF, the abundance of pro-inflammatory flora, such as Lactobacillus and Enterococcus, increased, while that of anti-inflammatory flora, including Butyricicoccus, Sutterella, Lachnospira, and Ruminiclostridium, decreased [68].

A variety of metabolites serve as messengers of the gut-heart axis. Indole-3-propionic acid (IPA) is derived from dietary tryptophan through transformation by GMB such as Lactobacillus reuteri, Akkermansia muciniphila, and Clostridium sporogene [69–72]. Wang et al. discovered that the serum IPA level decreased in two HFpEF cohorts and the mouse model, and it showed a negative correlation with diastolic cardiac function. After IPA supplementation, it could alleviate weight gain and fat accumulation in mice, improve diastolic function and metabolic homeostasis, and also mitigate GMB dysbiosis and intestinal epithelial barrier damage. Further mechanistic investigation indicated that the beneficial effects of IPA on fat accumulation and diastolic function were exerted, at least in part, by inhibiting the expression of nicotinamide N - methyltransferase (NNMT) and restoring the levels of nicotinamide, NAD^+/NADH, and silent information regulator 3 (SIRT3) [44].

Trimethylamine N-oxide (TMAO), an oxidative amine, occurs naturally in our diet like fish. It can also be generated from its metabolic precursors, including substances like choline and carnitine in food [73]. GMB, such as Firmicutes, Proteus, and Actinomyces, are involved in the metabolic production process of TMAO [74]. Guivala et al. found that in the obesity-related HFpEF rat model, the serum TMAO level increased significantly, and it showed a positive correlation with the degree of diastolic dysfunction [67]. Elevated TMAO demonstrates significant positive correlations with body mass index (BMI), E/e' ratio, and B-type natriuretic peptide (BNP) levels [75]. Heightened TMAO levels detected at hospital discharge serve as an independent predictor for cardiac events in HFpEF [76]. Combined TMAO and BNP evaluation offers a potential approach for risk stratification in HFpEF patients [75].

SCFAs are organic fatty acids containing fewer than six carbon atoms, such as acetic acid, propionic acid, and butyric acid. They are derived from the fermentation of various dietary fiber substances by GMB [77]. SCFAs can reduce the levels of circulating long-chain fatty acids (LCFAs) and glucose, contributing to the prevention of cardiac steatosis and glucotoxicity, which are regarded as the initiating events in the pathogenesis of obesity-related HFpEF [78, 79]. Additionally, SCFAs possess anti-inflammatory and antioxidant properties [80]. In terms of inflammation regulation, SCFAs can inhibit the up-regulation of pro-inflammatory genes in cardiac tissues, such as IL-1β, NOD-like receptor family pyrin domain containing 3 (NLRP3), and monocyte chemoattractant protein-1 (MCP-1) [81, 82]. Additionally, they can prevent cardiac remodeling by promoting the generation of regulatory T cells [83]. Regarding antioxidant effects, SCFAs can decrease oxidative stress; for example, butyrate can reduce the level of lipid peroxidation [84]. These effects sever the crucial link between metabolic syndrome and HFpEF [64].

In conclusion, the gut-heart axis plays a crucial role in the pathogenesis of cardiometabolic HFpEF, and multiple metabolites (like IPA, TMAO and SCFAs) have been demonstrated to be involved in this inter-organ crosstalk. The development of related drugs may be beneficial for the treatment of cardiometabolic HFpEF.

Adipose-heart axis

Clinical evidence establishes adipose tissue dysfunction as a robust predictor of cardiovascular events and HF progression in populations with obesity, metabolic syndrome, and established T2DM [85, 86]. Visceral adipose tissue releases free fatty acids and pro-inflammatory factors (such as tumor necrosis factor-α (TNF-α) and IL-6), leading to systemic inflammation and insulin resistance, which indirectly exacerbate myocardial fibrosis and diastolic dysfunction [87].

The location of adipose deposits is also likely to be important [88–91]. Epicardial adipose tissue (EAT), a metabolically active fat depot situated between the myocardium and visceral pericardium, has emerged as a clinically significant entity in cardiovascular medicine [92]. HFpEF exhibits substantially greater EAT thickness compared to both healthy controls and other HF subtypes (including reduced or mid-range ejection fraction) [93, 94]. Excessive EAT deposition correlates with aggravated diastolic dysfunction, manifesting as more severe impairment of ventricular relaxation and maladaptive cardiac remodeling patterns in HFpEF [95–97]. Longitudinal

cohort evidence further establishes pericardial adiposity as an independent risk factor for predicting de novo cardiovascular events [98]. Notably, EAT demonstrates superior prognostic stratification capacity compared to conventional parameters such as left ventricular ejection fraction (LVEF) and New York Heart Association functional classification [99].

Both elevated EAT thickness and volume were observed in patients with prediabetes and T2DM, which were associated with adverse alterations in cardiac structure and cardiopulmonary performance [100–103]. In HFpEF, elevated EAT measurements demonstrate strong associations with arterial stiffness, as quantified by brachial-ankle pulse-wave velocity [104]. Asymptomatic HF patients with T2DM exhibit distinct EAT-related cardiac abnormalities, including LV remodeling, functional impairments, and reduced exercise tolerance [105]. Notably, preclinical cardiac dysfunction in obese individuals without overt cardiovascular disease appears linked to EAT accumulation, suggesting its contributory role in subclinical disease progression [106]. Obese patients with excessive EAT deposition experience disproportionately higher rates of adverse cardiovascular events compared to those with lower EAT volumes [107, 108]. Therefore, EAT demonstrates multifaceted interactions with myocardial injury biomarkers, ventricular hypertrophy, elevated intracardiac pressures, systemic inflammation, insulin resistance, and impaired functional capacity - all characteristic hallmarks of HFpEF pathophysiology.

Recent advancements propose EAT radiodensity (rather than volumetric measures alone) as a superior predictor of cardiometabolic risk and prognostic stratification in HFpEF cohorts, with specific relevance to metabolic syndrome components [109–111]. Proteomics and transcriptomics analysis of EAT in HFpEF suggested their potential roles in inflammation, metabolic processes, and mitochondrial dysfunction [112–116]. The pathophysiological mechanisms of EAT in cardiometabolic HFpEF involve three principal pathways: (1) paracrine signaling of proinflammatory adipocytokines, (2) myocardial lipid deposition inducing lipotoxic injury, and (3) direct biomechanical compression through pericardial space restriction [88, 117].

All these reveal the diverse pathogenic mechanisms of EAT, unlike conventional adipose depots serving metabolic functions. Targeted therapeutic interventions aimed at modulating EAT quantity and metabolic activity show potential for improving myocardial recovery in HF patients with concurrent T2DM [118, 119].

Hematopoiesis system-heart axis

Emerging evidence supports the pivotal role of systemic inflammation in bridging comorbidities with structural and functional cardiac abnormalities in HFpEF [33, 120]. Proteomic profiling using Olink technology has identified growth differentiation factor-15 (GDF-15), urokinase plasminogen activator receptor (UPAR), tumor necrosis factor receptor-1(TNFR1), insulin-like growth factor binding protein 7 (IGFBP7) as principal mediators linking comorbidity burden with echocardiographic alterations [121]. Critical immune pathways involving NLRP3 inflammasome activation with IL-1β secretion, along with T-cell activation mechanisms, have been implicated in the pathogenesis of metabolic disorders (obesity, hypertension) and cardiac dysfunction associated with HFpEF [87].

Genetic studies using T-cell receptor-deficient mice have established the essential role of T lymphocytes in diastolic impairment and cardiomyocyte hypertrophy. Combinatorial treatment with HFD and Nω-Nitro-L-arginine methyl ester (L-NAME) induces differential cardiac infiltration patterns of immune cells (CD4+/CD8 + T cells, monocytes, neutrophils, B cells) compared to single intervention models [122]. Pharmacologically, SGLT2i exhibits dual therapeutic effects: ameliorating myocardial inflammation in HFpEF [123], while suppressing T-cell effector functions through metabolic rewiring in autoimmune conditions [124].

LCFAs activate multiple inflammatory cytokines released from macrophages, impinging on cardiomyocytes [123]. The pathophysiology of diastolic dysfunction involves elevated circulating monocyte levels and myocardial macrophage accumulation, primarily mediated through enhanced monocyte recruitment from hematopoietic organs (bone marrow and spleen) [125]. Notably, cardiac $CCR2^{+}$ macrophages demonstrate increased IL-10 production, promoting fibrogenic transformation *via* autocrine signaling pathways [125]. Bochra Tourki et al. have found the ALX deficiency expands $Ly6C^{hi}CCR2^{+}$ macrophage population in spleen, primes CCL2 cluster chemokines in the heart, and induces myocardium endothelial dysfunction [22]. These findings collectively highlight macrophage dynamics as a central modulator of diverse HFpEF phenotypic manifestations across experimental models. Neutrophil extracellular traps also contribute to the pathogenesis of HFpEF and HFrEF, which could induced mitochondrial dysfunction in cardiomyocytes, inhibiting mitochondrial biogenesis *via* the neutrophil elastase-toll-like receptor 4 (NE-TLR4)-mediated suppression of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) [126–128]. Recent breakthroughs have uncovered novel neuro-immune regulatory mechanisms, where fasting-induced neural signals modulate immune cell activity to establish interorgan crosstalk networks. These pathways critically regulate pancreatic endocrine function and systemic glucose metabolism [129]. Specifically, neuronal interactions with type 2 innate lymphoid cells (ILC2s) have been identified

Table 1 Randomized, placebo-controlled trials reflect therapeutic potential in HFpEF comorbid with obesity and/or diabetes

Trials	Interventions	Inclusion criteria	Eligible LVEF, %	Primary composite endpoint	Median follow-up	Treatment effect (primary endpoint)	Therapeutic applicable population
EMPEROR-Preserved, *n* = 5988[138]	Empagliflozin, 10 mg once daily	NYHA functional class II to IV, elevated NP, structural heart disease (LAE/ LVH) by echo- cardiography or prior HFH within 12 months	≥ 40%	Cardiovascular death or HFH	26.2 months	HR = 0.79; 95%CI, 0.69–0.90; *P* < 0.001	Reduce the combined risk of cardiovascular death or HFH, regardless of the presence or absence of diabetes
STEP-HFpEF, *n* = 529[141]	Semaglutide, 2.4 mg once-weekly	HFpEF and BMI ≥ 30	≥ 45%	KCCQ-CSS and the change in body weight	52 weeks	KCCQ-CSS: Δ = 7.8; 95%CI, 4.8–10.9; *p* < 0.001. Weight reduction: Δ=−10.7%; 95%CI, − 11.9 to − 9.4	Reduce weight, symptoms, physical limitations, and improve exercise function in patients with HFpEF and obesity.
STEP-HFpEF DM, *n* = 616[142]	Semaglutide, 2.4 mg once-weekly	HFpEF, T2DM and BMI ≥ 30	≥ 45%	KCCQ-CSS and the change in body weight	52 weeks	KCCQ-CSS: Δ = 7.3; 95%CI, 4.1–10.4; *P* < 0.001. Body weight change: Δ=−6.4; 95% CI, − 7.6 to − 5.2; *P* < 0.001	Reduce heart failure–related symptoms, physical limitations and body weight in obesity-related HFpEF and T2DM
SUMMIT, *n* = 731[145]	Tirzepatide, 15 mg once-weekly	HFpEF and BMI ≥ 30	≥ 50%	KCCQ-CSS, adjudicated death from cardiovascular causes or a worsening heart-failure event	104 weeks	Adjudicated death from cardiovascular causes or a worsening heart-failure event: HR = 0.62; 95%CI, 0.41–0.95; *P* = 0.026. KCCQ-CSS: Δ = 6.9; 95%CI, 3.3–10.6; *P* < 0.001	Reduce risk of a composite of death from cardiovascular causes or worsening heart failure and improve health status in HFpEF and obesity

Δ means between-group difference. BMI, body mass index; CI, confidence interval; HFH, heart failure hospitalization; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; NP, natriuretic peptide; NYHA, New York Heart Association; T2DM, type 2 diabetes mellitus

as key regulators of glucagon secretion and glucose homeostasis [129].

In conclusion, cardiometabolic HFpEF arises from chronic low-grade inflammation and immune cell activation. Metabolic derangements and inflammation form a vicious cycle. Therapeutic strategies targeting immune cell polarization or inflammatory mediators may restore metabolic adaptability and delay disease progression.

Diagnosis and treatment of diabetic HFpEF

Diagnosis of HFpEF is based on clinical symptoms (e.g., dyspnea, fatigue), elevated natriuretic peptides, imaging evidence of preserved LVEF (≥ 50%), and exclusion of alternative causes (e.g., valvular disease, infiltrative cardiomyopathies) using echocardiography, cardiac MRI, or invasive hemodynamic testing [130].

Notably, HFpEF is not a single disease entity but rather a heterogeneous condition characterized by multifactorial pathogenesis and diverse clinical presentations [6, 33]. Peters et al. identified three clinically significant HFpEF phenotypes through phenotype clustering analysis of 20 studies: (1) older, vascular ageing; (2) metabolic, obese; and (3) relatively younger, natriuretic peptide deficiency [6]. This subsection specifically addresses diabetic HFpEF., which accounts for 25–30% of HFpEF cases and has emerged as a distinct metabolic subtype receiving growing research attention [16, 131, 132]. Current treatment focuses on symptom relief, reducing hospitalizations, and managing comorbidities. We have summarized the medications demonstrating therapeutic potential in populations with HFpEF comorbid with obesity and/or diabetes (Table 1).

SGLT2i SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin) are cornerstone therapies, proven in trials (DELIVER, EMPEROR-Preserved) to reduce cardiovascular death and HF hospitalizations across the LVEF spectrum [133, 134]. The EMPEROR-Preserved trial revealed that empagliflozin lowered the composite risk of cardiovascular death or heart failure hospitalization in HFpEF, regardless of diabetes status [134]. SGLT2 inhibitors improve HFpEF through multiple molecular mechanisms: metabolic rewiring of cardiac and renal tissues to favor lipid/ketone utilization over carbohydrates, reducing oxidative stress and inflammation *via* suppression of pro-inflammatory mediators, and mitigating myocardial fibrosis [135]. They optimize ventricular loading through

diuresis and natriuresis, lowering cardiac preload and afterload. Additionally, SGLT2 inhibitors enhance renal hemodynamics by correcting hyperfiltration, albuminuria, and hypoxia, while modulating mitochondrial function and autophagy. These combined effects reduce systemic congestion, improve endothelial dysfunction, and attenuate pathological remodeling, thereby alleviating HFpEF progression [27]. Additionally, Wen et al. indicated that SGLT2i reduces cardiomyocyte senescence and restores cardiac function in diabetic conditions by suppressing forkhead box protein O1 (FOXO1)-mediated angiopoietin-like protein 4 (ANGPTL4) transcription [136].

Glucagon-like peptide-1 receptor agonist (GLP1-RA) In the STEP-HFpEF trial, the GLP1-RA semaglutide alleviated symptoms and physical limitations, improved exercise function, and promoted weight loss in HFpEF with obesity [137]. Similarly, the STEP-HFpEF DM trial demonstrated that semaglutide reduced symptoms and physical limitations while achieving weight loss in individuals with obesity-related HFpEF and concomitant T2DM [138]. HFpEF mouse model induced by advanced age, female, obesity and T2DM, Withaar et al. indicated that semaglutide improves HFpEF through multiple mechanisms beyond weight loss. It enhances LV cytoskeleton function, restores endothelial function, and reduces oxidative stress and systemic inflammation by upregulating antioxidant enzymes and inhibiting pro-inflammatory pathways. Additionally, it attenuates cardiac fibrosis, LV hypertrophy, and lung congestion. Semaglutide also modulates protective immune responses in visceral adipose tissue, promoting T-cell regulation and interferon-γ production [139]. These cardiometabolic effects are mediated *via* GLP-1 receptor activation, particularly in endothelial cells, improving myocardial performance independently of caloric restriction [139].

Twincretin Tirzepatide, a novel dual agonist targeting both glucose-dependent insulinotropic polypeptide and GLP-1 receptors, has received regulatory approval in multiple regions including the United States, European Union, and Japan [140]. It is indicated as an adjunctive therapy alongside dietary modifications and physical activity to optimize glycemic management in adult patients with T2DM [140]. The SUMMIT trial demonstrated that tirzepatide therapy reduced the composite risk of cardiovascular mortality or heart failure progression compared to placebo and enhanced health-related outcomes in obese individuals with HFpEF [141].

Conclusion

Diabetic HFpEF represents a complex, multisystem disorder driven by metabolic dysregulation, chronic inflammation, immune dysfunction, endothelial dysfunction and myocardial fibrosis. Emerging evidence highlights the pivotal role of inter-organ crosstalk, mediated by metabolites, cytokines, and exosomes, in perpetuating a vicious cycle of cardiac and systemic dysfunction. Key axes include the adipose-heart axis, where epicardial adipose tissue exacerbates inflammation and mechanical stress; the gut-heart axis, involving dysbiosis and metabolites like IPA, TMAO and SCFAs; the liver-heart axis, NASH to shared pathogenic pathways; and hematopoietic system contributions via immune cell activation. Therapeutic strategies targeting these pathways-such as SGLT2i, GLP1-RA, twincretin and NAD^+ supplementation show promise in disrupting this cycle. Future research should prioritize elucidating organ-specific molecular mechanisms and developing integrated, phenotype-specific therapies to address the heterogeneity of diabetic HFpEF. Breaking the inter-organ vicious cycle remains central to improving outcomes in this challenging syndrome.

Abbreviations

ANGPTL4	Angiopoietin-like protein 4
BMP	Bone morphogenetic protein
BNP	B-type natriuretic peptide
FA	Fatty acid
FGF21	Fibroblast growth factor 21
FOXO1	Forkhead box protein O1
GDF-15	Growth differentiation factor-15
GLP1-RA	Glucagon-like peptide-1 receptor agonist
GMB	Gut microbiota
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFD	High fat diet
IGFBP7	Insulin-like growth factor binding protein 7
IPA	Indole-3-propionic acid
LCFAs	Long-chain fatty acids
L-NAME	Nω-Nitro-L-arginine methyl ester
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MCP1	Monocyte chemoattractant protein-1
NE-TLR4	Neutrophil elastase-toll-like receptor 4
NLRP3	NOD-like receptor family pyrin domain containing 3
NASH	Nonalcoholic steatohepatitis
NNMT	Nicotinamide *N*-methyltransferase
PCSK9	Proprotein convertase subtilisin/kexin type 9
PGC1-α	Peroxisome proliferator-activated receptor gamma coactivator 1-α
Saa1/4	Serum amyloid A1/A4
SCFAs	Short-chain fatty acids
SGLT2i	Sodium-glucose co-transporter 2 inhibitor
SIRT3	Silent information regulator 3
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor-α
TNFR1	Tumor necrosis factor receptor-1
UPAR	Urokinase plasminogen activator receptor

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LD contributes to the conception and design of the work; YYZ and LYL have drafted the work; LD, YYZ and LYL substantively revised it. All authors have approved the submitted version.

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

Declarations

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Not applicable.

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Competing interests
The authors declare no competing interests.

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