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STATE-OF-THE-ART REVIEW

Cardiac-Adipose Axis in Heart Failure With Preserved Ejection Fraction

Mechanisms and Therapeutics

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately 50% of heart failure cases and lacks effective treatment. Among its 5 phenotypes, obesity-related HFpEF is common and linked to higher cardiovascular mortality. However, the molecular mechanisms remain unclear. Research indicates that in patients with obesity-associated HFpEF, epicardial adipose tissue (EAT) is significantly increased, whereas non-EAT adipose tissue also exhibits pathologic distribution and accumulation. This review explores how the cardiac-adipose axis drives HFpEF pathophysiology. EAT is notably increased in these patients and contributes to diastolic dysfunction through pericardial restriction. Both EAT and non-EAT promote cardiac dysfunction via adipokines, inflammatory mediators, and oxidative stress. The review also highlights EAT thickness as a diagnostic marker and suggests a dual-screening approach combining waist-to-height ratio with NT-proBNP. Finally, potential adipose-targeted therapies based on clinical and preclinical evidence are summarized, providing a foundation for future treatment strategies. (JACC Asia. 2026;■:■–■)

Heart failure with preserved ejection fraction (HFpEF), characterized by a left ventricular (LV) ejection fraction of ≥50%, accounts for over 50% of all HF cases, with a 5-year mortality rate as high as 75.3%.[1,2] Based on different causes, HFpEF is divided into 5 phenotypes.[3] The fifth phenotype, driven by obesity and metabolic syndrome (MetS), shows higher cardiovascular mortality, with up to 80% of patients with HFpEF being overweight or obese.[4] Obesity is a chronic, relapsing, and progressive global epidemic.[5] In China, the prevalence of overweight and obesity has increased rapidly over the past 4 decades; 48.9% of adults are overweight or have obesity, which has become a major public health concern.[6-8]

Patients with obesity-related HFpEF commonly exhibit pathologic distribution and accumulation of adipose tissue, primarily manifesting as central obesity and a significant increase in epicardial adipose tissue (EAT),[9,10] which promotes metabolic dysfunction, oxidative stress, inflammation, and neuroendocrine dysregulation and leads to myocardial hypertrophy, fibrosis, and diastolic dysfunction.[11-15] These patients often have comorbidities such as MetS, hypertension, type 2 diabetes (T2D), chronic kidney disease, coronary artery disease, atrial fibrillation (AF), and hypercholesterolemia.[2,13,16,17] According to the adipokine hypothesis, HFpEF results from adipose accumulation, causing an imbalance in adipokine secretion.[18] Protective

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BMI = body mass index

EAT = epicardial adipose tissue

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LV = left ventricular

MetS = metabolic syndrome

RV = right ventricular

T2D = type 2 diabetes

VAT = visceral adipose tissue

WHtR = waist-to-height ratio

adipokines such as APN[11] and CTRP3[19] are downregulated, whereas others such as ACE2[15] and FGF21[11] are upregulated, representing an insufficient compensatory response. These findings highlight the critical role of the cardiac-adipose axis in HFpEF pathogenesis.

In summary, HFpEF continues to have high prevalence and mortality rates, and obesity is a prevalent and critical issue requiring urgent attention in this patient group (**Central Illustration**). This paper systematically elucidates the molecular mechanisms by which EAT and non-EAT contribute to the pathogenesis of HFpEF through the release of adipokines, nonadipokines, and inflammatory factors, triggering pathologic processes such as metabolic dysregulation, oxidative stress, inflammatory responses, and neuroendocrine dysregulation. It also discusses the clinical value of adipose tissue as a diagnostic marker for HFpEF and, based on existing clinical and preclinical studies, suggests the potential of targeting adipose tissue for HFpEF treatment, aiming to provide a theoretical basis for the development of future therapeutic strategies and drugs targeting adipose tissue.

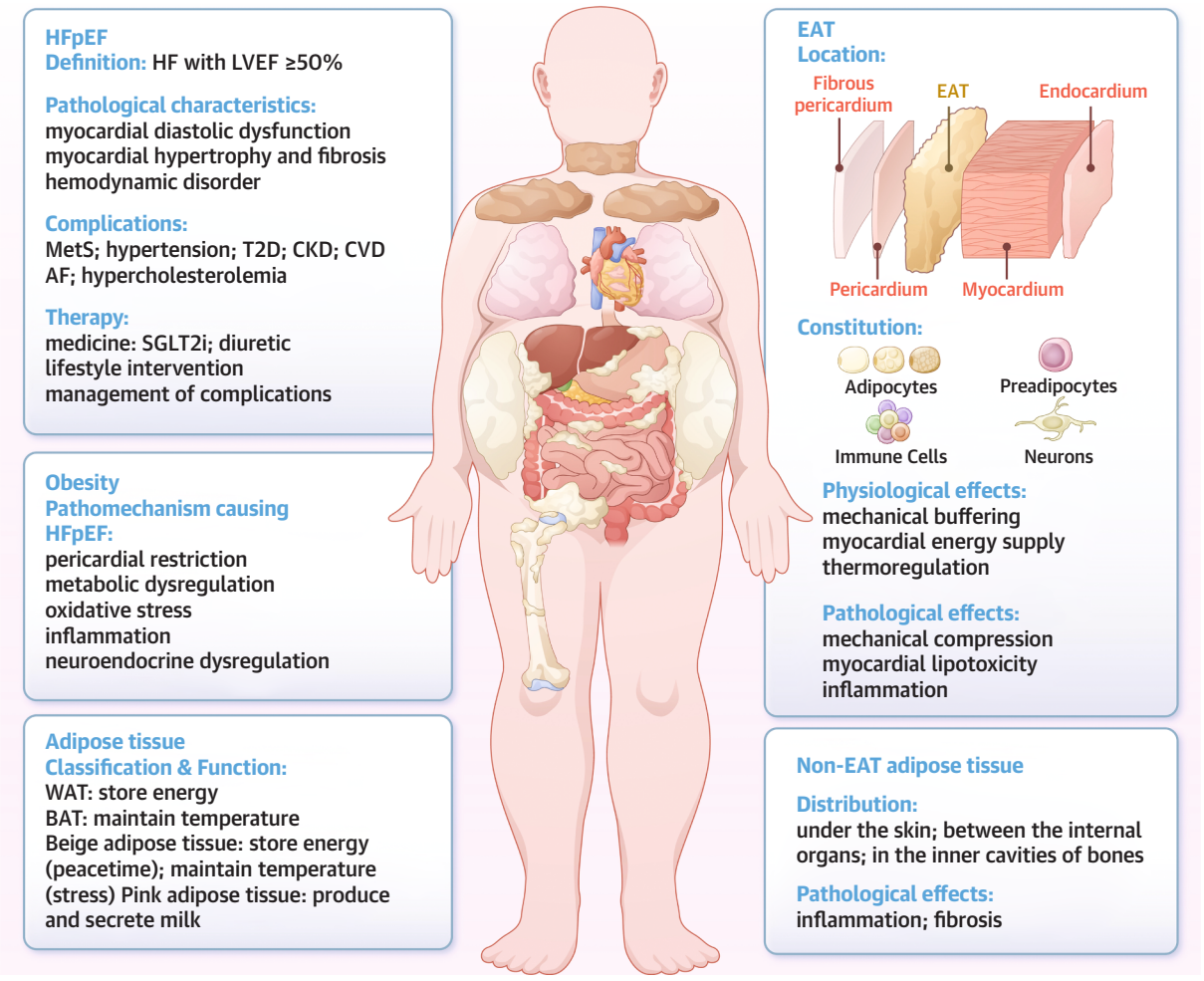
CLASSIFICATION AND PHYSIOPATHOLOGICAL CHARACTERISTICS OF ADIPOSE TISSUE

The adipose tissue of mammals primarily consists of 4 types of adipocytes: white, brown, beige, and pink adipocytes (**Central Illustration**).[20] White adipose tissue, predominantly composed of white adipocytes, is primarily distributed in visceral and subcutaneous depots, serving mainly as an energy reservoir while also participating in lipid secretion.[21] Visceral white adipose tissue increases the rate of triglyceride metabolism, whereas subcutaneous white adipose tissue decreases it, thereby predisposing patients to metabolic complications associated with overweight and obesity.[21] In healthy adults, brown adipose tissue is predominantly composed of brown adipocytes, which are most commonly distributed in the cervical region and supraclavicular area.[22,23] It primarily uses fuels such as fatty acids to maintain body temperature through UCP1-induced uncoupling of electron transport from adenosine triphosphate production.[24] Its activity declines under various pathologic conditions, including aging, obesity, and diabetes mellitus.[25] Browning is the process by which white adipocytes transform into beige adipocytes to form beige adipose tissue.[26] Upon cold exposure or other stimuli, it adopts a thermogenic phenotype resembling brown adipose tissue.[24,27] During pregnancy and lactation, white adipocytes in the mammary gland transdifferentiate into pink adipocytes, forming pink adipose tissue, which contributes to milk production and secretion.[28] The cellular composition of adipose tissue varies by anatomical location.

EPICARDIAL ADIPOSE TISSUE. EAT is the adipose tissue located between the myocardial surface and the visceral layer of the pericardium.[29] EAT directly contacts the myocardium and coronary arteries without fascial separation, exerting mechanical cushioning functions.[29,30] EAT shares a microvascular circulation system with the myocardium,[29] allowing its lipid metabolism–derived free fatty acid to serve as an energy source for the myocardium via paracrine pathways.[31] EAT primarily consists of adipocytes, nervous tissue, preadipocytes, and immune cells.[32] The adipocytes in EAT are predominantly white adipocytes yet uniquely demonstrate characteristics of both brown adipose tissue and beige adipose tissue, contributing to the thermoregulation of adjacent myocardium.[33,34] In pathologic conditions such as obesity, excessive expansion of EAT exerts mechanical compression on the heart, exacerbating ventricular filling abnormalities and cardiac work load, consequently leading to circulatory dysfunction.[35] Furthermore, excessive free fatty acid release from EAT induces myocardial free fatty acid overload, thereby triggering heart injury in cardiomyocytes.[36] Simultaneously, the macrophages derived from EAT exhibit a tendency to secrete profibrotic and proinflammatory adipokines.[30,37,38] Acting through paracrine pathways, these adipokines activate multiple signaling pathways in the heart, leading to metabolic, structural, and functional alterations in cardiomyocytes, which result in myocardial stiffness and diastolic dysfunction—manifesting the hallmark pathologic features of HFpEF.[30,33,39-41] Notably, the interplay between EAT and the heart is bidirectional because inflammatory responses within the myocardium can induce adipocyte dysfunction, immune cell infiltration, and accelerated fibrosis in the adjacent EAT.[30,32]

NON-EAT ADIPOSE TISSUE. Non-EAT adipose tissue, otherwise known as body fat, is connective tissue distributed throughout the body and includes subcutaneous adipose tissue under the skin, visceral adipose tissue (VAT) between the internal organs, and even bone marrow adipose tissue in the inner cavities of bones. It is primarily composed of white adipocytes, that is, white adipose tissue. Studies have demonstrated that VAT in patients with HFpEF

CENTRAL ILLUSTRATION **The Role of the Cardiac-Adipose Axis in HFpEF**



Tan R, et al. JACC Asia. 2026;■(■):■-■.

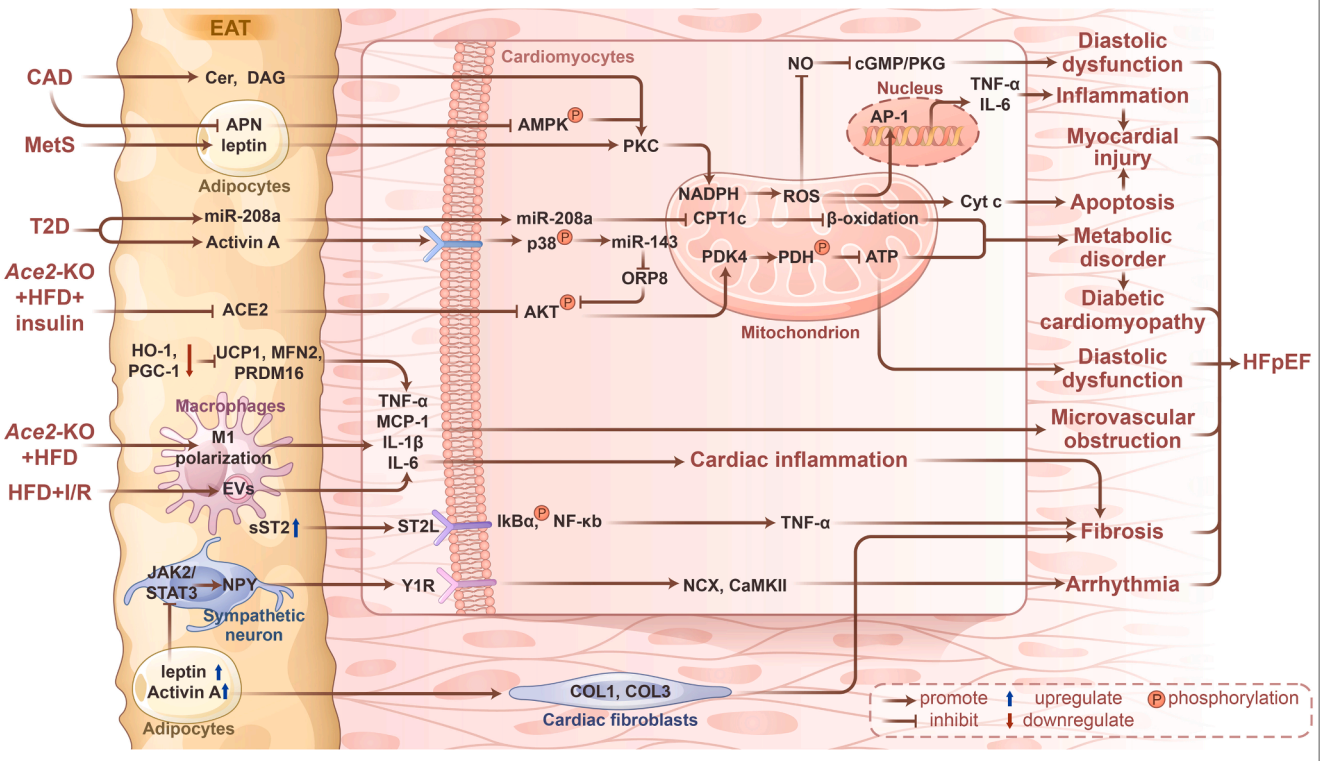
Excess adipose tissues including EAT and non-EAT adipose tissues contribute to HFpEF through pericardial restriction, metabolic dysregulation, oxidative stress, inflammation, and neuroendocrine dysregulation. AF = atrial fibrillation; CKD = chronic kidney disease; CVD = cardiovascular disease; EAT = epicardial adipose tissue; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; T2D = type 2 diabetes.

constitutes a significant source of proinflammatory cytokines, including TNF-α, IL-6, MCP-1, sST2, and OPN.[42-44] These proinflammatory cytokines collectively establish a robust proinflammatory and profibrotic network through 2 principal mechanisms: direct activation of profibrotic signaling pathways in cardiac fibroblasts and indirect induction of endothelial dysfunction coupled with cardiac macrophage infiltration.[44] This clearly explains the close association between central obesity and both HFpEF and cardiovascular mortality.[10,43] This also suggests that targeting adipose tissue and the associated inflammatory responses may represent a key area of research for the prevention and treatment of obesity-related HFpEF.[45-48]

THE UNDERLYING MECHANISMS OF ADIPOSE TISSUE-HEART CROSS TALK IN HFpEF

EAT CROSS TALKS WITH THE HEART TO PROMOTE HFpEF. Excessive EAT mediates cardiac diastolic dysfunction in HFpEF through pericardial restriction. In HFpEF, thickening of the EAT exacerbates pericardial restriction, leading to cardiac diastolic dysfunction

FIGURE 1 The Cross Talk Between Epicardial Adipose Tissue (EAT) and the Heart in Heart Failure With Preserved Ejection Fraction (HFpEF)



In coronary artery disease (CAD) and metabolic syndrome (MetS), down-regulated adiponectin (APN) in EAT induces oxidative stress in cardiomyocytes, thereby triggering diastolic dysfunction. EAT secretes miR-208a and Activin A, whereas the expression of angiotensin-converting enzyme (ACE)2 is suppressed, and both of these events induce metabolic disorders. Down-regulated HO-1 and PGC-1 treatment with *Ace2*-KO plus high-fat diet (HFD), or increased sST2 and Activin A, all lead to inflammation. High leptin expression inhibits the JAK2/STAT3 pathway in sympathetic neurons, thereby facilitating the release of NPY that acts on Y1R in cardiomyocytes, promoting the occurrence of arrhythmia. ATP = adenosine triphosphate; cGMP = cyclic guanosine monophosphate; IL = interleukin; MCP = monocyte chemoattractant protein; T2D = type 2 diabetes; TNF = tumor necrosis factor.

and consequent hemodynamic derangements. In female patients with HFpEF, the presence of a squared root sign on the right ventricular (RV) pressure waveform, which is associated with increased EAT, correlates with a higher right atrial pressure-to-pulmonary capillary wedge pressure ratio.[49] Compared to patients with HFpEF who have EAT ≤5 mm, those with EAT >5 mm exhibited lower three-dimensional RVEF and a more impaired peak tricuspid annular plane systolic excursion to systolic pulmonary arterial pressure ratio, indicating pericardial restriction-induced RV-arterial uncoupling, which exacerbates cardiac mechanical and hemodynamic compromise.[50] Furthermore, in patients with obesity-related HFpEF, those with increased EAT exhibit elevations in the LV eccentricity index, the ratio of right-sided to left-sided filling pressures, and the RV end-diastolic pressure, which also suggests the presence of enhanced pericardial constraint.[51] By attenuating wall stress and NT-proBNP release,[9] pericardial restriction initiates a pathophysiological sequence that promotes plasma volume expansion and ventricular remodeling, leading to hemodynamic compromise, and consequently, diminished exercise capacity.[9,51]

Excessive EAT mediates cardiac metabolic dysregulation in HFpEF via microRNAs and adipokines. EAT impairs cardiac metabolism and mitochondrial function via paracrine pathways (Figure 1). Gene expression related to zinc and copper ion metabolism within the mitochondrial respiratory chain (eg, *MT1E, MT2A, MT1X,* and *MT1G*) is significantly upregulated across nearly all major cell types in the EAT of adult patients with HF, suggesting a potential link between EAT and metabolism in the HF process.[52] Compared to insulin-infused normal mice on a high-fat diet, the further reduced phosphorylated AKT in the hearts of *Ace2* knockout mice increases phosphorylated PDH

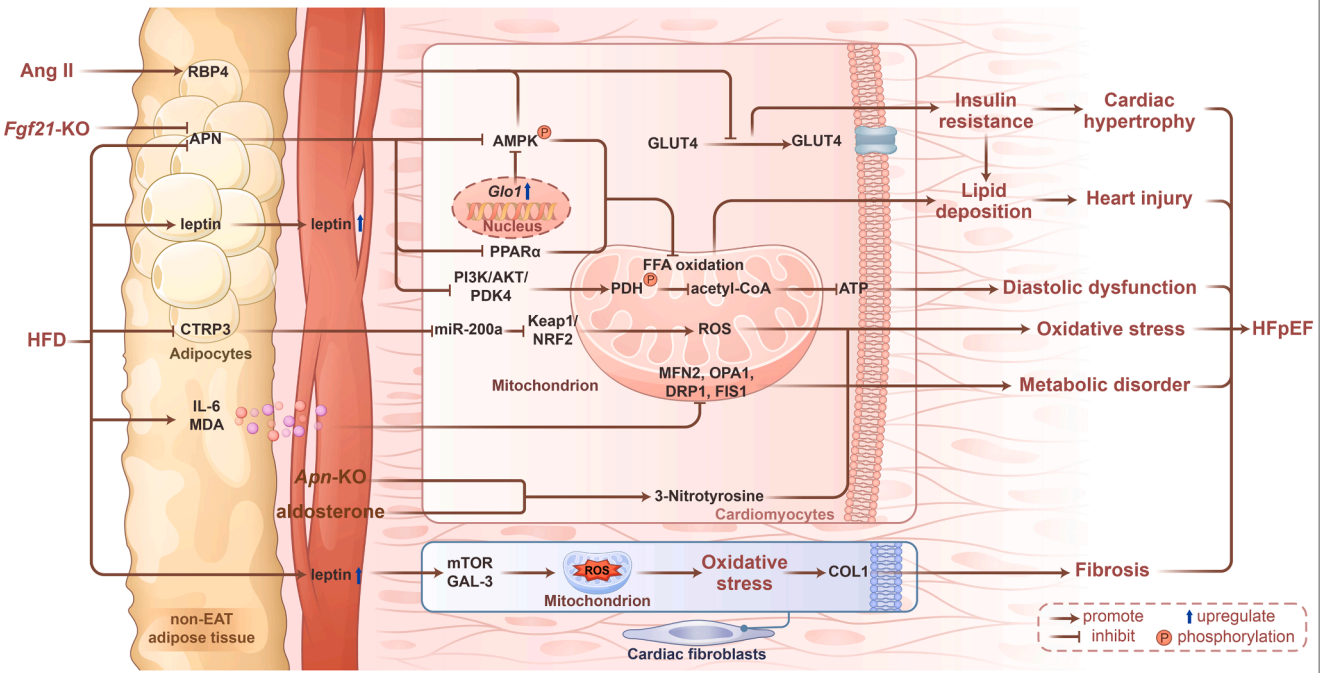
via upregulated PDK4.[15] This leads to a significant decrease in adenosine triphosphate production from glucose oxidation, ultimately contributing to the development of HFpEF through diastolic dysfunction.[15] In primary adult rat cardiomyocytes incubated with EAT-conditioned medium from patients with T2D, microRNA-208a was activated, leading to reduced expression of CPT1c and thereby impairing mitochondrial β-oxidation, which is associated with the development of diabetes-related cardiomyopathy.[53] Activin A released from T2D-associated EAT promotes cardiomyocyte p38 phosphorylation via a paracrine pathway, induces microRNA-143 expression, and subsequently reduces insulin-stimulated AKT phosphorylation and glucose uptake through downregulated ORP8, thereby contributing to the development of diabetic cardiomyopathy.[54]

Excessive EAT mediates myocardial oxidative stress in HFpEF via adipokines and free fatty acids. Within EAT, dysregulation of adipokines along with the release of free fatty acids leads to myocardial oxidative stress (**Figure 1**). In mice with MetS, leptin released from EAT activates the PKC/nicotinamide adenine dinucleotide phosphate oxidase/reactive oxygen species signaling pathway in cardiomyocytes.[55] The elevated expression of reactive oxygen species not only promotes AP-1 nuclear translocation, leading to increased IL-6 and TNF-α expression, but also causes mitochondrial swelling and cristae disruption, releasing cyt c to trigger cardiomyocyte apoptosis.[55] These processes collectively induce MetS-associated myocardial injury.[55] In patients with coronary artery disease, reduced APN expression in EAT suppresses myocardial AMPK phosphorylation,[56] whereas EAT-derived nonesterified fatty acids such as ceramide and diacylglycerol activate myocardial PKC,[57] with both pathways converging to upregulate nicotinamide adenine dinucleotide phosphate oxidase activity and generate excessive reactive oxygen species.[55,56] More importantly, the burst of reactive oxygen species reduces nitric oxide availability by generating peroxynitrite through reaction with nitric oxide and inducing endothelial nitric oxide synthase uncoupling, thereby downregulating the nitric oxide/cGMP/PKG signaling pathway and ultimately promoting the development of HFpEF.[58]

Excessive EAT mediates inflammation in HFpEF via inflammatory factors. Under pathologic conditions, the disorder of adipokines in EAT induces an inflammatory response, leading to cardiac remodeling and injury (**Figure 1**). Research in patients with HFpEF has shown a positive correlation between EAT thickening and levels of neutrophils and CRP.[59] In patients with HFpEF, the level of the inflammatory biomarker sST2 is also proportional to the thickness of EAT.[59] sST2 competes with fibroblast-derived IL-33 for binding to the ST2L receptor on cardiomyocytes.[60,61] This competition antagonizes IL-33 to suppress Ang II/phenylephrine-induced phosphorylation of IκBα and NF-κB activation, thereby promoting TNF-α expression and ultimately leading to cardiac fibrosis and hypertrophy.[60,61] *Ace2* knockout mice fed a high-fat diet demonstrated an expansion and M1 polarization of resident macrophages within the EAT, which subsequently secreted proinflammatory factors (TNF-α, MCP-1, IL-1β, and IL-6), triggering cardiac inflammation and fibrosis and eventually resulting in HFpEF.[15] Both diastolic dysfunction and HFpEF prevalence correlate positively with levels of the proinflammatory adipokine Activin A.[62] In patients undergoing coronary artery bypass grafting, adipose tissue–secreted Activin A is increased, which subsequently activates fibroblasts through paracrine pathways, inducing expression of COL1 and COL3, thereby promoting myocardial fibrosis.[63] In these patients, decreased levels of PGC-1 and HO-1 in the EAT suppress UCP1, PRDM16, and MFN2 expression; this mitochondrial dysfunction subsequently triggers the release of nitric oxide, IL-4, and TNF-α, a process also linked to cardiac dysfunction.[64] Additionally, in mice fed a high-fat diet subjected to cardiac ischemia/reperfusion, the high-burden EAT promoted microvascular obstruction by releasing extracellular vesicles, which led to inflammatory cell recruitment, M1 macrophage polarization, an increased profile of IL-6, IL-1β, and TNF-α, and a decreased profile of IL-10 and TGF-β.[38]

Excessive EAT mediating cardiac dysfunction in HFpEF via neuroendocrine dysregulation. EAT-induced neuroendocrine dysregulation might contribute to the pathogenesis of HFpEF (**Figure 1**). The high prevalence and frequent coexistence of HFpEF and AF indicate a strong association between them, pointing to possible shared mechanisms in their development.[65,66] Coculture experiments using sympathetic neurons, cardiomyocytes, and EAT from patients with AF demonstrated that EAT-derived leptin promotes NPY release from sympathetic neurons via the inhibited JAK2/STAT3 pathway, with NPY subsequently binding to the cardiomyocyte Y1 receptor, enhancing NCX and CaMKII activity, and ultimately triggering arrhythmias.[67] An increase in EAT in patients with cardiovascular disease can lead to elevated expression levels of AGT.[68] Furthermore, studies in a mouse model of HFpEF induced by a high-fat diet combined with N[ω]-nitro-l-arginine methyl ester treatment have revealed that increased AGT in the liver and plasma acts on cardiac endothelial cells

FIGURE 2 Non-Epicardial Adipose Tissue (EAT) Mediates Heart Failure With Preserved Ejection Fraction (HFpEF) Through Metabolic Dysregulation and Oxidative Stress



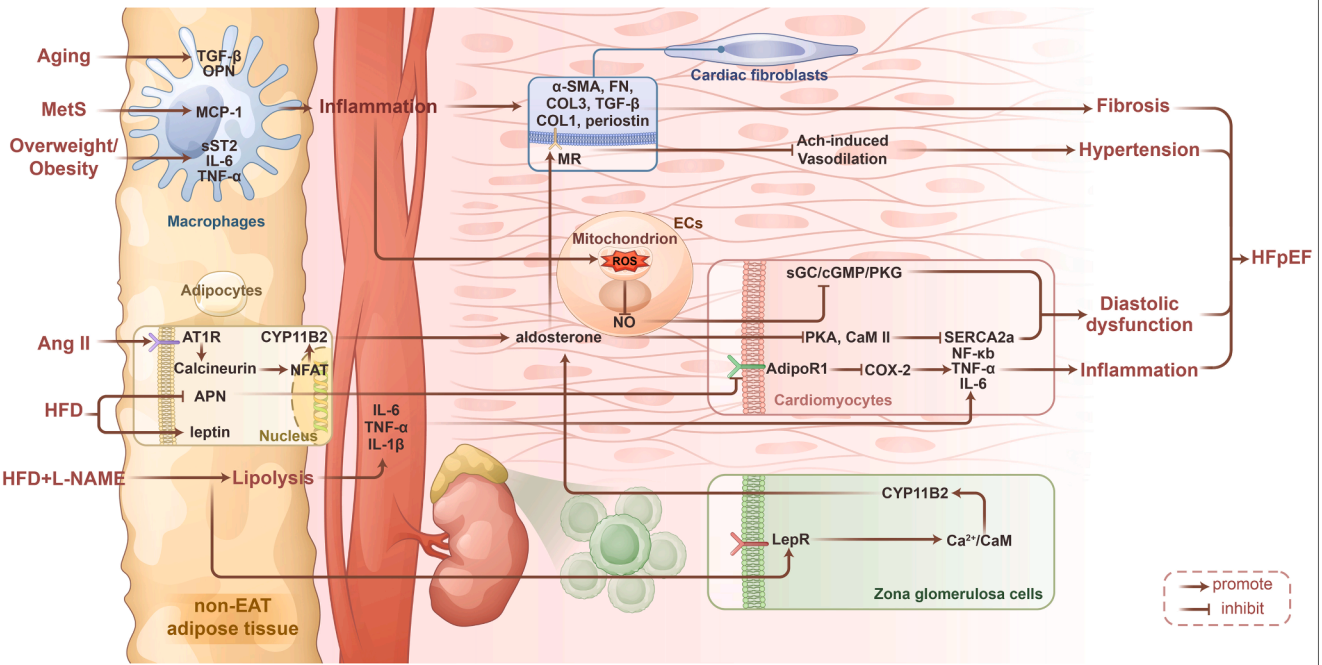
In adipocytes of non-EAT, Ang II, *Fgf*21-KO, and high-fat diet (HFD) promote the release of RBP4 and leptin into the bloodstream while inhibiting the secretion of APN and CTRP3. This leads to metabolic dysfunction and oxidative stress in cardiomyocytes, as well as oxidative stress in cardiac fibroblasts, ultimately contributing to the development of HFpEF. Furthermore, a high-fat diet also stimulates the release of IL-6 and MDA from non-EAT adipose tissue, resulting in metabolic disorder in cardiomyocytes and subsequent progression to HFpEF. ATP = adenosine triphosphate; HFpEF = heart failure with preserved ejection fraction; IL = interleukin.

via the LRP2, suppressing the GATA2/PIM3 signaling axis, which subsequently impairs cardiac microvascular generation, ultimately exacerbating diastolic dysfunction and promoting the development of HFpEF.[69] Hence, we hypothesize that EAT might elevate AGT expression and thus promote the pathogenesis of HFpEF.

NON-EAT ADIPOSE TISSUE CROSS TALKS WITH THE HEART TO PROMOTE HFpEF. **Non-EAT adipose tissue mediates cardiac metabolic dysregulation in HFpEF through adipokines.** Alterations in the adipose tissue secretome play a critical role in the pathogenesis of cardiometabolic disorders (Figure 2). In *Fgf21*-knockout HFpEF mice, reduced APN production from adipocytes impaired the activation of the cardiomyocyte PI3K/AKT/PDK4 axis, leading to PDH phosphorylation and inactivation and reduced acetyl coenzyme A and adenosine triphosphate production and ultimately inducing diastolic dysfunction.[11] A high-fat diet also reduces myocardial APN levels in mice, leading to decreased activity of AMPK and PPARα.[70] Research shows that AMPK and PPARα are related to free fatty acid oxidation and lipid deposition, and numerous studies indicate that these processes in the heart promote the development of HFpEF.[15,31,56,70] In mice with Ang II-induced cardiac hypertrophy, increased secretion of RBP4 from adipocytes impairs GLUT4-mediated glucose uptake in cardiomyocytes, leading to insulin resistance.[71] Similarly, in spontaneously hypertensive rats, decreased membrane translocation of GLUT4 in the heart and white adipose tissue leads to insulin resistance via reduced AMPK phosphorylation resulting from increased *Glo1* activity.[72] In Lee-Sung minipigs fed a high-fat diet, the increased levels of IL-6 and malondialdehyde in VAT and pericardial fat altered the secretion profile of adipose tissue and inhibited the expression of mitochondria-related autophagy proteins (MFN2, OPA1, DRP1, and FIS1) in cardiomyocytes in conditioned medium, leading to reduced adenosine triphosphate production and ultimately causing cardiac dysfunction.[73]

Non-EAT adipose tissue mediate cardiac oxidative stress in HFpEF through adipokine. Adipokine imbalance contributes to cardiac oxidative stress (Figure 2).

FIGURE 3 **Non-Epicardial Adipose Tissue (EAT) Mediates Heart Failure With Preserved Ejection Fraction (HFpEF) Through Inflammation and Neuroendocrine Disorders**



Aging, metabolic syndrome (MetS), overweight/obesity, and a high-fat diet (HFD) + L-NAME promote the release of inflammatory factors from non-EAT adipose tissue. This leads to collagen release from cardiac fibroblasts, inflammatory responses in cardiomyocytes, and endothelial dysfunction, ultimately resulting in cardiac diastolic dysfunction and the development of HFpEF. Ang II stimulation promotes aldosterone release from adipocytes within non-EAT adipose tissue. In addition, a HFD induces leptin expression in adipocytes, which in turn stimulates aldosterone secretion from zona glomerulosa cells of the adrenal cortex. These processes contribute to hypertension and cardiac diastolic dysfunction, ultimately leading to HFpEF. APN = adiponectin; IL = interleukin; MCP = monocyte chemoattractant protein; TNF =tumor necrosis factor.

Apn knockdown exacerbates the pathology of hypertensive HFpEF by enhancing aldosterone-induced myocardial 3-nitrotyrosine formation and promoting oxidative stress.[74,75] In mice with high-fat diet-induced HFpEF, reduced adipose tissue secretion of CTRP3 downregulates cardiomyocyte microRNA-200a expression, impairing Keap1 mRNA-mediated NRF2 activation, leading to excessive reactive oxygen species generation and oxidative stress, and ultimately exacerbating myocardial injury.[19] Rats with high-fat diet-induced obesity show increased levels of leptin in both serum and cardiac tissue.[76] Cardiac leptin activates mTOR and upregulates GAL-3 in fibroblasts, triggering reactive oxygen species production, which mediates the synthesis of COL1 and ultimately leads to interstitial fibrosis.[76]

Non-EAT adipose tissue mediates inflammation in HFpEF through inflammatory factors. Inflammatory factors derived from adipose tissue lead to diastolic dysfunction both through the indirect route of inducing a systemic inflammatory response and through the direct action of causing myocardial inflammation and fibrosis (**Figure 3**). HFpEF features a distinct obesity-inflammation phenotype, characterized by high circulating levels of inflammatory mediators (VCAM-1, IL-6, TNF-α, IFN-γ, IL-1β, MCP-1), which is linked to elevated fibrotic biomarkers (PIIINP, CITP, GAL-3, IGFBP-7) and greater HF severity.[77,78] Male mice on a high-fat diet and with N[ω]-nitro-l-arginine methyl ester-induced HFpEF showed increased lipolysis and elevated release of IL-6, IL-1β, and TNF-α from gonadal white adipose tissue, which was correlated with the presence of diastolic dysfunction and LV hypertrophy.[79] Comorbidities such as overweight/obesity trigger a systemic proinflammatory state (elevated IL-6, TNF-α, and sST2), which increases reactive oxygen species and decreases nitric oxide in endothelial cells, thereby mediating downregulation of sGC/cGMP/PKG pathway in cardiomyocytes, leading to diastolic dysfunction and HFpEF progression.[80] Aging-induced upregulation of OPN and TGF-β in

epididymal white adipose tissue activates cardiac fibroblasts, promoting the expression of α-SMA, FN, and COL3, leading to interstitial fibrosis and HFpEF.[81] In rats with MetS, macrophage infiltration occurs in the retroperitoneal adipose tissue and LV, accompanied by increased expression of MCP-1 and OPN, which then induce LV hypertrophy, fibrosis, and diastolic dysfunction through endocrine and paracrine pathways by upregulating cardiac COL1, COL3, and TGF-β.[44] Additionally, APN levels were significantly reduced in the serum of patients with HFpEF.[11] In rats on a high-fat diet, reduced APN downregulates COX-2 expression through myocardial AdipoR1, triggering an inflammatory response with elevated NF-κB, TNF-α, and IL-6 and leading to cardiac remodeling.[82]

Non-EAT adipose tissue mediates cardiac dysfunction in HFpEF via neuroendocrine dysregulation. Adipose tissue contributes to the pathogenesis and progression of HFpEF by modulating the renin-angiotensin-aldosterone system (**Figure 3**). In patients with HFpEF, adipose tissue-derived leptin levels are elevated.[83,84] Animal experiments have further demonstrated that either aldosterone infusion alone or leptin receptor deficiency alone induced only mild diastolic dysfunction in mice, whereas a combination of 4-week aldosterone infusion and leptin receptor deficiency led to obesity, cardiac hypertrophy, and significant diastolic dysfunction and ultimately manifested as HFpEF.[12] Leptin acts on leptin receptors on the zona glomerulosa cells of the adrenal cortex in high-fat diet mice, subsequently increasing the expression of CYP11B2 and aldosterone release through up-regulation of calcium/CaM, ultimately leading to increased cardiac COL1 and periostin expression via mineralocorticoid receptors, resulting in myocardial fibrosis.[85] Leptin mediates the impairment of acetylcholine-induced vasodilation through the CYP11B2/aldosterone pathway in female agouti yellow obese hyperleptinemic mice, resulting in elevated blood pressure.[86] Studies have demonstrated that Ang II plays a critical role in the pathogenesis of HFpEF associated with hypertension and diabetes.[87] In a diabetic-obese mouse model, Ang II binding to Ang II type 1 receptor in adipocytes activates the calcineurin/NFAT pathway, up-regulating CYP11B2 expression and stimulating aldosterone production.[88] Studies also indicate that aldosterone infusion systemically down-regulates the cardiac β-adrenergic pathway in uninephrectomized mice, characterized by decreased PKA and CaMKII activity, resulting in suppressed SERCA2a expression and consequent diastolic dysfunction leading to HFpEF.[74]

DIAGNOSTIC VALUE AND THERAPEUTIC POTENTIAL OF EAT/non-EAT IN HFpEF

DIAGNOSTIC VALUE. The thickness of EAT as a diagnostic indicator of HFpEF. EAT has been demonstrated to be an independent risk factor for HFpEF and exhibits greater prognostic value than LVEF and NYHA functional classification.[89,90] Studies have shown that in patients with HFpEF, EAT thickness measured by transthoracic echocardiography is inversely correlated with LV function.[91] EAT, predominantly located around the RV free wall on echocardiography, is measured in the parasternal long-axis view, with a thickness ≥9 mm defined as increased.[92] Echocardiographically measured EAT thickness has emerged as a novel marker of cardiac and visceral adiposity and may aid in cardiometabolic risk stratification.[93] In the multicenter, prospective PROMIS-HFpEF (a cohort that study prevalence of microvascular dysfunction in HFpEF), patients with increased echocardiographically measured EAT exhibited a distinct clinical profile characterized by a higher body mass index (BMI), lower NT-proBNP levels, smaller indexed LV and left atrial volumes, and a lower Kansas City Cardiomyopathy Questionnaire clinical summary score.[92] In summary, using echocardiography to measure EAT thickness might have some clinical value in predicting, diagnosing, and assessing prognosis in HFpEF.

Waist-to-height ratio (WHtR) combined with NT-proBNP: a dual-parameter screening strategy. The PARAGON-HF trial (a study that prospectively compares the overall efficacy of ARNI and ARB in heart failure patients with a ejection fraction of 45% or higher) demonstrated that 49% of patients with HFpEF were classified as obese (BMI ≥30 kg/m^2), whereas 96% had central obesity (WHtR ≥0.5).[10] Moreover, patients with HFpEF and central obesity have a significantly higher risk of all-cause mortality than those without central obesity.[94] Thus, compared with BMI, the WHtR serves as a superior predictor of abdominal adiposity and holds broader clinical utility in the diagnosis and management of HFpEF.[10,95] The WHtR ratio showed a linear relationship with HFpEF risk, where increasing values were associated with a higher likelihood of the disease, translating to improved identification of high-risk individuals.[10,96] Moreover, a higher WHtR has been demonstrated to be an independent risk factor for all-cause mortality in Chinese patients with HFpEF.[97]

NT-proBNP levels have diagnostic and prognostic value in patients with HF.[98-100] Although NT-proBNP levels are elevated in both HFpEF and HF with reduced ejection fraction compared to healthy

controls, the degree of elevation is typically less marked in HFpEF than in HF with reduced ejection fraction.[9,92,101] Compared with patients with HFpEF who do not have obesity, those with obesity exhibit lower NT-proBNP levels.[9,92,101] Furthermore, in patients with metabolic diseases, elevated BNP/NT-proBNP levels are associated with increased EAT thickness, whereas they demonstrate an inverse relationship with BMI.[102,103] These findings indicate that NT-proBNP levels are, to a certain degree, affected by obesity. The relative reduction in NT-proBNP levels in patients with obesity-related HFpEF may be associated with three mechanisms—1) Decreased NT-proBNP production: This results from pericardial restriction caused by markedly increased EAT in patients with obesity-related HFpEF, which reduces NT-proBNP release by decreasing myocardial wall stress.[9] 2) Increased natriuretic peptide clearance: Diet-induced fat accumulation enhances adipocyte expression of natriuretic peptide clearance receptor and enkephalinase.[104-106] 3) Adipokine dysregulation in patients with obesity-related HFpEF may interfere with NT-proBNP metabolism.

Based on the close associations of a waist-to-height ratio and NT-proBNP with HFpEF and obesity, we propose a screening strategy using the combination of a WHtR and NT-proBNP. Given that NT-proBNP levels correlate with muscle mass,[101] whereas the WHtR is independent of bone or muscle mass,[10] this complementary profile enhances the robustness of a combined screening strategy.

THERAPEUTIC POTENTIAL. Current clinical practice guidelines for HFpEF management primarily include three aspects: first, pharmacologic treatments such as SGLT2 inhibitors and diuretic agents; second, lifestyle interventions such as weight loss and exercise; and third, management of comorbidities such as hypertension control.[107,108] Although several drug classes (GLP-1 receptor agonists,[109] ARNI,[110] MRAs,[111] and SGLT2 inhibitors[112]) have shown clinical benefits in HFpEF—and approaches such as Fgf21,[11] Apn,[74] or melatonin[19] have shown promise in animal models—no approved therapy has yet reduced all-cause mortality. Moreover, effective treatments specifically for obesity-related HFpEF are lacking, and traditional HF drugs (eg, beta-blockers) may be ineffective or harmful because of the high heterogeneity of HFpEF.[111,113-115]

Exercise therapy may improve HFpEF by reducing VAT. Exercise therapy has also demonstrated favorable clinical benefits in patients with HFpEF. In 2023, 60 randomized trials involving over 8,500 patients with HF indicated that exercise-based cardiac rehabilitation reduces the risk of all-cause hospitalization in both the short and long term and improves health-related quality of life as measured by the Minnesota Living With Heart Failure total score.[116] This suggests that exercise-based cardiac rehabilitation may also be beneficial for patients with HFpEF. Assessing the 6-minute walk distance and peak oxygen uptake, the study finds that exercise training significantly improves the physical quality of life in patients with HFpEF, with high-intensity interval training and moderate continuous training showing comparable effects.[117] One year of endurance combined with resistance training improves clinical parameters in patients with HFpEF, including peak oxygen uptake and NYHA functional class.[118] Furthermore, studies have shown that the significant improvement in symptoms and quality of life in patients with HFpEF resulting from exercise is associated with the reversal of atrial remodeling and LV diastolic function.[119] Additionally, exercise effectively reduces VAT and waist circumference in patients who are overweight and those with obesity,[120] which may offer greater benefits for those with obesity-related HFpEF. Research has been conducted in older patients with obesity and stable HFpEF, and the results show that caloric restriction, exercise, and the combination of exercise and caloric restriction can all reduce body weight, decrease adipose tissue, improve exercise capacity, and enhance quality of life.[121] However, current evidence regarding exercise interventions specifically for patients with obesity-related HFpEF remains insufficient. Whether exercise can improve cardiac function by reducing VAT and subsequently influencing systemic metabolism requires further investigation. Moreover, determining how to establish safe and effective exercise intensity for these patients remains a significant challenge that needs to be addressed.

GLP-1 receptor agonists improve HFpEF by reducing VAT. GLP-1 receptor agonists, such as liraglutide, somapacitan, and semaglutide, demonstrate pleiotropic benefits in patients with obesity-related HFpEF, irrespective of diabetes status (**Table 1**). This class of drugs effectively reduces body weight, CRP, and NT-proBNP levels; improves ventricular remodeling, Kansas City Cardiomyopathy Questionnaire clinical summary score, and 6-minute walk distance; and lowers the risk of the composite endpoint of cardiovascular death or worsening HF events.[17,109,122-125] GLP-1 receptor agonist therapy also reduces loop diuretic dosage in these patients, which demonstrates a linear relationship with the increase in Kansas City Cardiomyopathy Questionnaire clinical summary score and the reductions in

TABLE 1 Clinical and Preclinical Therapeutic Strategies Targeting Adipose Tissue to Alleviate HFpEF

Therapeutic Strategy	Disease (Models)	Species	Target	Effect	References
GLP-1 receptor agonist (semaglutide)	Patients with obesity-related HFpEF	Human	VAT	Reduces CRP, inflammation, NT-proBNP and body weight; improves 6-minute walk distance, the hierarchical composite endpoint and Kansas City Cardiomyopathy Questionnaire clinical summary score; attenuates progression of left atrium remodeling and RV enlargement; reduces the risk of the composite endpoint of cardiovascular death or worsening HF events and worsening HF events	17,109,122-126, 146
GLP-1 receptor and GIP dual receptor agonist (tirzepatide)			EAT and VAT	Decreases LV mass, body weight, visceral adiposity, EAT, and the occurrence of cardiovascular death or worsening HF events; improves 6-minute walk distance, 5-level European quality of life-5 dimensions health index, and NYHA functional class	127,128
GLP-1 receptor agonists, plus SGLT2 inhibitors			EAT and VAT	Lowers risk of HF exacerbations, all-cause emergency department visits/ hospitalizations, new-onset atrial arrhythmias, new-onset acute kidney injury, and pulmonary hypertension	129
SGLT2 inhibitors (dapagliflozin/ empagliflozin)			EAT and VAT	Reduces EAT, LV mass, BMI, CRP, and BNP; reduces the combined risk of cardiovascular death or worsening HF events across the spectrum of age; improves 6-min walking distance and Kansas City Cardiomyopathy Questionnaire clinical summary score	130-133
SGLT2 inhibitors + nonsteroidal mineralocorticoid receptor antagonists			EAT	Reduces the risk of the primary endpoint of cardiovascular death or first worsening HF event	139
Adeno-associated virus-*Fgf 21*	*Fgf21*KO mice with obesity-related HFpEF	Mice	Adipokine	Elevates circulating FGF21 levels, inhibits *Anp*, *Bnp*, and *Myh7* mRNA expression, enhances mitochondrial bioenergetics, and reverses *Fgf21* deficiency-induced cardiac diastolic dysfunction, cardiac hypertrophy, cardiac oxidative stress, and cardiac fibrosis	11
Atgl knockout	Male mice with obesity-related HFpEF		Adipose tissue	Inhibits adipose tissue lipolysis and improves obesity-related inflammation, cardiac remodeling, and dysfunction	79
Adenovirus-APN	Mice with aldosterone-induced HFpEF		Adipokine	Improves LV cardiomyocyte hypertrophy, myocardial fibrosis, and oxidative stress	74
Melatonin	Mice with obesity-related HFpEF		Adipokine	Increases CTRP3, improves diastolic function, attenuates oxidative stress and apoptosis, and body weight gain, and reduces *Anp* and *Bnp* mRNA expression and LV end-diastolic pressure	19
AdipoRon			Receptors of adipokines	Up-regulates AdipoR1/2, reduces lipid droplet accumulation, alleviates fibrosis, cardiac diastolic function, functional phenotype, and glucose intolerance, and restores the balance of myocardial fatty acid intake, transport, and oxidation	70
Ang 1-7	*ACE2*KO-high-fat diet mice with HFpEF		EAT	Improves EAT inflammation and cardiac insulin resistance, reduces ANP, BNP, and LV end-diastolic pressure, and improves active relaxation and passive stiffness	15

BMI = body mass index; EAT = epicardial adipose tissue; HFpEF = heart failure with preserved ejection fraction; HF = heart failure; LV = left ventricular; RV = right ventricular; VAT = visceral adipose tissue.

body weight and CRP.[126] In addition, tirzepatide, a dual GLP-1 receptor and glucose-dependent insulinotropic polypeptide receptor agonist, has also demonstrated beneficial effects in patients with obesity-related HFpEF. This agent reduces VAT and body weight, lowers LV mass, and similarly improves quality of life, NYHA functional class, and the risk of adverse HF outcomes.[127,128] Studies have shown that among patients with cardiovascular disease, those with greater EAT thickness exhibit higher gene expression levels of the GLP-1 receptor.[32] This may represent a potential therapeutic target for GLP-1

receptor-based interventions. In patients with HFpEF who are overweight or who have obese HFpEF with T2D, adding a GLP-1 receptor agonists to SGLT2 inhibitor therapy significantly lowered the risk of HF worsening, hospitalizations, atrial arrhythmias, acute kidney injury, and pulmonary hypertension compared to SGLT2 inhibitors alone.[129]

SGLT2 inhibitors improve HFpEF by reducing EAT and VAT. SGLT2 inhibitors, such as empagliflozin and dapagliflozin (Table 1), are a class of agents that improve exercise capacity and reduce the risk of the composite endpoint of worsening HF and cardiovascular death in patients with HFpEF.[130-133] SGLT2 inhibitors reduce adipocyte hypertrophy and adipose tissue expansion in EAT and VAT under cardiovascular and diabetic conditions by improving metabolism and decreasing the secretion of proinflammatory chemokines.[134,135] By stabilizing mitochondrial function and attenuating inflammatory and fibrotic pathways in the heart, SGLT2 inhibitors lower the ratio of early diastolic mitral inflow to early diastolic mitral annular velocity, mean arterial pressure, and LV filling pressures, resulting in improved diastolic function in HFpEF.[46,136,137] Additionally, SGLT2 inhibitors can improve volume overload in HFpEF through osmotic diuresis and reduce the dosage of diuretic agents required.[138,139]

The inhibitors of PCSK9 may improve HFpEF by targeting EAT. Research has demonstrated that PCSK9 inhibitors can reduce the risk of HF by lowering levels of LDL-C and ApoB, which are pivotal in coronary heart disease pathogenesis.[140] When LDL-C levels are below 20 mg/dL or even in single digits, PCSK9 inhibitors can significantly reduce the risk of cardiovascular events.[141] However, whether PCSK9 inhibitors can improve HFpEF by targeting EAT has not been reported. Cardiac PCSK9 deficiency impairs mitochondrial electron transport chain-associated protein expression, thereby reducing tricarboxylic acid cycle flux and fatty acid oxidation, which forces a shift to an aerobic metabolism and ultimately promotes lipid accumulation and heart injury.[115] This suggests that inhibiting cardiac PCSK9 may exacerbate cardiac dysfunction. Currently, clinically available PCSK9-targeted therapies, primarily monoclonal antibodies and gene-silencing approaches, function by inhibiting PCSK9 in the liver or circulation without directly affecting cardiac metabolism or function.[115] However, these conflicting findings require extensive further validation through animal studies and analysis of clinical samples, and whether they can be translated into clinical applications necessitates more evidence.

Preclinical studies on targeting adipose tissue or adipokines to improve HFpEF. Adipose triglyceride lipase inhibitors can specifically inhibit lipolysis, improving inflammation, insulin resistance, cardiac remodeling, and diastolic dysfunction in male mice with obesity-related HFpEF.[79] Treatment with Ang1-7 reduces EAT inflammation and ameliorates cardiac insulin resistance in *Ace2*KO mice fed a high-fat diet (Table 1), thereby preventing the development of obesity-related HFpEF.[15] Furthermore, overexpression of *Fgf21* significantly alleviates diastolic dysfunction, pulmonary congestion, and exercise intolerance in mice with obesity-related HFpEF by improving cardiac mitochondrial function, reducing oxidative stress, and attenuating cardiac fibrosis.[11] Melatonin therapy reduces myocardial oxidative stress and apoptosis by increasing adipose tissue CTRP3 secretion, thereby attenuating obesity-related HFpEF.[19] Treatment with adenovirus-*Apn* improves oxidative stress, myocardial hypertrophy, and diastolic dysfunction in aldosterone-induced HFpEF mice.[74] Additionally, the AdipoR agonist reduces excessive myocardial lipid accumulation and cardiac interstitial fibrosis in mice by upregulating the AdipoR in the myocardium and also improves HFpEF.[70]

In summary, exercise, GLP-1 receptor agonists, and SGLT2 inhibitors are all clinically valuable for obesity-related HFpEF. Exercise reduces visceral fat and improves heart function. GLP-1 agonists promote weight loss and reduce heart inflammation. SGLT2 inhibitors decrease heart and belly fat, improve heart metabolism, and help with fluid control. Since GLP-1 agonists and SGLT2 inhibitors are already widely used for diabetes with good safety records and are included in HFpEF guidelines, they hold strong promise for treating obesity-related HFpEF. In contrast, other cardiovascular drugs need careful evaluation. PCSK9 inhibitors may worsen fat buildup and heart damage, and beta-blockers may be ineffective or harmful in HFpEF. Finally, several promising preclinical treatments (such as Fgf21, melatonin, and *Apn*) still need more clinical evidence to prove they can safely target fat without disrupting overall body balance (Table 1).

CONCLUSION AND PERSPECTIVE

Obesity and metabolic disorders are among the primary risk factors for HFpEF. Hence, the management of obesity and metabolic diseases is a key strategy for treating HFpEF as a prevalent public health issue. Obesity is a major global health crisis. In 2021, 2.11

HIGHLIGHTS

- HFpEF accounts for approximately 50% of HF cases; 80% of these patients are overweight or obese.
- Obesity-associated HFpEF increased EAT and redistributed non-EAT adipose.
- EAT thickness shows great potential as a diagnostic marker.
- Combining WHtR with NT-proBNP serves as an early screening indicator of HFpEF.
- Exercise and weight-loss medications are beneficial for obesity-associated HFpEF.

billion adults worldwide (45.1%) were overweight or obese, including 402 million in China. By 2050, this is projected to reach 3.8 billion (60% of adults), with 627 million in China.[142] Obesity increases pericardial restriction through elevated EAT, raising cardiac pressure and impairing diastolic function. Simultaneously, VAT contributes to the pathogenesis and progression of HFpEF by releasing adipokines, non-adipokines, and inflammatory factors, which lead to cardiac metabolic dysregulation, oxidative stress, and inflammatory responses and mediate neuroendocrine dysregulation. Additionally, VAT influences EAT through releasing proinflammatory factors and free fatty acids,[143] creating a vicious cycle that drives HFpEF development. Based on these mechanisms, we propose that targeting these inflammatory factors may be a promising treatment strategy for obesity-related HFpEF.

Notably, both *Ace2* knockout and *Fgf21* knockout can attenuate the cardiac AKT/PDK4/PDH axis, thereby improving insulin resistance and metabolism. Whether leptin up-regulation or APN down-regulation occurs in EAT, both can activate the myocardial AMPK/PKC/nicotinamide adenine dinucleotide phosphate oxidase/reactive oxygen species axis, inducing oxidative stress. This suggests that targeting these common pathways may have better therapeutic value. Given that current research on adipokines largely remains at the stage of clinical observation, future studies should further elucidate how adipokines precisely regulate the functions of EAT, cardiomyocytes, and fibroblasts and their interaction networks, which could provide more precise therapeutic targets for obesity-related HFpEF.

Interestingly, there are notable sex differences in the incidence of obesity-related HFpEF. Men and women without obesity have similar HFpEF risk, but women with obesity have a higher risk than men with obesity, and the risk is more strongly linked to BMI in women.[16] In HFpEF, there are more women among severely obese patients compared to those with mild obesity.[122,144] This may be attributed to the sex-specific differences in adipose tissue distribution observed in obesity. In female patients with HFpEF, intramyocardial fat shows a significant correlation with poorer LV diastolic function parameters, such as the ratio of early diastolic mitral inflow to early diastolic mitral annular velocity and left atrial volume index,[144] both pulmonary capillary wedge pressure and right atrial pressure during exercise demonstrated a positive correlation with VAT area.[145] However, in men with HFpEF, EAT is associated with certain LV diastolic parameters, including left atrial volume index and LV peak filling rate.[144]

Given the complexity of adipose tissue–mediated mechanisms in HFpEF pathogenesis and the current insufficiency of evidence, future research should prioritize elucidating the specific mechanisms and interactive regulatory networks involving adipokines. This will aid in developing treatment strategies for obesity-related HFpEF, strengthen obesity monitoring and management in this study group, and ultimately improve quality of life and reduce mortality.

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