

METHODOLOGY AND MECHANISMS CORNER

Excess and Dysfunctional Fat as a Primary Driver of Heart Failure With Preserved Ejection Fraction



From Institutional Recognition to Clinical Integration

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HIGHLIGHTS

- The American Heart Association identifies dysfunctional fat as the upstream cause of CKM and HFpEF.
- Adipose-specific silencing confirms the causal role of proinflammatory adipokines in HFpEF.
- Adipose signaling may drive HFpEF, even when caused experimentally by other disorders.
- Imaging and biomarkers are being developed to identify biologically active visceral fat.
- Clinical trials are focusing on adipokine modulators in a broad population of HFpEF.

ABSTRACT

Epidemiological and Mendelian randomization studies demonstrate a strong link between central obesity, visceral adiposity, and heart failure with preserved ejection fraction (HFpEF). The AHA (American Heart Association) has specifically identified excess and dysfunctional fat as the primary upstream cause of the "cardiovascular-kidney-metabolic" syndrome, noting that biologically abnormal adipose tissue exerts adverse effects through its action to secrete proinflammatory adipokines. Experimental studies confirm the causal role of these adipose tissue secretions in the pathogenesis of HFpEF. The earliest clinical evidence of excess and dysfunctional fat is the presence of abdominal obesity, and HFpEF represents the advanced stage of the cardiovascular-kidney-metabolic syndrome for many patients. The AHA also recognizes excess and dysfunctional fat as the major upstream driver of hypertension, type 2 diabetes, metabolic dysfunction-associated steatotic liver disease, and chronic kidney disease—the common comorbidities of HFpEF. Adipose signaling may amplify the development of HFpEF, even when caused experimentally by other disorders (such as pressure overload), because the hemodynamically stressed heart can signal to adipose tissue, whose secretions act on the heart to reinforce the severity of cardiac injury. Additional work is needed to validate clinical, imaging, and biomarker approaches for identifying biologically active (ie, inflamed) visceral adiposity in individual patients. Ongoing and anticipated clinical trials favor the development of adipose biological modulators for use in a broad population of HFpEF. In conclusion, the role of excess and dysfunctional fat in the genesis of HFpEF is well recognized, likely representing a primary or major upstream contributing cause in the large majority of patients. (JACC Heart Fail. 2026;14:103046) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

**ABBREVIATIONS
AND ACRONYMS****CKM** = cardiovascular-kidney-metabolic**GLP** = glucagon-like peptide**HFpEF** = heart failure with preserved ejection fraction**HFREF** = heart failure with reduced ejection fraction**SGLT2** = sodium-glucose cotransporter 2

Hear failure with preserved ejection fraction (HFpEF) is defined as signs and symptoms of heart failure (related to increased left ventricular filling pressures at rest or during exercise) in a patient with an ejection fraction $\geq 50\%$, following the exclusion of other disorders (ie, HFpEF mimics), which include cardiac amyloidosis, valvular heart disease (eg, aortic stenosis and mitral regurgitation), hypertrophic and infiltrative cardiomyopathies, pericardial disorders, and end-stage chronic kidney disease (Figure 1).¹⁻³ These HFpEF mimics are expected to be identified during the initial patient evaluation; they have been systematically excluded from participation in randomized controlled clinical trials or formal registries of patients with HFpEF; and they are managed with specifically targeted therapies. It has been estimated that $\sim 30\%$ of patients with heart failure and an ejection fraction $\geq 50\%$ have a disorder that qualifies as a HFpEF mimic,⁴ but the true prevalence of HFpEF mimics is not known.

HFpEF was first recognized as a clinical disorder when physicians observed that elderly patients with uncontrolled hypertension presented with signs and symptoms of heart failure accompanied by echocardiographic evidence of cardiac hypertrophy but without evidence of systolic dysfunction;⁵⁻⁷ yet, these patients responded poorly to treatment with antihypertensive drugs.⁷ For the next 20 years, HFpEF was envisioned as a disease of diastolic dysfunction leading to left ventricular underfilling.⁸ However, careful evaluation of left ventricular function suggested that, in HFpEF, the left ventricle was an overfilled chamber with impaired distensibility^{9,10} and that the left ventricular end-

diastolic pressure-volume relationship was shifted to the right (rather than to the left) in proportion to the number of comorbidities.¹¹ Investigators began to focus attention on the potential pathogenetic importance of these comorbidities, postulating that hypertension, diabetes, obesity, and chronic kidney disease (acting individually) might possibly ignite a state of systemic inflammation that caused coronary microvascular dysfunction, resulting in deficient nitric oxide-cyclic guanosine monophosphate signaling.¹² Yet, drugs that alleviated this deficient signaling did not produce clinical benefits.¹³⁻¹⁷

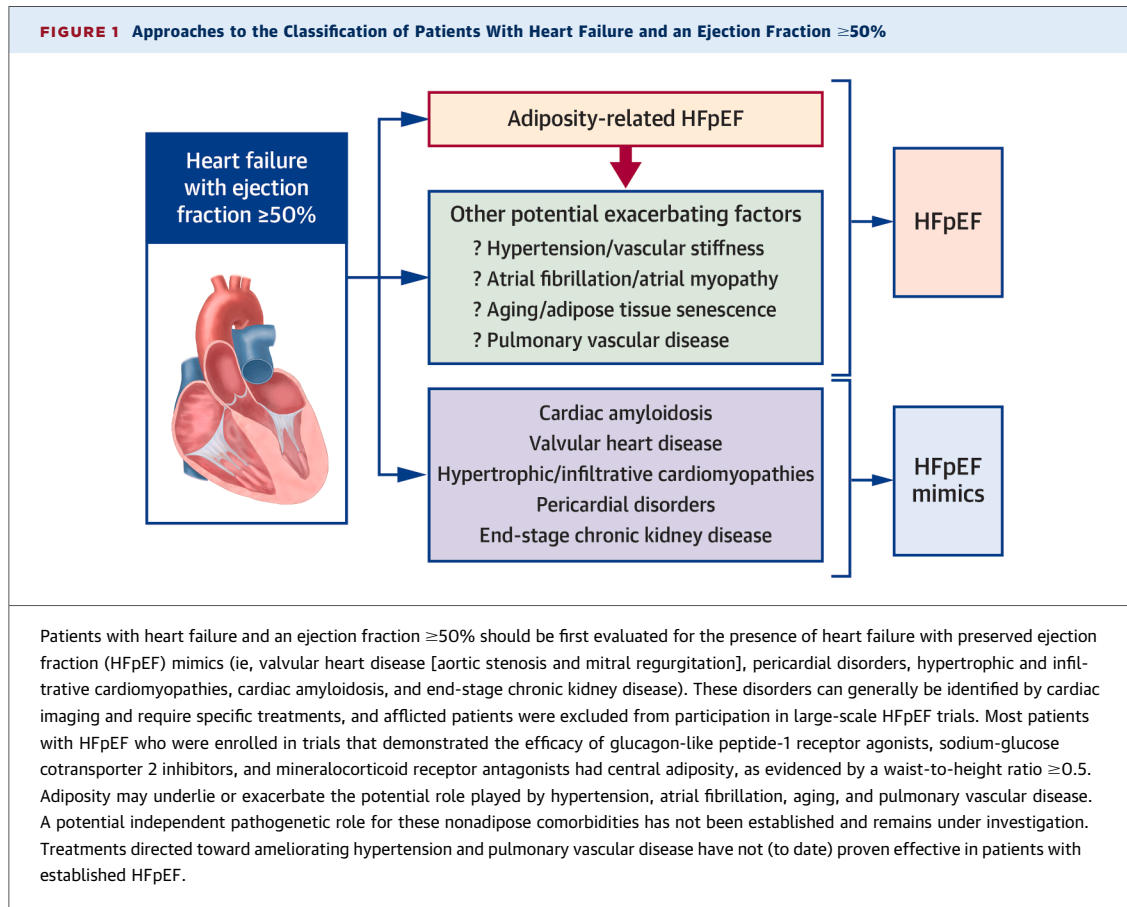
EMERGENCE OF ADIPOSITY AS THE DRIVER OF HFpEF

Over the past several decades, one comorbidity has emerged as a dominant feature of HFpEF. A surge of HFpEF in the community has corresponded to the epidemic of obesity, while the prevalence of uncontrolled hypertension has diminished.^{18,19} In the early 2010s, obesity was identified as a prominent characteristic of HFpEF,²⁰ and it became apparent that higher body mass index was associated with a greater risk of HFpEF than of heart failure with reduced ejection fraction (HFREF).²¹⁻²³ In the United States, $>80\%$ of patients with HFpEF are overweight, and 55% to 65% of patients with HFpEF have a body mass index of ≥ 30 kg/m².^{21,24-27}

Obokata et al²⁸ first defined the features of obesity-related HFpEF, which was characterized by plasma volume expansion and increases in pulmonary capillary wedge pressures that closely paralleled the increase in body mass index but were higher than might be estimated by the measurement of circulating levels of natriuretic peptides. Patients with HFpEF and obesity had worse exercise tolerance,

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greater degrees of systemic inflammation, and an increased risk of heart failure hospitalizations.^{28,29} Patients with HFpEF and obesity did not have evidence of a leftward shift in the left ventricular end-diastolic pressure-volume relationship that appeared to characterize patients with hypertensive hypertrophic disease.^{11,28}

Myocardial biopsies of patients with HFpEF show sarcomere disruption and sarcolysis, impairments in calcium-activated tension development, mitochondrial swelling with cristae separation and dissolution, lipid droplet accumulation, and suppression of fatty acid processing and oxidation and mitochondrial respiratory proteins—with the magnitude of these changes being related to the degree of obesity.³⁰⁻³³

THE EMERGENCE OF ADIPOSITY-RELATED HFpEF AS THE DOMINANT CLINICAL PHENOTYPE. In subsequent work, Obokata et al³⁴ noted that many patients with HFpEF were overweight (rather than obese), and that they experienced the metabolic syndrome, with abdominal obesity and visceral adiposity being prominent features of “cardiometabolic HFpEF,” which was operationally defined by the

authors as HFpEF coexisting with the “metabolic syndrome.” They proposed that the pathophysiological features that were characterized in patients with obesity-related HFpEF also applied to patients with HFpEF who had abdominal obesity.

Mendelian randomization analyses and large-scale epidemiological cohort studies have confirmed an important link between central obesity, visceral adiposity, and HFpEF.³⁵⁻³⁷ Central obesity (a waist-to-height ratio ≥ 0.5) and visceral adiposity precedes and predicts the development of heart failure (and specifically, HFpEF) by years,³⁶⁻³⁹ and in patients with established HFpEF, the magnitude of adiposity is related to the hemodynamic and clinical severity of the disease as well as its prognosis.^{21,40,41} Accordingly, the concept of obesity-related HFpEF has been expanded to “adiposity-related HFpEF.”⁴²

Interestingly, sexual dimorphism in adiposity-related cardiovascular risk may explain the known female predominance of HFpEF. Specifically, elevated body mass index predisposes to HFpEF, more so in women than in men.²² Furthermore, among individuals without HFpEF, the association of

visceral adipose tissue with biomarkers of adiposity, inflammation, and fibrosis is more pronounced in women than in men.⁴³ Among patients with HFpEF, women have higher visceral adipose volume, which is associated with worse exercise hemodynamics, whereas this association is not observed among men with HFpEF.⁴⁴

The primary pathophysiological abnormality of HFpEF is an expansion and biological transformation of visceral adipose tissue.⁴² Systemic insulin resistance has been linked to molecular abnormalities specifically residing in adipocytes,⁴⁵ and Mendelian randomization studies have linked visceral adiposity as a major cause of type 2 diabetes.⁴⁶ Interestingly, although type 2 diabetes is a common comorbidity in HFpEF, the principal feature of the diabetic heart is cardiac steatosis rather than insulin resistance.⁴⁷ The infiltration of inflamed visceral fat into and surrounding the heart parallels the same abnormalities in the liver in metabolic dysfunction-associated steatotic liver disease and the kidney in patients with fatty kidney disease—2 other disorders related to an expansion and biological transformation of visceral fat depots.^{48–51}

THE EMERGENCE OF CARDIOMETABOLIC HFpEF AS AN EXPERIMENTAL ENDOTYPE. In parallel with these developments, investigators who were exploring clinically relevant experimental models of HFpEF shifted their focus from stresses that involved hemodynamic loading to stresses that involved caloric excess and metabolic derangements. For many years, the conventional animal model for HFpEF was transverse aortic constriction, in the expectation that this model might mimic HFpEF caused by prolonged uncontrolled hypertension.⁵² However, that hemodynamically driven model yielded primarily a hypertrophic cardiomyopathy, which produced the features of HFpEF only transiently, leading primarily to HFrEF during long-term follow-up.^{53,54} In contrast, in clinical practice, in the absence of an interim myocardial infarction, patients with HFpEF typically do not evolve into HFrEF even after many years.⁵⁵

Consequently, investigators began to develop HFpEF models that depended on dietary nutrient excess.⁵⁶ The ingestion of a high-fat diet for prolonged periods could produce HFpEF,⁵⁷ and the time frame for its evolution could be accelerated if an additional stressor were imposed (eg, activation of the renin-angiotensin system or suppression of endogenous nitric oxide synthesis).^{58–60} Accordingly, Schiattarella et al⁵⁹ proposed the “2-hit model” of HFpEF; however, all variations of this model of cardiometabolic HFpEF have relied on excess adiposity as a key prerequisite to their

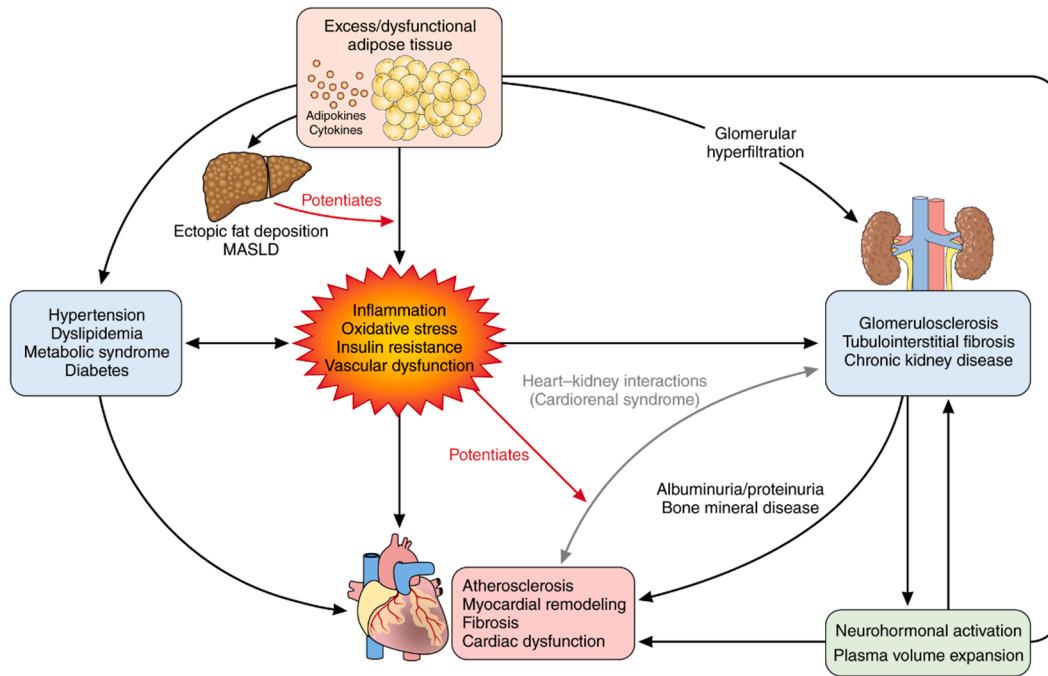
development.^{42,56,61} The cardiometabolic HFpEF endotype in experimental models corresponds closely to the adiposity-related HFpEF phenotype that is dominant in the clinical setting.⁴²

INSTITUTIONAL RECOGNITION OF THE ROLE OF EXCESS AND DYSFUNCTIONAL FAT IN HFpEF

In 2023, the AHA (American Heart Association) specifically recognized the primary upstream role of adipose tissue expansion and dysfunction in the development of heart failure.^{62,63} The AHA Presidential Advisory and its accompanying Scientific Statement on the cardiovascular-kidney-metabolic (CKM) syndrome presented several findings:

1. Excess or dysfunctional adipose tissue is specifically identified as the primary upstream cause of the CKM syndrome.
2. Visceral adiposity exerts adverse effects on the heart, vasculature, and kidney through the secretion of molecules (eg, adipokines) that have proinflammatory and profibrotic effects, leading to HFpEF (Figure 2).⁶⁴
3. The common comorbidities of HFpEF are the downstream consequences of excess or dysfunctional adipose tissue. Specifically, most instances of hypertension are related to adiposity or other metabolic risk factors.⁶⁵ Furthermore, hypertriglyceridemia, the metabolic syndrome, and type 2 diabetes are almost entirely downstream effects of excess or dysfunctional adipose tissue.⁴⁷ Excess and dysfunctional adipose tissue also contributes to chronic kidney disease.⁶⁶
4. In addition to the systemic effects of adipose tissue, ectopic fat may be a local source of mediators and can produce compressive organ damage, especially when deposited in the epicardium and pericardium and within and around the kidney.^{28,49}
5. The earliest clinical evidence of the state of excess and dysfunctional fat is the presence of abdominal obesity, measured by the waist circumference or the waist-to-height ratio. Patients with central adiposity with no evidence of metabolic abnormalities or organ dysfunction or injury are considered to have stage 1 CKM. The statements link adiposity closely with HFpEF, and HFpEF represents the advanced stage (stage 4) of the disease for many patients.
6. Excess and dysfunctional fat adversely affects not only the heart, vasculature, and kidney, but also the liver, leading to hepatic steatosis, which can further potentiate the deleterious systemic effects of biologically abnormal adipose tissue.

FIGURE 2 Central Role of Excess/Dysfunction Adipose Tissue and Its Secretory Products in the Pathogenesis of the Cardiovascular-Kidney-Metabolic Syndrome (as Depicted in the American Heart Association Scientific Statement)



This figure from the American Heart Association depicts excess/dysfunctional adipose tissue and its secretion of adipokines as the upstream events that are responsible for: 1) the cardiac remodeling, fibrosis, and dysfunction typically seen in HFpEF; and 2) the common comorbidities seen in patients with HFpEF (ie, hypertension, diabetes, metabolic syndrome, hepatic steatosis, and chronic kidney disease). Reproduced with permission from Ndumele et al.⁶³ MASLD = metabolic dysfunction-associated steatotic liver disease.

The 2025 ACC (American College of Cardiology) Statement on Obesity and Heart Failure emphasized similar points.¹ The statement indicated that avoidance of excess adiposity throughout a person’s lifespan is key to the prevention of incident heart failure, particularly HFpEF, thus reinforcing the finding that excess and dysfunctional fat is the primary upstream causal mechanism of HFpEF. Additionally, the ACC recommended direct assessment of excess adiposity using an anthropometric criterion (eg, waist-to-height ratio) or by the measurement of body composition (eg, dual x-ray absorptiometry).

Subsequent work has identified specific molecular mediators by which dysfunctional adipose tissue might cause HFpEF.⁶⁴ A causal role for these adipokines is supported by experimental studies that demonstrate that silencing of individual adipokines—selectively and specifically in adipose tissue (and not in the heart or kidney)—prevents the development of HFpEF.^{57,58,64}

TARGETING DYSFUNCTIONAL FAT IN THE CLINICAL SETTING

The AHA statements recommend that physicians should target dysfunctional fat when managing the CKM syndrome throughout all its stages, specifically through lifestyle interventions and pharmacological interventions to ameliorate the mass and biology of dysfunctional fat and prevent its adverse effects on the heart, kidney, and vasculature.^{62,63}

Large-scale long-term trials of incretin drugs have demonstrated their effect to reduce the risk of cardiovascular events in people with obesity.⁶⁷ Glucagon-like peptide (GLP)-1 receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and mineralocorticoid receptor antagonists have been shown to improve heart failure and kidney outcomes in patients with diverse manifestations of CKM,^{62,63} and they produce clinical benefits in patients with established HFpEF.⁶⁸⁻⁷¹ Interestingly, all 3 classes of drugs lessen visceral adiposity and alleviate the

altered biology that is characteristic of dysfunctional fat,⁶⁴ although they also exert direct effects on the heart, vasculature, and kidneys. It is noteworthy that GLP-1 receptor agonists, SGLT2 inhibitors, and mineralocorticoid receptor antagonists act directly on adipocytes, especially those residing in epicardial adipose tissue to normalize their biological derangements.⁷²⁻⁷⁶ Conversely, experimental upregulation of the mineralocorticoid receptor—specifically and selectively in adipose tissue—reproduces the features of the metabolic syndrome and vascular dysfunction.⁷⁷

ESTIMATING THE IMPORTANCE OF ADIPOSITY IN HFpEF IN THE CLINICAL COMMUNITY. The efficacy of SGLT2 inhibitors and mineralocorticoid receptor antagonists in HFpEF has been established in large-scale trials that primarily enrolled patients who had abdominal obesity. In these trials, >50% of participants had a body mass index ≥ 30 kg/m² and >95% of patients had a waist-to-height ratio ≥ 0.5 .^{40,41} These estimates are particularly impressive, because these trials specifically excluded patients with the most severe degrees of obesity, as reflected by eligibility criteria that blocked the enrollment of patients with a body mass index >40 to 45 kg/m² or patients without meaningful increases in circulating natriuretic peptides at baseline (who are likely to have the most marked adiposity). Outside of the context of large-scale trials, excess visceral fat mass by imaging has been noted in ~85% of patients with HFpEF,⁷⁸ and in a study of community-dwelling people living in rural China, ~80% of patients with HFpEF had abdominal obesity.⁷⁹

MEETING THE CHALLENGE OF IDENTIFYING AND QUANTIFYING DYSFUNCTIONAL FAT. There is institutional recognition of the importance of measuring visceral adiposity as predecessor, clinical characteristic, and prognostic feature of HFpEF.^{1,32,38-41} On a population level, the measurement of waist circumference outperforms body mass index as a metric of visceral fat mass.⁸⁰⁻⁸³ On an individual level, there is a reasonable correlation ($r \approx 0.65-0.70$) between the measurement of waist-to-height ratio and mesenteric fat measured by dual x-ray absorptiometry, computed tomography, or cardiac magnetic resonance,^{80,81} but these relationships vary with age, sex, and ethnicity.⁸⁰⁻⁸³ For the same waist circumference, South Asians and the elderly have substantially greater mesenteric adipose tissue volume.^{84,85} The relationship of waist circumference with epicardial and pericardial fat is somewhat weaker than its relationship with mesenteric adipose tissue,⁸⁶ an

important consideration if dysfunctional fat exerts adverse effects on the heart primarily through a paracrine mechanism.⁶⁴ These paracardiac fat depots are best imaged by cardiac computed tomography or cardiac magnetic resonance (**Central Illustration**).⁸⁷

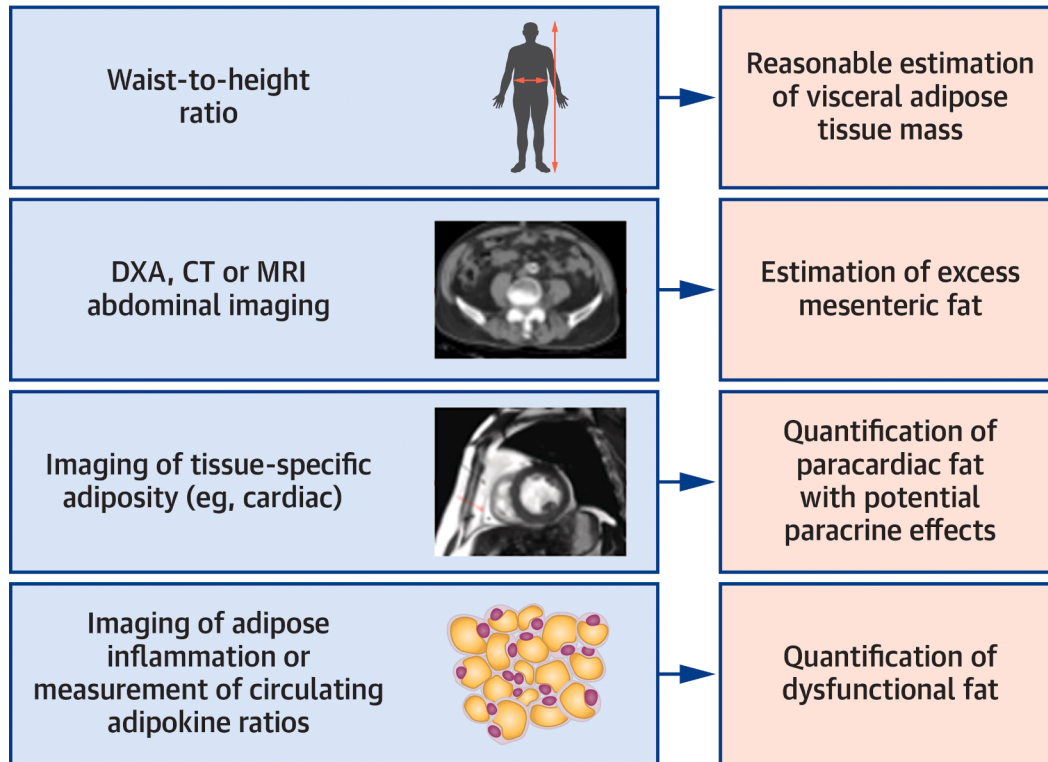
However, the assessment of adipose tissue that is most relevant to HFpEF is the biological state (rather than the quantity) of visceral fat, as it is dysfunctional and inflamed fat that secretes deleterious signaling molecules. Computed tomography to discern fat attenuation,⁸⁸ cardiac magnetic resonance to observe changes in fatty acid content,⁸⁹ and ¹⁸F-fluorodeoxyglucose uptake by positron emission tomography to measure metabolically active fat⁹⁰ are being developed to identify epicardial adipose tissue inflammation; yet, these methods are not currently scaled for large populations. On the other hand, it may be possible to estimate the burden of dysfunctional fat by measuring its secretory products in the bloodstream (eg, by quantifying a ratio of proinflammatory to anti-inflammatory adipokines). Preliminary observations suggest that these ratios might have utility in the evaluation of patients with visceral adiposity and insulin resistance,⁹¹⁻⁹⁴ but this approach requires further exploration and validation.

DYSFUNCTIONAL FAT AS BOTH A PRIMARY CAUSE AND ESSENTIAL ACCELERANT OF HFpEF. The identification of excess and dysfunctional fat as a causal mechanism does not obviate the potential contribution of other mechanisms that may be relevant in the pathogenesis of HFpEF. However, visceral adiposity is known to drive these other mechanisms, and a role for these mechanisms (independently of adiposity) has not (to date) been established in interventional clinical trials (**Figure 1**).^{47,65,66,95}

Arterial stiffness and hypertension. The predilection of uncontrolled hypertension to cause ventricular hypertrophy and HFpEF still exists in clinical practice (as it did in the 1980s), but the incidence of uncontrolled hypertension has declined.¹⁵ Furthermore, it is visceral adiposity that underlies the development of vascular stiffness and the resistance of patients to antihypertensive drugs.⁶⁵ The relevance of visceral adiposity as an “accelerant” of arterial stiffening is supported by a recent trial demonstrating that SGLT2 inhibition increases arterial compliance in patients with HFpEF, reducing the hypertensive response to exercise, in proportional to the degree of weight loss.⁹⁶ GLP-1 receptor agonists and bariatric surgery also produce beneficial effects on arterial stiffness.^{97,98}

CENTRAL ILLUSTRATION Approaches to Estimating and Quantifying the Contribution of Excess and Dysfunctional Fat in Patients at Risk of or With Established HFpEF

Approaches to the Measurement of Dysfunctional Fat



Packer M, et al. JACC Heart Fail. 2026;14(6):103046.

The measurement of waist-to-height ratio (as a metric of abdominal obesity) represents a reasonable population-level approach to estimating visceral fat mass. More precise individual measurements of mesenteric fat can be provided by dual x-ray absorptiometry (DXA), computed tomography (CT), or magnetic resonance imaging (MRI) of the abdomen. Cardiac-specific imaging can quantify paracardiac fat (pericardial and epicardial adipose tissue) with potential paracrine effects. However, dysfunctional fat is defined not by its mass, but rather by its proinflammatory biology. Discernment of epicardial adipose tissue inflammation requires highly specialized imaging methods (CT fat attenuation, MRI measurements of the fatty acid content of adipose tissue, or ¹⁸F-fluorodeoxyglucose positron emission tomography). Alternatively, a heightened ratio of proinflammatory and anti-inflammatory adipokines measured in circulating blood may allow for the quantification of dysfunctional fat, but this approach requires further exploration and validation.

Atrial myopathy and atrial fibrillation. Atrial fibrillation is a risk factor for HFpEF, although it is not yet clear whether it is a causal mechanism for HFpEF, reflects long-standing increases in left ventricular filling pressures, or is a biomarker of a concomitant atrial myopathy that results from an expansion and inflammation of epicardial adipose tissue.^{95,99} Weight loss is associated with a reduction in atrial fibrillation burden,¹⁰⁰ and in patients with HFpEF, treatment with GLP-1 receptor agonists decreases left atrial volume, a marker of underlying atrial myopathy.¹⁰¹ Both SGLT2 inhibitors and GLP-1

receptor agonists appear to reduce the incidence of atrial fibrillation in meta-analyses of clinical trials.^{102,103} A large-scale randomized trial to address the possibility that catheter ablation can improve outcomes in HFpEF (independent of adiposity) is ongoing (NCT05508256).

Aging and adipose tissue senescence. Aging is a major determinant of HFpEF, potentially because visceral adipose tissue markedly accumulates as people grow older.^{85,104} Aging-related increases in adiposity has been linked to inflammation-related cardiovascular disease in the elderly and may afflict

TABLE 1 Drugs Targeting Adipose Tissue Mass and Biology Under Consideration or Being Evaluated in Ongoing Trials of HFpEF

	Mechanism of Action	Clinical Development
Incretin drugs (maridebart cafraglutide)	Dual GIP receptor antagonist and GLP-1 receptor agonist; enhancement of cardioprotective adipokines and suppression of proinflammatory adipokines	Large-scale phase 3 trial in HFpEF is ongoing
Metformin	Activation of AMPK; enhancement of cardioprotective adipokines and suppression of proinflammatory adipokines	Phase 2 clinical trials are ongoing
FGF21 agonists and analogues	Potential of the actions of the counter-regulatory adipokine, FGF21	Amelioration of metabolic dysfunction-associated steatotic liver disease in clinical trials, now positioned for trials in HFpEF
Aldosterone synthase inhibitors or mineralocorticoid receptor antagonists (vicirostat, bicalcirenone)	Inhibition of synthesis or actions of aldosterone, a proinflammatory adipokine	Large-scale phase 3 trials in HFpEF are ongoing
Activin type II receptor traps (sotatercept, HS235)	Antagonists of activin A and other proinflammatory adipokines	Positive results in pulmonary arterial hypertension with or without HFpEF; well positioned for phase 3 HFpEF trial
Antibody inhibitor of IL-6 ligand (ziltivekimab)	Antagonist of the proinflammatory adipokine (cytokine subdomain), IL-6	Large-scale phase 3 trial in HFpEF is ongoing
miR-132-3p inhibitor (CDRI32L)	Antagonist of proinflammatory adipokine, miR-132-3p	Entering clinical trials in HFpEF
Endotrophin antagonists (PRV-101, VS-041)	Inhibition of release or actions of the proinflammatory adipokine, endotrophin	Entering clinical trials in HFpEF

AMPK = adenosine monophosphate-activated protein kinase; FGF = fibroblast growth factor; GIP = glucose-dependent insulinotropic polypeptide; GLP = glucagon-like peptide; HFpEF = heart failure with preserved ejection fraction; IL = interleukin.

major organs, even when it is not discerned by changes in conventional assessments of abdominal obesity.^{104,105} With aging, senescent cells accumulate in adipose tissue to promote the multisystem abnormalities associated with HFpEF,¹⁰⁶ and they stimulate the secretion of proinflammatory adipokines.¹⁰⁷ Senolytic interventions targeting these cells improves insulin sensitivity, suppresses inflammation, ameliorates albuminuria, and improves cardiac diastolic filling dynamics.¹⁰⁶

In experimental models of HFpEF, it often takes 2 causal triggers, acting in concert, to produce HFpEF. Yet, in these two-hit models, dietary nutrient excess is a necessary prerequisite.^{42,56} In some studies, adiposity alone is sufficient to cause HFpEF, whereas in others it provides a requisite foundational stress.^{57,58} Importantly, adipose tissue signaling may be a critically important amplifier to the development of HFpEF, even when the igniting cause is pressure overload.¹⁰⁸ Under such circumstances, the hemodynamically stressed heart signals to adipose tissue, whose secretions act on the heart to aggravate the extent and consequences of the initial injury.¹⁰⁹⁻¹¹¹ This positive feedback loop may be particularly important in a patient with concomitant central obesity, which appears to be the case for most patients with HFpEF who were enrolled in large-scale trials.

ENVISIONING THE NEXT GENERATION OF CLINICAL TRIALS IN HFpEF.

Given the importance of excess

and dysfunctional fat in HFpEF, how should the next generation of clinical trials in HFpEF be envisioned? For the past 30 years, investigators and sponsors who have designed and carried out randomized controlled clinical trials in HFpEF have not generally followed a phenotype-specific strategy. Instead, these trials enrolled a broad range of patients, and the protocol-specified exclusion of HFpEF mimics yielded populations with a near-universal presence of abdominal obesity.⁴¹ Such a broad-based approach to patient eligibility is likely to continue, as (except for waist-to-height ratio) there is (to date) no scalable and validated metric that identifies individuals with excess or dysfunctional visceral fat, either by imaging or by assay of blood-borne adipokines. These circumstances resemble the approach of investigators who evaluated the role of neurohormonal activation in HFpEF, in which clinical trials were carried out using broad-based criteria and patients were not selected for eligibility based on the measurement of neurohormonal factors in the bloodstream.

Novel approaches to the treatment of HFpEF are targeting derangements in adipose tissue mass and biology (Table 1). A large-scale HFpEF outcomes trial with an incretin drug—maridebart cafraglutide—is ongoing (NCT07037459), following favorable results with other incretin drugs in HFpEF in smaller trials^{70,71} and based on the premise that modulation of GLP-1 and GIP receptor signaling may have favorable effect on adipocyte mass and adipokine

signaling.^{64,112,113} Metformin exerts favorable effects on adipose biology, acting to normalize adipokine imbalances,⁶⁴ and its use has been reported to exert benefits in experimental HFpEF and in observational studies of patients with HFpEF;¹¹⁴⁻¹¹⁷ phase 2 randomized controlled trials are ongoing (NCT05093959, NCT03629340). Fibroblast growth factor 21 is a counterregulatory adipokine that opposes the adipogenic and prohypertrophic effects of proinflammatory adipokines;⁶⁴ drugs that act as analogues of fibroblast growth factor 21 or agonists of its receptor have been shown to ameliorate hepatic steatosis in clinical trials and to alleviate experimental HFpEF, and are being positioned for testing in HFpEF.^{118,119} Activin type II receptor ligand traps (eg, sotatercept and HS235) act as proinflammatory adipokine antagonists and have produced benefits in experimental HFpEF¹²⁰ and in patients with HFpEF who have pulmonary hypertension (NCT04945460); these drugs should be evaluated for the treatment of patients with HFpEF who do not have intrinsic pulmonary vascular disease. Other antagonists of proinflammatory adipokines (miR-132-3p and endotrophin) have shown favorable effects in experimental cardiac hypertrophy¹²¹ and are entering early clinical trials (NCT06979362, NCT07219511). Drugs that inhibit the synthesis or actions of aldosterone (a proinflammatory adipokine) may act improve adipose tissue biology and are being studied in trials of HFpEF (NCT06307652, NCT06424288). Interleukin-6 levels are increased in patients with HFpEF and are associated with an adverse prognosis,¹²²⁻¹²⁶ largely because of excess production of the proinflammatory adipokine by adipose tissue;¹²⁷ a large-scale trial of the interleukin-6 antagonist ziltivekimab in patients with HFpEF and increased high-sensitivity C-reactive protein is ongoing (NCT05636176). Trials of new drugs for HFpEF are well positioned to measure hepatic and renal function in addition to heart failure outcomes.⁵¹

CONCLUSIONS

In its 2023 statements describing the CKM syndrome, the AHA recognized the primary role played by excess or dysfunctional adipose tissue in secreting molecules that produce proinflammatory and profibrotic effect on the heart, vasculature, and kidney. The earliest clinical evidence of the state of excess and dysfunctional fat is the presence of abdominal obesity, and conversely, HFpEF represents the advanced stage of the disease for many patients.

Many of the common comorbidities of HFpEF (eg, hypertension, type 2 diabetes, hepatic steatosis, atrial fibrillation and myopathy, and chronic kidney disease) are established downstream consequences of excess or dysfunctional adipose tissue. In the clinical setting, ~60% of patients with HFpEF have a body mass index ≥ 30 kg/m² and ~80% to 95% have abdominal and visceral adiposity. Aging is accompanied by an expansion and biological transformation of fat in visceral organs in a manner that may not be discerned by changes in waist circumference. Therefore, excess and dysfunctional fat is poised to represent a primary cause of or a critically important upstream accelerant of other potential mechanisms of HFpEF in the large majority of patients with the disease.

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