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The Adipokine Hypothesis of Heart Failure With a Preserved Ejection Fraction

A Novel Framework to Explain Pathogenesis and Guide Treatment

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ABSTRACT

HYPOTHESIS The paper proposes a novel unifying hypothesis—that heart failure with preserved ejection fraction (HFpEF) arises primarily from the expansion and dysfunctional transformation of visceral adipose tissue, leading to the secretion of altered suite of signaling molecules (adipokines), which causes systemic inflammation, plasma volume expansion, and cardiac hypertrophy and fibrosis.

ELEMENTS OF THE FRAMEWORK The framework groups adipokines into 3 domains. Domain I adipokines are cardioprotective molecules but are suppressed in patients with excess adiposity. Domain II adipokines are cardioprotective molecules that are up-regulated by adiposity as a compensatory response mechanism. Domain III adipokines, whose secretion is heightened in adiposity, have proinflammatory, prohypertrophic, profibrotic, and antinatriuretic effects. HFpEF results from an adiposity-driven imbalance that promotes Domain III adipokines but suppresses Domain I adipokines, with Domain II adipokines representing an inadequate counter-regulatory response.

KEY LINES OF EVIDENCE 1) Obesity and dietary nutrient excess are the major drivers of experimental HFpEF; 2) changes in visceral adiposity and circulating adipokines are observed years before and predict the diagnosis of HFpEF (but not heart failure with a reduced ejection fraction) in the general community; 3) central obesity or visceral adiposity is present in >95% of patients with HFpEF and tracks with disease severity; 4) obesity and HFpEF exhibit striking parallelism in their molecular, pathophysiological, and clinical features; 5) characteristic changes in the adipokine profile occur in parallel in central obesity and heart failure and are correlated with disease severity; 6) adipokines have established effects on cardiac structure and function that can lead to HFpEF; 7) bariatric surgery or drug treatments for HFpEF cause shrinkage of visceral fat depots (disproportionate to changes in body weight), while simultaneously increasing Domain I adipokines and decreasing Domain III adipokines; 8) excess adiposity appears to identify patients most likely to respond to current treatments for HFpEF; and 9) experimental interventions that target only adipose tissue to selectively increase or decrease its secretion of specific adipokines cause distant effects on the heart to modulate cardiac structure and the evolution of cardiomyopathy.

CONCLUSIONS The totality of evidence suggests that HFpEF evolves—not as a heterogenous disorder related to diverse comorbidities and not as a primary disorder of cardiomyocytes—but as an adipose-driven derangement that is disseminated (through endocrine-paracrine signaling) to the heart. (JACC. 2025;■:■–■) © 2025 The Author. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AMPK = adenosine monophosphate protein kinase

GLP-1 = glucagon-like peptide-1

HFpEF = heart failure with a preserved ejection fraction

MRA = mineralocorticoid receptor antagonist

mTOR = mechanistic target of rapamycin

NAD+ = nicotinamide adenine dinucleotide

PGC-1α = peroxisome proliferator-activated receptor-gamma coactivator-1alpha

PPARα/γ = peroxisome proliferator-activated receptor-alpha/gamma

SIRT1 = sirtuin-1

SGLT2 = sodium-glucose cotransporter 2

OUTLINE

For the past 3 decades, the neurohormonal hypothesis has represented a unifying framework to explain heart failure with a reduced ejection fraction (HFrEF).[1] That hypothesis postulated that the activation of neurohormonal mechanisms—rather than hemodynamic factors (such as cardiac contractility and systemic vasoconstriction)—was critical in promoting the evolution and progression of heart failure. The paradigm focused on signaling molecules that were released from peripheral nerves or the kidney (catecholamines and angiotensin II), which accelerated the evolution and progression of cardiomyopathy. Subsequent work has largely validated the hypothesis, ie, trials of hemodynamic interventions have yielded disappointing or deleterious results,[2-4] whereas trials with beta-blockers, mineralocorticoid receptor antagonists (MRAs), and neprilysin inhibitors supported a role for neurohormonal mechanisms.[5,6] Although some approaches to neurohormonal inhibition did not represent favorable therapeutic targets,[7,8] the overarching framework reshaped our understanding and treatment of HFrEF.

In contrast with HFrEF, no unifying biological framework has been proposed to explain the pathogenesis of heart failure with a preserved ejection fraction (HFpEF), currently the most incident and prevalent heart failure phenotype. HFpEF is typically regarded as being exceptionally heterogenous—described as the end result of numerous comorbidities that (acting individually or in concert) have been hypothesized to cause coronary microvascular endothelial dysfunction and myocardial remodeling, exacerbated by heightened arterial load, diverse metabolic derangements, and systemic inflammation—all coexisting phenomena but without a common driving mechanism.

Challenging this prevailing wisdom, this paper proposes that the diverse features of HFpEF are linked by a common pathway, ie, that HFpEF arises from a nutrient excess-driven expansion and biological transformation of visceral adipose tissue, which leads to the secretion a dysfunctional suite of signaling molecules—known as adipokines. These molecules produce deleterious cardiac, vascular, renal, and systemic inflammatory effects that recapitulate all the pathophysiological and clinical features of HFpEF. Drawing from decades of experimental research and clinical observations, the proposed adipokine hypothesis provides a novel conceptual framework for understanding the development of *both* HFpEF and its associated comorbidities. As in the case of the neurohormonal hypothesis of HFrEF, the new hypothesis of HFpEF provides a coherent, testable, and falsifiable structure to guide current thinking and future research.

PART I: EVOLUTION OF THE ADIPOKINE HYPOTHESIS FOR UNDERSTANDING HFpEF

In 2017, Obokata et al. proposed that obesity might represent a distinct phenotype of HFpEF,[9] raising the possibility that an expansion of adipose tissue could be a primary driver of the disorder. However, obesity is conventionally defined by body mass index, a metric that is heavily influenced by bone and skeletal muscle mass and is not a reliable measure of fat mass, particularly in ethnically diverse populations. Furthermore, not all fat depots are

clinically important; ie, when compared with subcutaneous fat depots, visceral adipose tissue is more biological active, exerts endocrine and paracrine effects on vital organs, and produces deleterious systemic and cardiometabolic effects.[10] Central adiposity, defined by waist-to-height ratio, represents the most reliable approach to the assessment of visceral fat mass on a population level.[11]

It is therefore noteworthy that, although obesity (defined as a body mass index ≥30 kg/m^2) characterizes 60% to 70% of patients with HFpEF,[9] central adiposity (identified by a waist-to-height ratio ≥0.5) is present in >95% patients with HFpEF.[12] The near-universal prevalence of excess adiposity in HFpEF has been confirmed by quantification of fat mass.[13] Importantly, visceral adiposity (assessed by imaging) precedes and predicts the development of HFpEF (but not HFrEF) in the general population,[14] and the magnitude of visceral adiposity and obesity in HFpEF closely parallels with the hemodynamic and clinical severity of the disease.[15,16]

IDENTIFYING A ROLE FOR ADIPOKINE SIGNALING IN THE PATHOGENESIS OF HFpEF. In human obesity, adipose tissue comprises a very substantial proportion of body weight, and thus, it represents the body's largest secretory organ. As a result, it is responsible for the substantial synthesis and release of numerous biologically active molecules, which exert outsized effects on interorgan signaling.

The expansion of visceral fat mass transforms the adipocyte secretome so that adipocytes secrete an altered suite of molecules that (acting in an endocrine or paracrine manner) promote renal and splanchnic sympathetic activation, heightened signaling through angiotensin II and aldosterone, sodium retention and plasma volume expansion, and systemic and pulmonary hypertension.[11,17] At the same time, the shift in the adipokine profile triggers systemic and regional inflammation[17] (leading to destruction of the coronary microvasculature and myocardial fibrosis[18,19]) and promotes ventricular hypertrophy, all acting in concert to impair ventricular distensibility.

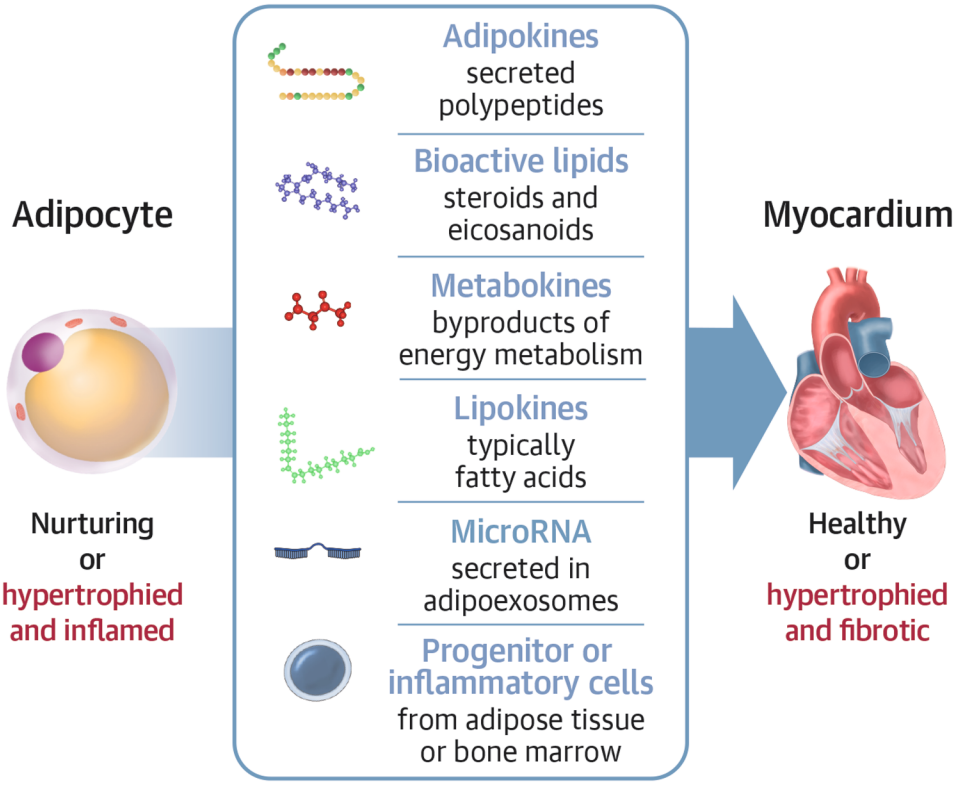
The end result is increased filling of the left ventricle, coincident with a meaningful impairment in the capacity of the chamber to tolerate filling. The fundamental abnormality in HFpEF is not a loss of cardiomyocytes, but it is the diminished ability of the left ventricle to tolerate the exaggerated hemodynamic stresses imposed upon it. The secretion of prohypertrophic, proinflammatory and antinatriuretic adipokines from dysfunctional visceral fat can explain the established pathophysiological features of HFpEF (**Figure 1**), and it can also account for its prevalent comorbidities.

BUILDING BLOCKS OF THE ADIPOKINE HYPOTHESIS. In 2018, the interplay of 3 adipocyte-derived hormonal signaling molecules—leptin, aldosterone, and neprilysin—was identified as central to the pathogenesis of HFpEF. Acting in concert, these adipokines could explain the occurrence of neurohormonal activation, sodium retention, hypertension, systemic inflammation, and end-organ fibrosis.[20,21] During the past 7 years, experimental studies have provided substantial support for the importance of the leptin-aldosterone-neprilysin axis. Notably, delineation of the axis anticipated the success of MRAs and neprilysin inhibitors in patients with HFpEF.[22-27] The adipocyte-centered framework also provided a foundational basis for the efficacy of drugs—sodium-glucose cotransporter 2 (SGLT2) inhibitors and incretin-based drugs—that act to shrink visceral fat depots or reverse their proinflammatory biological features, thereby emerging as functional adipokine modulators.[22]

In parallel with the description of the leptin-aldosterone-neprilysin axis, it was recognized that dysfunctional epicardial adipose tissue could secrete molecules that could exert paracrine effects on the heart.[28] The epicardium shares an unobstructed microcirculation with the adjoining myocardium, and thus, an expansion and biological transformation of epicardial adipose tissue would lead to the secretion of molecules that could cause inflammation and fibrosis directly in adjacent underlying cardiac tissue.

Viewed from this perspective, epicardial adipose tissue acts as a transducer that focuses the effects of system-wide adipocyte-driven inflammation onto the myocardium through the action of locally-secreted proinflammatory adipokines. This adipocyte-derived paracrine mechanism was considered to be particularly relevant to the development of HFpEF,[28] because epicardial fat expansion is a characteristic feature of patients with HFpEF, but not those with HFrEF.[29] An increased epicardial fat mass identifies patients with obesity who have underlying cardiac abnormalities and are likely to develop heart

FIGURE 1 The Adipokine Hypothesis: Secretion of Adipokines From Biologically Transformed Visceral Adipose Tissue Leads to HFpEF



The expansion and biological transformation of visceral adipose tissue leads to an altered suite of adipokines, whose interplay enhances renal tubular sodium reabsorption (leading to sodium retention and plasma volume expansion), provokes systemic inflammation, and promotes myocardial hypertrophy, coronary microvascular dysfunction, and fibrosis. The end result is increased filling of the left ventricle, coincident with a meaningful impairment in the capacity of the chamber to tolerate filling—the hallmark of heart failure with a preserved ejection fraction (HFpEF).

failure[30] as well as patients with HFpEF who have an adverse prognosis, even after accommodating for body mass index.[31]

Over the past decade, dozens of both proinflammatory and cardioprotective adipokines have been shown to directly influence oxidative and organellar stress within cardiomyocytes, renal tubular sodium reabsorption, cardiac hypertrophy and fibrosis, and the development of cardiomyopathy. Changes in these adipokines have been shown to precede the onset of HFpEF and to track closely with the clinical severity and prognosis of established HFpEF. Interventions that selectively target adipose tissue have been shown experimentally to exert distant effects on the structure and function of the heart.

Together, the totality of evidence points to an adiposity-induced shift in the balance of proinflammatory and cytoprotective adipokines, which promotes the evolution and progression of HFpEF. Accordingly, the current paper proposes the "adipokine hypothesis of HFpEF" as a coherent, mechanistically grounded and testable framework to guide the understanding and treatment of this disorder—a conceptual model that is likely to be applicable to vast majority of people with HFpEF (Box 1).

FRUSTRATION WITH THE LACK OF A UNIFYING FRAMEWORK FOR HFpEF. HFpEF is currently

BOX 1. The Neurohormonal Hypothesis and the Adipokine Hypothesis: Conceptual Parallels

1. **Neurohormonal Hypothesis of HFrEF**

This hypothesis describes the mechanisms that drive the evolution and progression of HFrEF. HFrEF progresses because of the enhanced and sustained release of cardiotoxic signaling molecules from peripheral nerves, the kidney, or the adrenal gland (eg, catecholamines, angiotensin II, and aldosterone) coupled with the attenuated signaling of cardioprotective molecules (eg, natriuretic peptides).

2. **Need for a New Framework for HFpEF**

A unifying explanatory model for HFpEF is needed. The prevailing view—that HFpEF is an exceptionally heterogeneous syndrome driven by multiple, loosely connected comorbidities—has provided limited insights and has not produced a clear foundation for research or therapeutic drug development.

3. **Adipokine Hypothesis of HFpEF**

This hypothesis proposes that the evolution and progression of HFpEF is driven by the enhanced sustained secretion of proinflammatory and profibrotic signaling molecules from adipose tissue (eg, leptin and others) coupled with suppressed synthesis and secretion of adipose-derived cardioprotective signaling molecules (eg, adiponectin and others). These biologically active molecules, collectively termed adipokines, act on the heart and vasculature through endocrine and paracrine mechanisms.

regarded as a heterogenous disorder whose pathogenesis is driven in different cohorts by numerous independently acting comorbidities (eg, sedentary aging, systemic and pulmonary hypertension, diabetes, coronary artery disease, aortic stiffness, cardiac hypertrophy and fibrosis, atrial fibrillation with atrial myopathy, microvascular abnormalities, systemic inflammation, natriuretic peptide deficiency, and chronic pulmonary or kidney disease). For some, hypertension is the main driver of cardiac hypertrophy in HFpEF; for others, diabetes drives glucotoxicity in the heart; and for still others, the interplay of comorbid conditions triggers adverse changes in the coronary endothelium.[19] To many, impressed by its predilection to afflict elderly women, HFpEF has been regarded as the outcome of cardiac and vascular aging, exacerbated by atherosclerotic disease—even though large-vessel coronary artery disease is uncommon among patients with HFpEF. The presence of systemic inflammation in HFpEF is well recognized, but its origin has not been clearly defined.

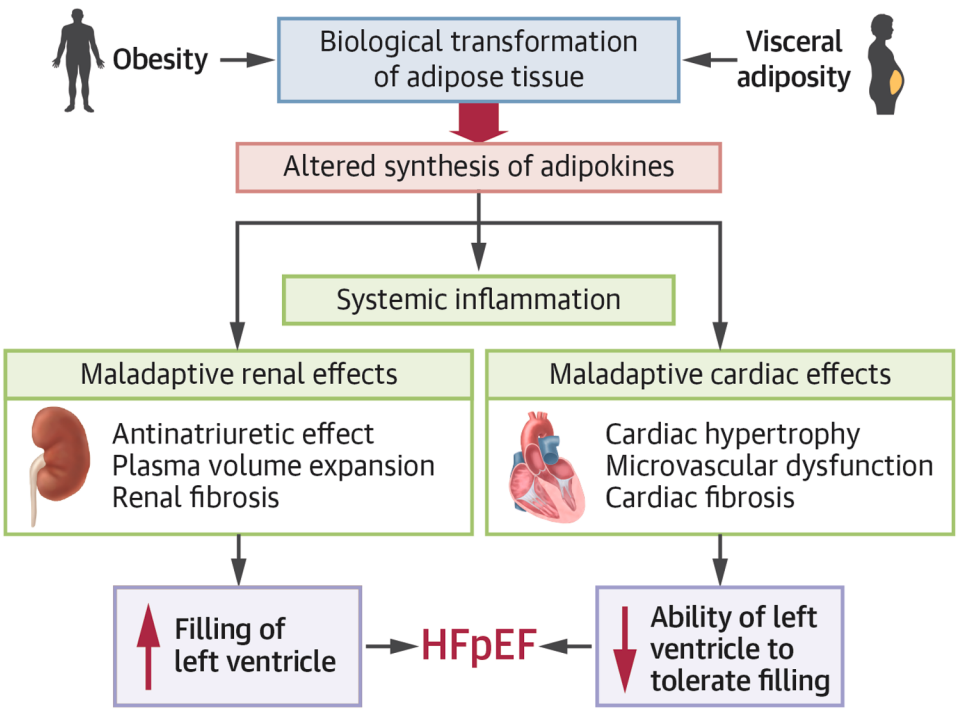
The prevailing view that HFpEF arises from numerous independent mechanisms has left the field without a coherent unifying evidence-based framework. Systemic and pulmonary hypertension, diabetes, cardiac hypertrophy, vascular disease, and atrial myopathy are obvious features of the disease, but there is no evidence that these phenotypic characteristics represent distinct causal mechanisms or pathways. These comorbidities are also seen in patients with HFrEF, in whom they are not believed to carry any special mechanistic significance. Furthermore, the comorbidities of HFpEF have not identified a particular group of responders in clinical trials, and the treatment of these coexistent conditions has not influenced the clinical course of HFpEF. The convergence of comorbidities in HFpEF suggests a common origin, rather than distinct mechanisms.

The adipokine hypothesis offers an alternative perspective. Rather than considering hypertension, diabetes, chronic kidney disease, atrial myopathy, and systemic inflammation as representing individual candidate pathways, the "adipokine hypothesis of HFpEF" proposes that these coexisting disorders are the expected manifestations of a single underlying pathogenetic mechanism: the presence of an overabundant and dysfunctional mass of visceral adipose tissue, which secretes adipokines that increase blood volume and blood pressure and cause insulin resistance, systemic inflammation, atrial fibrosis and electrical instability, cardiac hypertrophy, and vascular and glomerular injury, with the aging heart being particularly vulnerable to the effects of adipokines.

Epidemiologic observations support this reconceptualization. The emergence of HFpEF as a dominant clinical phenotype has coincided with a global epidemic of obesity and with the recognition that obesity acts as an accelerant for numerous disorders. Central obesity and adiposity precede HFpEF and are features of nearly every patient with HFpEF.[12] The expanded visceral adipose tissue mass in obesity is a secretory factory that manufactures numerous deleterious cardioactive molecules that have been implicated in experimental HFpEF. Accordingly, this paper puts forth a unifying hypothesis for HFpEF, proposing a single dominant pathway that applies to most patients, which explains both HFpEF and its comorbidities through one mechanism.

TERMINOLOGY AND SCOPE FOR THIS INITIAL PRESENTATION OF THE ADIPOKINE HYPOTHESIS. In this paper, the term "adipokine" designates all molecules or cellular elements that are secreted by adipocytes and act in an endocrine or paracrine manner to exert effects on the heart and blood vessels. Adipokines may be secreted by any cell type within adipose tissue, including adipocytes,

FIGURE 2 Mediators of Adipocyte Dysfunction to the Heart



Adipose tissue can secrete a broad array of molecules and cellular constituents that can act in an endocrine or paracrine manner to exert favorable or deleterious effects on the heart.

endothelial cells, mesenchymal stem cells, macrophages, and fibroblasts—although adipocytes are playing the initiating role in states of nutrient excess.

As shown in Figure 1, adipokines can include a broad range of signals:

- Polypeptides and proteins (eg, leptin, adiponectin)
- Steroids and eicosanoids (eg, aldosterone, prostaglandin, and leukotrienes)[31]
- Lipokines (byproducts of lipolysis, eg, fatty acids)
- Metabokines (byproducts of cellular energy metabolism)[32]
- Adipoexosomes—nanosized extracellular vesicles that not only contain proteins, but also microRNAs that regulate gene transcription in distant tissues.[33] The quantity of adipoexosomes increases markedly when adipocytes assume a proinflammatory profile, as in patients with obesity or HFpEF.[34]
- Circulating inflammatory or mesenchymal stem cells derived from adipose tissue or adipose progenitor cells in the bone marrow, which are capable of homing to the heart to alter its biological characteristics.

For this initial presentation of an adipose tissue-centered framework for HFpEF (Figure 2), this paper focuses primarily on *polypeptides and proteins* secreted by adipose tissue, because they have been exceptionally well-characterized and been targeted by therapeutic innovations. However, studies of the role of bioactive lipids, lipokines, metabokines, microRNAs, and adipose- or bone marrow-derived cell constituents in adiposity-mediated HFpEF are emerging rapidly and warrant inclusion in the framework.

An essential dimension of HFpEF is its strong predilection to afflict women. Women show disproportionate increases in left ventricular filling pressures following increases in central blood volume and have greater ventricular and arterial stiffness than men. Importantly, adipose tissue comprises a larger proportion of total body weight in women, as compared with men. In fact, women are particularly predisposed to epicardial and intramyocardial fat expansion and to imbalances in adipocyte-associated proinflammatory mediators.[35] Hence, the adipokine hypothesis is positioned to integrate these

observations. The influence of sex—as well as race and ethnicity—on adipose tissue biology and adipokine signaling are important topics to be addressed in future work.

Finally, although the term "obesity" has commonly been used in both experimental and clinical research studies, in clinical practice, it is defined by body mass index. However, the mechanisms discussed in this paper are closely linked to excess and dysfunctional visceral fat, and not to changes in skeletal muscle or bone mass. Therefore, the adipokine hypothesis is applicable to the large number of people with *excess visceral adiposity*, many of whom do not meet the definition of "obesity." The term "visceral fat" includes fat surrounding and residing within major organs as well as the abdomen.

PART II: SUBSTANTIAL OVERLAP IN THE BIOLOGY, PATHOPHYSIOLOGY, AND CLINICAL FEATURES OF OBESITY AND HFpEF SUGGEST A COMMON MECHANISTIC LINK

Obesity, visceral adiposity, and HFpEF show substantial overlap in epidemiological studies and in the clinical setting,[11-13] and both obesity and HFpEF are characterized by exceptionally similar cardiac structural and functional abnormalities, neurohormonal and proinflammatory profiles, and similar molecular biosignatures of cardiomyocyte stress. The striking parallelism of the 2 disorders, depicted in **Table 1** (and described in Parts II and III) suggests that obesity and HFpEF reflect a shared mechanistic origin (Box 2).

HEMODYNAMIC, NEUROHORMONAL, AND CARDIAC ABNORMALITIES IN EXCESS ADIPOSITY. Obesity is accompanied by augmented renal tubular sodium reabsorption, occurring along the entire span of the nephron.[36] Heightened renal sympathetic nerve activity together with elevated levels of angiotensin II, aldosterone, and leptin in obesity contribute to renal sodium retention, and both leptin and angiotensin II directly stimulate the release of aldosterone by the adrenal gland.[37,38] Hypertrophied adipocytes are an additional major source of aldosterone production (through a calcineurin-dependent pathway), and obesity is accompanied by aldosterone-independent activation of the mineralocorticoid receptors.[38-40] The additional effect of obesity to suppress circulating levels of natriuretic peptides—through enhanced expression of neprilysin or augmented clearance natriuretic peptides[41,42]—can promote further sodium retention, peripheral vasoconstriction, and hypertension. Due to the confluence of these factors, obesity is typically accompanied by volume-dependent hypertension, which is responsive not only to MRAs and neprilysin inhibitors, but also to incretin-based drugs.[43-45]

The neurohormonal derangements in obesity contribute directly to cardiomyocyte stress and derangements in cardiac structure and function. Increases in leptin, angiotensin II, and aldosterone together with diminished natriuretic peptide

TABLE 1 Pathophysiological and Mechanistic Overlap Between Obesity and HFpEF

	Obesity/ Visceral Adiposity	Heart Failure with Preserved Ejection Fraction
Central obesity (increased waist-to-height ratio)	Nearly universal.	
Visceral adipose tissue	Increased epicardial and visceral fat. Molecular and cellular adipose tissue dysfunction.	
Blood pressure	Hypertension in majority of patients.	
Plasma volume	Expanded, with redistribution toward central compartment.	
Left ventricular structure	Left ventricular hypertrophy with coronary microvascular endothelial dysfunction and rarefaction. Mild fibrosis in obesity, variable fibrosis in HFpEF.	
Left ventricular volume and diastolic filling	Mild-to-moderate LV enlargement, with LV overfilling and abnormal diastolic filling dynamics.	
Abnormalities of signal transduction and cellular homeostasis in cardiomyocytes and adipocytes	Activation of nutrient surplus signaling (mTOR) and suppression of nutrient deprivation signals (SIRT1/AMPK). Increased oxidative stress and proinflammatory signaling, leading to mitochondrial dysfunction and impaired calcium kinetics.	
Myocardial injury	Mild increase in cardiac troponin, reduced by weight loss.	
Renal tubular sodium reabsorption	Enhanced at multiple tubular sites because of activation of renal sympathetic nerves, renin-angiotensin system, aldosterone, and leptin.	
Changes in renal structure and function	Glomerular hyperfiltration in obesity. Renal inflammation and fibrosis caused by angiotensin II, aldosterone, leptin, and other proinflammatory mediators.	
Systemic inflammation	Large proportion of afflicted individuals have increased serum levels of high sensitivity C-reactive protein or other inflammatory mediators.	
Sympathetic nervous system and renin-angiotensin system	Activated renal and mesenteric sympathetic nerves and angiotensin II contributing to sodium retention, blood volume expansion and redistribution, and LV hypertrophy.	
Aldosterone and mineralocorticoid receptors	Angiotensin II- and leptin-dependent stimulation of aldosterone by adrenal gland, contributing to renal sodium retention and LV fibrosis. Secretion of aldosterone by adipocytes. Aldosterone-independent activation of mineralocorticoid receptors.	
Natriuretic peptides	Disproportionately low circulating levels and diminished responsiveness to natriuretic peptides, leading to tissue cyclic GMP deficiency.	
Leptin	Heightened circulating levels of leptin contribute to sodium retention, LV hypertrophy and myocardial fibrosis, and to renal inflammation and fibrosis.	
Insulin sensitivity	Insulin-resistant state, often accompanied by type 2 diabetes.	
Responsiveness to antihypertensive drugs	Excellent blood pressure lowering in patients with obesity in response to mineralocorticoid receptor antagonism and incretin-based drugs.	

AMPK = adenosine monophosphate activated protein kinase; GMP = guanosine monophosphate; LV = left ventricular; mTOR = mechanistic target of rapamycin; SIRT1 = sirtuin-1.

BOX 2. Reasons to Explore an Adipose-Centered Hypothesis for HFpEF

1. The surge in the incidence and prevalence of HFpEF over the past 30 years has coincided with the global epidemic of obesity.
2. Visceral adiposity in the general community is a harbinger of the subsequent development of HFpEF (but not the development of HFrEF) across diverse populations.
3. Central adiposity is present in nearly all patients with HFpEF, and obesity (defined by a body mass index of ≥30 kg/m^2) characterizes 60%-70% of patients with HFpEF. Conversely, a substantial proportion of people with obesity are likely to have mild (unrecognized) HFpEF as an explanation for their exercise intolerance.
4. Both obesity (visceral adiposity) and HFpEF share exceptionally similar and overlapping clinical presentations, cardiac structural and functional abnormalities, neurohormonal and proinflammatory profiles, and molecular biosignatures of adipocyte and cardiomyocyte stress.
5. In obesity, visceral fat undergoes hypertrophy, inflammation, and fibrosis, and in parallel, they secrete an altered suite of biologically active molecules that produce hypertrophy, inflammation, and fibrosis of the heart. The changes in adipokine profile seen in patients with visceral adiposity are strikingly similar to those seen in HFpEF.

signaling activate prohypertrophic and profibrotic pathways in the heart, leading to increased ventricular mass.[20,21,46] Leptin and aldosterone (along with the dysregulation of perivascular fat) also promote abnormalities in arterial stiffness.[47] Additionally, people with obesity but without clinical cardiovascular disease demonstrate markedly increased systemic inflammation (ameliorated by weight loss), leading to widespread endothelial dysfunction, particularly of the coronary microvasculature, often with mild subclinical fibrosis.[48,49]

In obesity, cardiomyocytes experience substantial increases in oxidative and other cellular stresses, which lead to mitochondrial dysfunction, impaired calcium handling, and potential loss of cardiomyocyte viability.[50-52] Cardiac troponin levels are increased in obesity and decline following marked weight loss.[53,54] In the absence of symptoms or a diagnosis of cardiovascular disease, obesity impairs ventricular distensibility as a result of myocardial hypertrophy, fibrosis, and oxidative stress.

When the constrained left ventricle is challenged by hypervolemia and by decreases in systemic venous capacitance,[15,55] people with obesity exhibit heightened left ventricular filling pressures at rest or exercise, increased left atrial chamber dimensions, and abnormal diastolic filling dynamics.[47,56,57] These derangements may be clinically relevant, even if they do not meet current diagnostic thresholds for HFpEF. Patients with obesity also exhibit glomerular hyperfiltration, which (together with the profibrotic effects of angiotensin II, aldosterone, leptin and neprilysin, and perirenal fat) promotes the development of underappreciated chronic kidney disease.[20,58]

HEMODYNAMIC AND NEUROHORMONAL ABNORMALITIES IN HFpEF. All pathophysiological mechanisms that are activated in people with obesity and visceral adiposity (described in the previous text) are also upregulated in patients with HFpEF.

Renal sodium retention, plasma volume expansion, and hypertension are seminal features of HFpEF. HFpEF impairs the ability of the kidney to excrete salt,[59] and nearly all patients with HFpEF have a history of hypertension. Those with concurrent obesity or visceral adiposity have an expanded plasma volume whose magnitude is proportional to the increase in left ventricular filling pressure.[11,15,60] Sympathetic nerve traffic is increased to both the kidneys and splanchnic bed, the latter leading to reduced systemic venous capacitance and increased stressed blood volume in HFpEF.[16,61] Renal and splanchnic denervation has been reported to produce favorable hemodynamic and clinical responses in patients with HFpEF.[62,63]

Increased serum aldosterone levels in patients with HFpEF are correlated with changes in ventricular geometry and have prognostic significance,[64,65] and mineralocorticoid receptors are activated in experimental models of HFpEF independent of aldosterone.[66] Patients with HFpEF have increased circulating levels of leptin and suppressed levels of natriuretic peptides,[67] and they show resistance to natriuretic peptide signaling, potentially related to increased circulating neprilysin.[59,68,69] The elevated blood pressure in patients with HFpEF is responsive to neprilysin inhibition, MRAs, and incretin-based drugs.[70-72]

The neurohormonal abnormalities that characterize HFpEF contribute to derangements in cardiac structure and function. Increases in leptin and aldosterone and diminished natriuretic peptide signaling in HFpEF promote the activation of prohypertrophic and profibrotic pathways in HFpEF.[21,22,64] In addition, most people with HFpEF demonstrate evidence of marked systemic inflammation (with or without obesity),[73,74] and coronary microvascular endothelial

inflammation leads to rarefaction and fibrosis, both contributing to impaired ventricular distensibility.[18,19] Furthermore, in experimental HFpEF, cardiomyocytes experience substantial increases in oxidative and nitrosative stresses, which lead to mitochondrial dysfunction, suppressed autophagic flux, and dysfunctional calcium handling.[75-78] Cardiac troponin is increased in patients with HFpEF, particularly during exercise and proportionally to the increase in left ventricular filling pressures.[79]

In patients with both HFpEF and obesity, incretin-based drugs ameliorate left ventricular hypertrophy and mitigate systemic inflammation and the release of troponin.[72] In experimental and clinical HFpEF, the action of natriuretic peptides to inhibit oxidative stress in the kidney and renal fibrosis is lost, but neprilysin inhibition can improve renal function and slow progression to end-stage kidney disease.[80]

DECIPHERING THE SEQUENCE OF THE ADIPOSITY-HFpEF OVERLAP: VISCERAL ADIPOSITY AND CENTRAL OBESITY PRECEDES AND PREDICTS THE DEVELOPMENT OF HFpEF (BUT NOT HFrEF). The available evidence indicates that both obesity and HFpEF result from the shared interplay of exceptionally similar pathophysiological mechanisms, which include sodium retention, neurohormonal activation, systemic inflammation and end-organ fibrosis, and enhanced signaling through the leptin-aldosterone-neprilysin axis. Yet, this parallelism (by itself) does not indicate whether one condition precedes the other.

Therefore, it is important to note that genetic obesity or dietary nutrient excess precedes and induces HFpEF (but not HFrEF) in experimental models.[48,75-77] More importantly, in the general community, both excess visceral adiposity and central obesity precedes and is a consistent harbinger of the subsequent development of HFpEF (but not the development of HFrEF)[14,81,82]—a finding that has been consistent across diverse populations. The ability of visceral fat to predict heart failure events follows a dose-response relationship and is particularly meaningful for fat depots surrounding the heart.[30,83] By the time that a formal clinical ascertainment of HFpEF has been made, nearly all patients with HFpEF have excess adiposity or central obesity,[12,13] and the severity of hemodynamic and clinical abnormalities parallels the degree of adiposity.[9,15] A substantial proportion of people with obesity (or visceral adiposity) are likely to have unrecognized HFpEF as an explanation for their exercise intolerance.[84]

The substantial mechanistic and clinical overlap of obesity and HFpEF—and the consistent finding that an expanded fat mass presages the development of experimental and clinical HFpEF—points to visceral adiposity as the driving force in the pathogenesis of HFpEF. The adipokine hypothesis proposes that hypertrophied and inflamed visceral adipose tissue can disseminate its dysfunctional state of heightened cellular stress to the heart, vasculature, and kidneys—by virtue of the secretion and endocrine/paracrine delivery of an altered suite of biologically active molecules (ie, adipokines) (**Figure 1**). Surgical removal of visceral fat can ameliorate adverse systemic effects.[85]

ALTERNATIVE CONSIDERATIONS FOR A PATHOGENETIC ROLE OF VISCERAL ADIPOSE TISSUE. Are there mechanisms—other than the secretion of adipokines—that might account for a causal relationship between excess visceral adiposity and HFpEF?

Both obesity and HFpEF are insulin-resistant states, and some have proposed that diminished responsiveness to insulin has adverse metabolic consequences. In contrast, others have proposed that such resistance is adaptive,[86] and it is the reactive hyperinsulinemia that promotes the development of HFpEF. However, there is little evidence that either insulin deficiency or hyperinsulinemia drive the cardiovascular abnormalities in either obesity or HFpEF, because drugs with strikingly different effects on insulin signaling (eg, incretin-based agents and SGLT2 inhibitors) demonstrate similar effects to reduce the risk of heart failure events in patients with HFpEF.[24,26] Furthermore, prolonged therapeutic elevation of circulating insulin levels neither increases nor decreases the risk of heart failure.[87]

Instead, insulin resistance appears to merely represent a biomarker of a shift in the expression of glucose transporter isoforms in skeletal muscle and adipose tissue. As a result of alterations in intracellular nutrient signaling, both obesity and heart failure induce a change in expression from an insulin-sensitive isoform (GLUT4) typically seen in healthy individuals to an insulin-insensitive isoform (GLUT1) typically seen during embryonic development. Downregulation of GLUT4 in adipocytes, as a result of visceral adiposity, is the primary cause of systemic insulin resistance.[88]

It is also possible that an expanded visceral adipose tissue mass might influence cardiac function because of physical forces. Specifically, an increase in fat mass might encroach onto the pericardial space to create a constraint on right and left ventricular filling,[9] a state that would be alleviated by pericardiectomy.[89] However, the importance of pericardial constraint as a mechanism of HFpEF in patients

with obesity remains a matter of debate, especially in light of evidence that a marked drug-induced shrinkage of pericardial fat results in a decrease—rather than an increase—in left ventricular volumes in patients with obesity and HFpEF.[27]

PART III: PARALLELISM OF NUTRIENT SENSING PATHWAYS IN ADIPOSE TISSUE AND THE HEART POINTS TO INTERORGAN SIGNALING IN BOTH HEALTH AND DISEASE

In healthy people, adipose tissue typically exhibits nurturing functions, characterized by the storage and timely release of scarce fuel, the combustion of disruptive fatty acids, and the suppression of inflammation. However, in states of nutrient excess or HFpEF, the expansion of visceral white fat is accompanied by heightened adipocyte stress, a prerequisite for growth and replication. Nutrient-driven adipose tissue inflammation in obesity accelerates the endothelial-to-mesenchymal transition (thus promoting fibrosis), while causing mesenchymal stem cells to lose their regenerative capacity and to adopt a senescence profile.[90] These transformative changes in adipose tissue are mediated by the enhanced production of adipocyte-derived molecules that promote the local cellular oxidative and proinflammatory stresses that are essential for the proliferation of adipose tissue. However, once secreted, these molecules transmit the state of adipose tissue dysfunction, inflammation, and fibrosis to other organs, particularly the heart.

Adipocytes are capable of synthesizing >600 proteins,[91,92] and they can release countless nonprotein signaling molecules. The balance of adipokines favors a cytoprotective effect in healthy people, whereas a proinflammatory profile is dominant in states of adiposity and HFpEF. The effects of adipocyte-secreted polypeptides are mediated through well-defined intracellular signal transduction pathways, operating in both fat and cardiac tissue. There is a striking parallelism of nutrient deprivation and nutrient surplus signaling in adipose tissue and the heart, both in health and disease.

IMBALANCE OF NUTRIENT-SENSITIVE SIGNAL TRANSDUCTION PATHWAYS IN HEART FAILURE. In the healthy heart, cardiomyocyte stress is minimized by the dominance of nutrient deprivation signaling, which acts to enhance the oxidation of long-chain fatty acids, ATP production, and mitochondrial health, while promoting cellular housekeeping (ie, autophagy), and maintaining cellular viability. Nutrient deprivation signals are mediated by sirtuin-1 (SIRT1), adenosine monophosphate protein kinase (AMPK) and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α).[93,94] However, the failing heart is characterized by a state of perceived intracellular nutrient excess, with enhanced uptake of glucose, the cytosolic accumulation of deleterious metabolic byproducts, impaired autophagic flux, and mitochondrial dysfunction.[94,95] This dysfunctional state is accompanied by increased oxidative and organellar stress and enhanced sustained signaling through proliferative, prohypertrophic, proinflammatory, and profibrotic pathways, eg, phosphoinositide-3 kinase-Akt-mechanistic target of rapamycin (PI3K-Akt-mTOR).[93-95] At the same time, the failing heart exhibits suppression of nutrient deprivation signals, ie, SIRT1, AMPK, and PGC-1α—thereby limiting their ability to exert cytoprotective actions and oppose the action of nutrient surplus signals.

IMBALANCE OF NUTRIENT-SENSITIVE SIGNAL TRANSDUCTION PATHWAYS IN OBESITY. An expansion of visceral fat mass is also characterized by a dominance of nutrient surplus signaling (as evidenced by enhanced mTOR signaling) and a suppression of nutrient deprivation signaling (as evidenced by diminished AMPK/SIRT1 signaling) within hypertrophied and proliferating adipose tissue.[96-98] The shift in signal transduction pathways in inflamed adipocytes is strikingly parallel to that seen in the failing heart.

This parallelism does not appear to be coincidental; instead, it represents a coordinated interplay between the 2 organs, as evidenced by experimental adipose-specific interventions. Adipose-specific knockout of mTOR activity prevents obesity,[99] and mTOR inhibition ameliorates both adipose tissue inflammation and the features of HFpEF in obese (but not in lean) mice.[100] Additionally, selective SIRT1 up-regulation in adipose-derived stem cells alleviates diabetes-induced HFpEF,[101] and adipocyte-specific up-regulation of heme oxygenase-1 (which reinforces SIRT1 signaling[102]) improves the biological profile of cardiac and vascular tissues in experimental obesity.[103] Therefore, the parallel up-regulation of stress-enhancing intracellular signaling in adipocytes and cardiomyocytes appears to be driven by biological events in adipose tissue.

OTHER INTRACELLULAR SIGNAL TRANSDUCTION PATHWAYS RELEVANT TO OBESITY AND HEART FAILURE. Many other signal transduction pathways show parallel derangements in both the expanded fat depots and in the failing heart, and they act to modulate hypertrophy, inflammation, and fibrosis. For this review, the most relevant are as follows:

- Wnt signaling, either canonical signaling through Wnt/β-catenin or noncanonical Wnt signaling that is linked to Ca^{2+} or to Jun N-terminal kinase (JNK);
- Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling;
- G-protein coupled receptors, which signal through cyclic AMP and phosphoinositol 4,5 bisphosphate;
- Activin receptors, which allow members of the transforming growth factor-β (TGF-β) superfamily to signal to the nucleus through intracellular Smad proteins.

PART IV: KEY LINES OF EVIDENCE SUPPORTING THE ADIPOKINE HYPOTHESIS OF HFpEF

Numerous independent and interdependent lines of evidence support the hypothesis that visceral adiposity is the preceding event and dominant feature of HFpEF and that adipokines are responsible for the transmission of the biological state of dysfunctional adipose tissue to influence the biological state of the heart, thus causing HFpEF (Box 3 and Central Illustration 1).

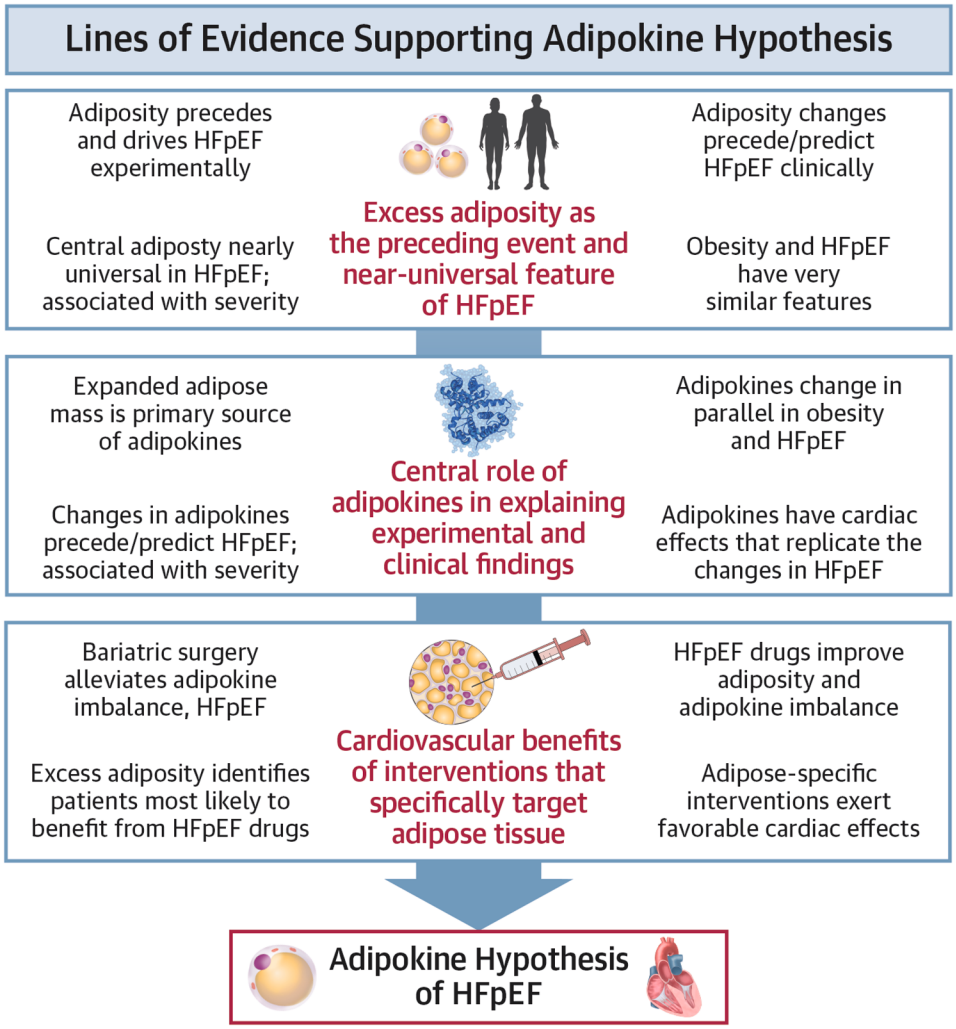
A SUMMARY OF FINDINGS POINTING TO VISCERAL ADIPOSITY AND MALADAPTIVE SHIFTS IN ADIPOKINE SECRETION PROFILES AS THE KEY MEDIATORS IN THE PATHOGENESIS HFpEF. Excess adiposity as the preceding event and near-universal feature. Obesity and adiposity from genetic causes or dietary excess represent the major mechanism that drives the development of HFpEF in experimental models. In the clinical setting, changes in visceral adiposity are observed years before the diagnosis of HFpEF and predict the development of HFpEF (but not the development of HFrEF). Central obesity (indicative of excess visceral adiposity) is nearly ubiquitous in patients with HFpEF, and the degree of adiposity is a major determinant of hemodynamic and clinical severity of HFpEF as well as its prognosis. Obesity and HFpEF exhibit striking similarities and parallelism and substantial overlap in their pathophysiological and clinical features and their molecular signatures. These findings are characterized in Parts II, III, and IV.

Central role of adipokines in explaining experimental and clinical findings. Adipocytes (but not cardiomyocytes) synthesize and secrete cardioactive adipokines. In people with visceral adiposity or obesity, the expanded adipose tissue mass emerges as the dominant source of proinflammatory adipokines. In the general community, changes in circulating levels of adipokines are observed years before the diagnosis of

BOX 3. Lines of Evidence That Visceral Adiposity and Maladaptive Shifts in the Adipokine Secretion Profile Are the Principal Cause of HFpEF

1. The heightened prevalence of HFpEF in clinical practice has coincided with the global epidemic of obesity.
2. Obesity and adiposity represent a major cause of HFpEF in experimental models.
3. Obesity and HFpEF exhibit striking similarities and parallelism and substantial overlap in their pathophysiological and clinical features and their molecular signatures.
4. Changes in visceral adiposity and in circulating levels of adipokines are observed years before the diagnosis of HFpEF and predict the development of HFpEF (but not the development of HFrEF) in the general community.
5. Central obesity (indicative of excess visceral adiposity) is nearly ubiquitous in patients with HFpEF, and the degree of adiposity is a major determinant of hemodynamic and clinical severity of HFpEF as well as its prognosis.
6. Adipocytes (but not cardiomyocytes) typically (and often uniquely) synthesize and secrete cardioactive adipokines. In people with visceral adiposity or obesity (where fat mass comprises as much as 50% of body weight), adipose tissue emerges as the dominant source of proinflammatory adipokines.
7. The pattern of changes in adipokines in experimental or clinical obesity closely parallels the pattern of changes in adipokines in experimental or clinical HFpEF. The magnitude of changes in circulating adipokine levels parallels the clinical severity and prognosis of HFpEF.
8. Adipokines have well-characterized effects on cardiac structure and function, and these actions have been implicated in the pathogenesis of cardiomyopathy and HFpEF in experimental studies.
9. Bariatric surgery or drug treatments for HFpEF cause shrinkage of visceral fat depots, to a degree that is disproportionately larger than the decline in body weight. Such shrinkage is accompanied by a simultaneous increase in circulating levels of adaptive adipokines and decrease in the circulating levels of maladaptive adipokines, leading to amelioration of HFpEF. The responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a cardioprotective profile.
10. An expanded adipose tissue mass is a primary driver of the upregulation of angiotensin II, aldosterone and neprilysin in HFpEF, explaining why excess adiposity has identified patients most likely to respond to current drugs for HFpEF in clinical trials.
11. Molecular interventions that target only adipose tissue so as to selectively increase or decrease its secretion of specific adipokines have been demonstrated to cause parallel effects on the heart through an endocrine mechanism, thereby modulating cardiac structure and the evolution of cardiomyopathy.

CENTRAL ILLUSTRATION 1 Lines of Evidence Supporting the Adipokine Hypothesis of HFpEF



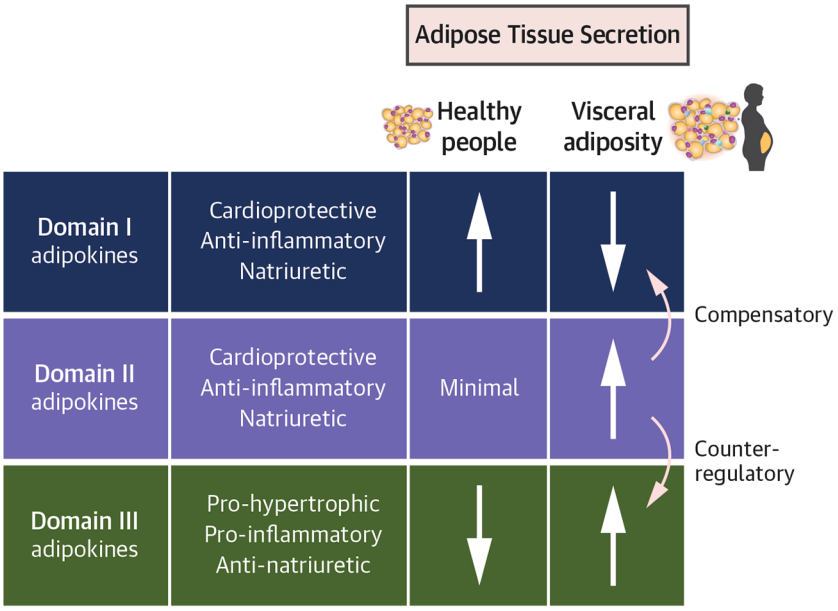
Packer M, JACC. 2025;■(■):■-■.

HFpEF = heart failure with preserved ejection fraction.

HFpEF and predict the development of HFpEF. The pattern of changes in adipokines seen in experimental or clinical obesity closely parallels the pattern of changes in adipokines seen in experimental or clinical HFpEF. The magnitude of changes in circulating adipokine levels parallels the clinical severity and prognosis of HFpEF. Adipokines have well-characterized effects on cardiac structure and function, and they have been implicated in the pathogenesis of cardiac stress, cardiomyopathy and HFpEF in experimental studies. These findings are characterized in Parts V, VI, and VII.

Cardiovascular benefits of interventions that target adipose tissue and adipokines. Bariatric surgery or drug treatments for HFpEF cause shrinkage of visceral fat depots to a degree that is disproportionately larger than the decline in body weight. Such shrinkage is accompanied by increases in circulating levels of cytoprotective adipokines and decreases in the levels of proinflammatory adipokines. These responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a cardioprotective profile. An expanded

FIGURE 3 Characterization of Adipokine Domains



In healthy people, adipocytes primarily secrete Domain I adipokines, with minimal secretion of Domain II adipokines and with suppression of Domain III adipokines. In people with visceral adiposity or obesity, adipose tissue secretes primarily Domain III adipokines, with suppression of Domain I adipokines. At the same time, adipocytes emerge as an important source of Domain II adipokines, acting as a compensatory response to the loss of Domain I adipocytes and as a counter-regulatory response to Domain III adipokines.

adipose tissue mass is the primary driver of the neurohormonal activation in HFpEF, explaining why excess adiposity may identify patients likely to benefit from current drugs for HFpEF. These findings are characterized in Part VIII.

Importantly, molecular interventions that target only adipose tissue so as to selectively increase or decrease its secretion of specific adipokines cause parallel effects on the heart, thereby modulating the evolution of cardiomyopathy. When HFpEF is produced experimentally in mice by transverse aortic constriction, the transplantation of bone marrow mesenchymal cells from HFpEF mice leads to recapitulation of the HFpEF phenotype in healthy recipient mice.[104] Similar cross-talk between adipocytes and the heart have been observed following the transplantation of adipose tissue.[105] In numerous studies, experimental overexpression or suppression of the secretion of specific adipokines—such that the effect occurs only in adipose tissue—exerts distant effects on the heart that are relevant to the pathogenesis of HFpEF. These findings are characterized in Part IX. Intriguingly, circulating adipokines may be capable of selectively targeting the heart as a result of cardiomyocyte-preferential expression of adipokine receptors.[106]

A NOVEL CLASSIFICATION OF CARDIOACTIVE ADIPOKINES DESCRIBES FUNCTIONAL ALIGNMENTS THAT ARE RELEVANT TO HFpEF. To promote an understanding of the mechanisms that underlie adipose-derived signaling in HFpEF, this paper introduces a novel, function-based classification of adiposity-relevant cardioactive adipokines, which groups adipokines into 3 domains (**Figure 3** and Box 4):

1. ***Domain I adipokines*** are secreted by healthy adipocytes, being abundant in lean individuals and suppressed by obesity and visceral adiposity. They typically inhibit fat mass expansion and inflammation and exert adaptive and cytoprotective effects on the heart. In obesity and visceral adiposity, the diminished secretion of these molecules leads to deleterious effects on the heart, because it allows the effects of prohypertrophic and proinflammatory adipokines to be unopposed (**Table 2**).
2. ***Domain II adipokines*** are secreted by adipocytes in heightened quantities in states of obesity and visceral adiposity, acting as a compensatory response to the deficiency of Domain I proteins (described in the previous text) or as a counterbalancing mechanism to oppose the adverse

BOX 4. Functional Classification of Adipokines Relevant to HFpEF

Domain I adipokines are secreted by healthy adipose tissue, being typically dominant in lean individuals and suppressed by obesity and visceral adiposity. They alleviate stress and inhibit inflammation in adipose tissue and produce similar adaptive effects in the heart. An expansion of visceral fat causes the diminished secretion of these cardioprotective molecules, leading to HFpEF.

Domain II adipokines are secreted by adipose tissue in heightened quantities in states of obesity and visceral adiposity, acting as a compensatory mechanism in response to a deficiency of the Domain I proteins (described in the previous text) or as a counterbalancing mechanism to oppose the adverse biological consequences of the Domain III proteins (described in the following text). These adipokines exert cardioprotective effects, but in states of obesity and visceral adiposity, the enhanced secretion of these cardiac stress-mitigating proteins is insufficient to prevent HFpEF, often because of biological resistance.

Domain III adipokines are secreted by hypertrophied or hyperplastic inflamed adipocytes, and their secretion is dominant in people with visceral adiposity. These adipokines not only promote further adipose stress, but they also cause cardiomyocyte dysfunction; pathological cardiac and vascular hypertrophy, myocardial inflammation and fibrosis, coronary microvascular disease, renal sodium retention and plasma volume expansion, and systemic and pulmonary hypertension.

consequences of Domain III proteins (described in the following text). The cardioprotective effects of Domain II adipokines are insufficient to prevent HFpEF, often because sustained hyperactivation leads to biological resistance (frequently related to impaired receptor signaling), Table 3.

3. ***Domain III adipokines*** are secreted by hypertrophied, hyperplastic, or inflamed adipocytes, and their secretion is dominant in people with visceral adiposity. These adipokines promote pathological cardiac and vascular hypertrophy, inflammation, and fibrosis as well as coronary microvascular disease, renal sodium retention and plasma volume expansion, and systemic and pulmonary hypertension (Table 4).

Importantly, in health and across a broad range of disease states, adipokines that belong to the same domain typically change in an aligned manner, and in general, changes in Domain I adipokines are directionally opposite to changes in Domain III adipokines.

The molecules included in each domain (described in Tables 2, 3, and 4 and Parts V, VI, and VII) represents a comprehensive, but not exhaustive, survey. This classification is intended as a working model, subject to refinement, as new adipokines are identified and the biological functions of currently recognized adipokines are better understood.

PART V: DOMAIN I ADIPOKINES: CARDIOPROTECTIVE MOLECULES THAT ARE SUPPRESSED IN OBESITY/VISCERAL ADIPOSITY AND HEART FAILURE

Domain I adipokines are synthesized by adipocytes in healthy lean individuals and act to reduce both adipose tissue and cardiac stress. They inhibit myocardial and vascular hypertrophy, inflammation and fibrosis, thus preventing the development of HFpEF (Figure 4).

DISTINCTIVE FEATURES OF DOMAIN I ADIPOKINES.

Domain I adipokines include adiponectin, C1q/tumor necrosis factor (TNF)-related proteins 3/9, omentin-1, secreted frizzled-related protein 5, extracellular nicotinamide phosphoribosyltransferase, zinc alpha 2-glycoprotein, and neuregulin-4.

Acting primarily in an endocrine manner, these adipokines can signal by up-regulation of nutrient deprivation pathways, eg, SIRT1, AMPK, and PGC-1α, but they also act through G-protein coupled receptors, and they modulate Wnt signaling. Except under exceptional stress, cardiomyocytes are not a major site of synthesis for Domain I proteins, and their effects on the heart are primarily driven by adipocyte synthesis (Box 5).

ADIPONECTIN AND ADIPONECTIN-LIKE ADIPOKINES.

Adiponectin. In lean people, the dominant adipokine in the body is adiponectin, which is typically synthesized only by adipocytes, acting to enhance insulin sensitivity and encourage lipid storage, thereby preventing ectopic lipid accumulation.[107] Remarkably, circulating levels of adiponectin are several orders of magnitude higher than ordinary hormones, supporting a major systemic role for this adipokine. In lean individuals, adiponectin is a key component of adipocyte-derived extracellular vesicles.[108]

Once secreted, adiponectin acts in an endocrine manner to target the heart,[106] where it promotes up-regulation of nutrient-deprivation cytoprotective signals, ie, SIRT1, AMPK, PGC-1α, and peroxisome proliferator-activated receptor-alpha/gamma (PPARα), thereby reducing oxidative stress and preserving mitochondrial health, while inhibiting myocardial hypertrophy, inflammation, and fibrosis.[109] Additionally, there exists a mutually antagonistic relationship between adiponectin and renal sympathetic nerve activity[110,111] and between adiponectin and aldosterone.[112,113] Adiponectin

TABLE 2 Domain I Adipokines

Adipokine (Protein or Family)	Origin and Signaling Pathways	Biological Effects in Adipose Tissue and the Heart	Changes in Obesity, Visceral Adiposity, and Heart Failure
Adiponectin	Endocrine signaling, often as a component of adipoexosomes, also epicardial fat secretion. Signals through SIRT1/AMPK/PGC-1α/PPARα.	Cytoprotective effects in adipose tissue. Adiponectin reduces inflammation and cellular stress in cardiomyocytes and inhibits sympathetic nerve traffic and aldosterone.	Adiponectin signaling is deficient in both obesity and HFpEF.
C1q/TNF-related proteins, particularly CTRP3 and CTRP9	Adiponectin paralogs, mimicking adiponectin. Endocrine effects and epicardial fat secretion. These can act through AMPK and SIRT, and they inhibit Wnt/β-catenin signaling.	Adipocyte-derived CTRP3/CTRP9 exert anti-inflammatory and cardioprotective effects. Adipocyte secretion is important, because cardiac-specific CTRP3/CTRP9 overexpression exacerbates hypertrophy.	Serum CTRP3 and CTRP9 levels are decreased in obesity and heart failure.
Omentin-1	Endocrine signaling and epicardial fat secretion. Omentin-1 inhibits the activin type II receptor and suppresses Wnt5a/Ca^{2+} signaling.	Omentin-1 reduces inflammation in adipose tissue. Adipocyte secretion inhibits maladaptive myocardial hypertrophy.	Omentin-1 is decreased in patients with visceral adiposity and heart failure, including HFpEF.
Secreted Frizzled-related protein 5 (SFRP5)	Endocrine or paracrine signaling, secreted by epicardial fat. SFRP5 acts as a soluble antagonist of Wnt5a.	SFRP5 inhibits ectopic fat accumulation. SFPR5 mitigates cardiac injury by reducing myocardial inflammation and fibrosis.	SFRP5 is suppressed in obesity and heart failure; correlated with diastolic filling abnormalities.
Extracellular nicotinamide phosphoribosyl-transferase (eNAMPT)	Endocrine action to promote synthesis of NAD+, the cofactor for SIRT1. eNAMPT antagonizes the receptor for C-C-chemokine ligand 5.	eNAMPT and NAD+ deficiency has adverse effects on cardiac hypertrophy and remodeling and promotes cardiomyopathy. eNAMPT inhibitors cause cardiotoxicity.	Obesity suppresses adipocyte eNAMPT expression. Cardiac NAMPT is depleted in HFpEF.
Zinc alpha 2-glycoprotein (ZAG)	ZAG signals through β2- and β3-adrenergic receptors and protein kinase A to exert endocrine effects.	ZAG stimulates lipolysis, mitochondrial function, and biogenesis; activates adiponectin and inhibits leptin; and shrinks visceral fat depots and inhibits cardiac fibrosis.	ZAG is suppressed in obesity and in patients likely to have HFpEF.
Neuregulin-4 (NRG-4)	Secreted by brown adipose tissue, NRG-4 acts in endocrine manner, signaling through ErbB4.	NRG-4 reduces oxidative and proinflammatory stress in adipocytes, thus alleviating obesity. Therapeutic delivery of NRG-4 ameliorates cardiomyopathy and nephropathy.	Suppressed expression of NRG-4 in obesity and in pressure-overload cardiac hypertrophy.

CTRP = C1q/TNF-related proteins HFpEF = heart failure with preserved ejection fraction; PGC-1a = peroxisome proliferator-activated receptor-gamma coactivator-1alpha; PPARa/g = peroxisome proliferator-activated receptor-alpha/gamma; other abbreviations as in Table 1.

antagonizes the actions of aldosterone to promote HFpEF.[114,115]

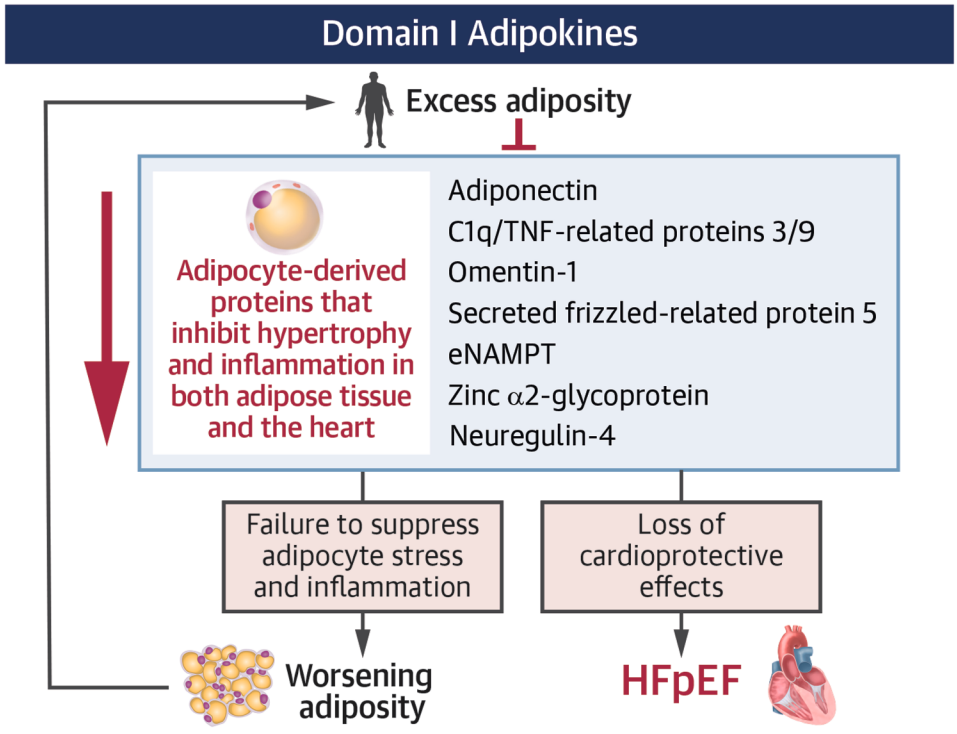
Obesity and visceral adiposity is accompanied by suppression of adiponectin,[116] and such suppression has been implicated in renal sodium retention and plasma volume expansion,[117] in the impaired tolerance of the heart to volume overload,[118] and in the pathogenesis of experimental cardiomyopathy and HFpEF.[114,115,119-121] In patients without overt heart failure, low serum adiponectin are associated with increased left atrial size and left ventricular mass, and they predict future cardiovascular events.[122-124] Serum levels of adiponectin are suppressed in patients with established HFpEF.[125]

Therapeutically, adiponectin adenoviral delivery ameliorates cardiomyopathy and heart failure,[126] and adiponectin receptor agonists produce favorable effects in HFpEF.[127] Although the stressed heart can secrete adiponectin as a paracrine mechanism,[128] as end-stage heart failure ensues, cardiac levels of adiponectin and its receptor become depleted, but adipocyte-derived circulating levels increase, presumably as a compensatory response.[129,130] In patients with advanced heart failure, mechanical ventricular unloading leads to lowering of the adipocyte secretion of adiponectin, demonstrating the bidirectionality of crosstalk between fat depots and the heart.[129]

C1q/TNF-related proteins (CTRP3 and CTRP9). C1q/TNF-related proteins (CTRPs) comprise a family of 15 structurally related paralogs of adiponectin, which form heterotrimers (often involving adiponectin) and exert endocrine functions, often signaling through the adiponectin receptor.[131] Secreted primarily by adipocytes, CTRP3 and CTRP9 reduce adipocyte mass and improve insulin sensitivity, while exerting endocrine- and paracrine-mediated cardioprotective, anti-inflammatory, and vasodilator effects. They activate SIRT and AMPK and inhibit Wnt/β-catenin signaling.[131-137]

Circulating levels of CTRP3 and CTRP9 are decreased in individuals with visceral adiposity and

FIGURE 4 Suppression of Domain I Adipokines Links Visceral Adiposity to HFpEF



Domain I adipokines, such as adiponectin, CTRP3/9, omentin-1, secreted frizzled-related protein 5 (SFRP5), extracellular nicotinamide phosphoribosyltransferase (eNAMPT), zinc α2-glycoprotein (ZAG), and neuregulin-4 (NRG-4), are secreted by healthy adipose tissue and act to alleviate adipocyte stress and suppress cardiac inflammation, hypertrophy, and fibrosis. Secretion of these adipokines is reduced in obesity and visceral adiposity, leading to loss of their cardioprotective effects, leading to heart failure with preserved ejection fraction (HFpEF).

in patients with heart failure.[138-140] Experimental myocardial injury signals to fat depots to cause a decline in the adipocyte expression of both CTRP3 and CTRP9.[141,142] At the same time, the cardioprotective effect of adipose-derived stem cell-conditioned medium is blunted when CTRP3 is knocked down, whereas the measured delivery of CTRP9 systemically or via adipose-derived stem cells acts to mitigate cardiac injury.[134,143] These observations demonstrate bidirectional endocrine cross-talk between adipocyte-derived CTRP3 and CTRP9 and the myocardium.

Importantly, the benefits of CTRPs appear to be specifically related to their measured production by adipocytes, because coerced cardiac-specific overexpression of CTRP3 and CTRP9 (bypassing the influence of adipocytes) has deleterious effects on pressure-overload hypertrophy.[144,145] Glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to alleviate the suppression of adipocyte CTRP3 expression seen in experimental insulin resistance.[146]

OTHER DOMAIN I ADIPOKINES. Omentin-1. Omentin-1 is secreted by visceral fat, typically acting in an endocrine manner, with circulating levels that are typically correlated with adiponectin.[147] Omentin-1 interferes with the cellular pathways that mediate the action of Domain III adipokines by inhibiting the activin type II receptor and suppressing Wnt5a/Ca^{2+} signaling, and it may also up-regulate AMPK.[148-150]

Experimentally, omentin-1 alleviates adipose tissue inflammation,[151] and it ameliorates myocardial ischemic injury and cardiac hypertrophy.[152,153] It also reduces oxidative and endoplasmic reticulum stress in endothelial cells[148] and promotes nitric oxide-mediated vasodilation, while alleviating hypertension.[154]

Clinically, circulating levels of omentin-1 are decreased in people with obesity and in patients with

BOX 5. Key Features of Domain I Adipokines

1. Adiponectin, the principal Domain I adipokine, is secreted almost exclusively by adipocytes and circulates in high concentrations in healthy adults. Adiponectin suppresses adipose tissue inflammation and maintains cardiomyocyte homeostasis. It antagonizes the activity of renal sympathetic nerves, the renin-angiotensin system and aldosterone, and it inhibits myocardial hypertrophy, inflammation, and fibrosis, thereby acting to prevent HFpEF. C1q/TNF-related proteins 3 and 9 are structural paralogs of adiponectin, with aligned actions.
2. Other Domain I adipokines—omentin-1, secreted frizzled-related protein 5, and extracellular NAMPT—exert effects on the heart that are similar to those of adiponectin, typically counteracting the actions of Domain III adipokines. Zinc alpha 2-glycoprotein is a major lipid mobilizing hormone that shrinks fat depots.
3. Domain I adipokines are suppressed in both obesity and in HFpEF in experimental models and in the clinical setting. In patients, this suppression is seen years before the onset of heart failure, and the magnitude of suppression is correlated with the severity of heart failure and prognosis.
4. Experimental overexpression or recombinant delivery of Domain I adipokines mitigates the development of cardiac hypertrophy and fibrosis and alleviates the evolution of cardiomyopathy and HFpEF.
5. Bariatric surgery, incretin receptor agonists, SGLT2 inhibitors, mineralocorticoid receptor antagonists, and angiotensin receptor neprilysin inhibitors enhance circulating levels of Domain I adipokines.

dilated cardiomyopathy and heart failure,[155,156] and those with the lowest levels have the most unfavorable prognosis.[156,157] Serum omentin-1 concentrations are also decreased in patients with HFpEF, being inversely related to biomarkers of inflammation,[158] but they increase following treatment with GLP-1 receptor agonists.[159]

Secreted frizzled-related protein 5. Secreted by adipocytes, secreted frizzled-related protein 5 (SFRP5) acts as a soluble decoy that antagonizes WNT5a, a Domain III adipokine, thereby inhibiting noncanonical Wnt/JNK signaling.[160,161] In adipose tissue, SFRP5 promotes insulin sensitivity, enhancing the storage of lipids and limits the formation of ectopic fat.[162-164] Additionally, SFPR5 exerts cardioprotective and renoprotective actions by improving mitochondrial function and reducing inflammation and fibrosis.[165-167]

Adipocyte expression of SFPR5 is suppressed in patients with obesity/visceral adiposity and inflammation,[164] and circulating levels of SFPR5 are reduced in obesity and in heart failure.[168-170] Patients with higher SFPR5 levels have better glycemic control, less systemic inflammation, and lower systolic blood pressures.[169] Conversely, patients with heart failure with the lowest serum SFPR5 levels have worse ventricular diastolic filling dynamics and a higher risk of adverse heart failure outcomes.[170-172]

Overexpression of SFPR5 or treatment with recombinant SFPR5 preserves systolic function and reduces cardiac inflammatory responses and adverse remodeling in experimental heart failure.[160,165] The effect of GLP-1 receptor agonism to mitigate experimental diabetic nephropathy is accompanied by elevated circulating levels of SFPR5.[173] In the clinical setting, weight loss or treatment with GLP-1 receptor agonists is accompanied by increases in circulating SFPR5.[174,175]

Extracellular nicotinamide phosphoribosyltransferase. Nicotinamide phosphoribosyltransferase (NAMPT) was initially characterized as a proinflammatory cytokine (referred to as visfatin),[176] but NAMPT is now recognized as the rate-limiting step in the salvage pathway for the systemic biosynthesis of nicotinamide adenine dinucleotide (NAD+), the principal cofactor for SIRT1 activation.[177] SIRT1 signaling plays a critical role in the mitigation of obesity-related microvascular dysfunction and the development of dysmetabolism-related HFpEF.[178,179]

NAMPT typically acts within cells, but an extracellular form of NAMPT (referred to as eNAMPT) is released from adipocytes in response to SIRT1 (often as a component of adipoexosomes[180]) to exert endocrine effects.[181-183] eNAMPT acts both as a systemic NAD+ biosynthetic enzyme[183] and as a natural antagonist of the receptor for C-C-chemokine ligand 5 (RANTES), a proinflammatory Domain III adipokine.[181]

Obesity and visceral adiposity are accompanied by a decrease in eNAMPT expression and intracellular NAD+ levels in adipocytes,[184] and these changes are reversed with weight loss.[185] Experimental adipocyte-specific NAMPT or eNAMPT suppression induces a systemic NAD+-deficiency, leading to multiorgan metabolic dysfunction.[186-188] These studies demonstrate the importance of adipocyte secretion as an endocrine mediator of adipose dysfunction to distant sites.

Extracardiac synthesis of eNAMPT, acting to sustain circulating levels of NAD+, alleviates experimental cardiac pressure overload.[189] Cardiomyocyte NAMPT deficits promote maladaptive hypertrophy,

degrade antioxidant defenses, impair cardiomyocyte viability, and exacerbate cardiomyopathy,[190-192] and NAMPT inhibition is accompanied by cardiotoxicity.[193] The expression of NAMPT is depleted in the myocardium of patients with HFpEF, and low serum levels of eNAMPT are associated with a poor prognosis in HFpEF.[194] In contrast, therapeutic augmentation of circulating levels of NAD+ improves metabolic and antioxidant profiles in HFpEF.[195,196]

Zinc α2-glycoprotein. Zinc α2-glycoprotein (ZAG) functions as a lipid-mobilizing adipokine, inhibiting lipogenesis and promoting lipolysis.[197,198] In adipocytes, ZAG interacts with β2- and β3-adrenergic receptors (and through G protein-coupled receptor signal transduction) stimulates uncoupling protein-1, augmenting mitochondrial function and biogenesis, and adipose tissue browning.[199,200] These actions cause marked shrinkage of subcutaneous and visceral fat depots and organ lipid content.

Cancers that cause cachexia promote the secretion of ZAG into the circulation, where it exerts endocrine effects to promote the catabolism of white adipose tissue.[201] However, in states of obesity, the presence of visceral adiposity and adipose tissue inflammation inhibits the expression of ZAG in adipocytes, promoting further adipogenesis.[197,198,201,202] Clinically, ZAG signaling is deficient in patients with obesity and visceral adiposity. Circulating levels of ZAG are inversely correlated with body mass index and indexes of visceral adiposity, and they track closely with levels of adiponectin.[203-206]

ZAG overexpression or recombinant ZAG induces lipolysis and reduces body weight, decreases blood pressure, and promotes urinary sodium excretion, and mitigates collagen deposition in the heart and kidneys.[207,208] These observations point to adiposity-related ZAG suppression as a potential contributor to the plasma volume expansion, hypertension, and cardiac fibrosis seen in HFpEF. ZAG levels in the circulation are sufficient to exert an antifibrotic effect,[207] further supporting an endocrine action.

Interestingly, serum levels of ZAG are increased in patients with severe HFrEF and may contribute to cardiac cachexia.[209] In marked contrast, serum ZAG levels are decreased in patients with a HFpEF phenotype (ie, those with hypertension who have central obesity or have diabetes with diastolic filling abnormalities).[210,211] Intriguingly, GLP-1 receptor agonism and SGLT2 inhibition up-regulate adipocyte expression of ZAG and increase circulating levels of ZAG in patients with insulin resistance.[207,212-214] These observations suggest that modulation of ZAG may contribute to the therapeutic effects of these drugs in adiposity-related HFpEF.

Neuregulin-4 (NRG-4). Neuregulins signal through receptor tyrosine kinases encoded by the ErbB family.[215] Interest in neuregulins was awakened when trastuzumab, an ErbB2 monoclonal antibody used in oncology, produced cardiotoxicity, leading to the disappointing development of neuregulin-1β3 for the treatment of heart failure.[216] However, ErbB4 (not ErbB2) plays a critical role in inhibiting lipogenesis and promoting adipose tissue browning,[217] and of the neuregulins, only neuregulin-4 (NRG-4) (which selectively binds to ErbB4) is primarily secreted by adipocytes (specifically by those residing in brown adipose tissue[218,219]) and functions in an endocrine manner.[220]

NRG-4 reduces oxidative and proinflammatory stress and improves mitochondrial function in adipocytes,[221-223] thus alleviating obesity and insulin resistance, possibly through an AMPK-dependent mechanism. However, serum levels and adipocyte expression of NRG-4 are decreased in obesity and visceral adiposity, fatty liver disease, and in diabetic chronic kidney disease.[224-229] Adipocyte-mediated bloodstream delivery of NRG-4 appears to be important.[230] Intraperitoneal NRG-4, intravenous NRG-4 gene transfer, adipocyte-specific expression of NRG-4, or transplantation of NRG-4-overexpressing adipose-derived mesenchymal stem cells act to alleviate hepatic steatosis, improve whole body metabolic health, and prevent obesity.[223,231-234]

Therapeutic administration of NRG-4 alleviates experimental cardiomyopathy[235-237] and diabetic nephropathy.[238] Pressure-overload hypertrophy is accompanied by decreased cardiomyocyte expression of NRG-4, but adenoviral delivery of NRG-4 inhibits maladaptive cardiomyocyte proliferation and ameliorates fibrosis,[239] supporting the potential relevance of NRG-4 to the pathogenesis of HFpEF.

PART VI: DOMAIN II ADIPOKINES: CARDIOPROTECTIVE MOLECULES WHOSE ENHANCED SECRETION IN OBESITY ACTS AS A COMPENSATORY OR COUNTERREGULATORY MECHANISM

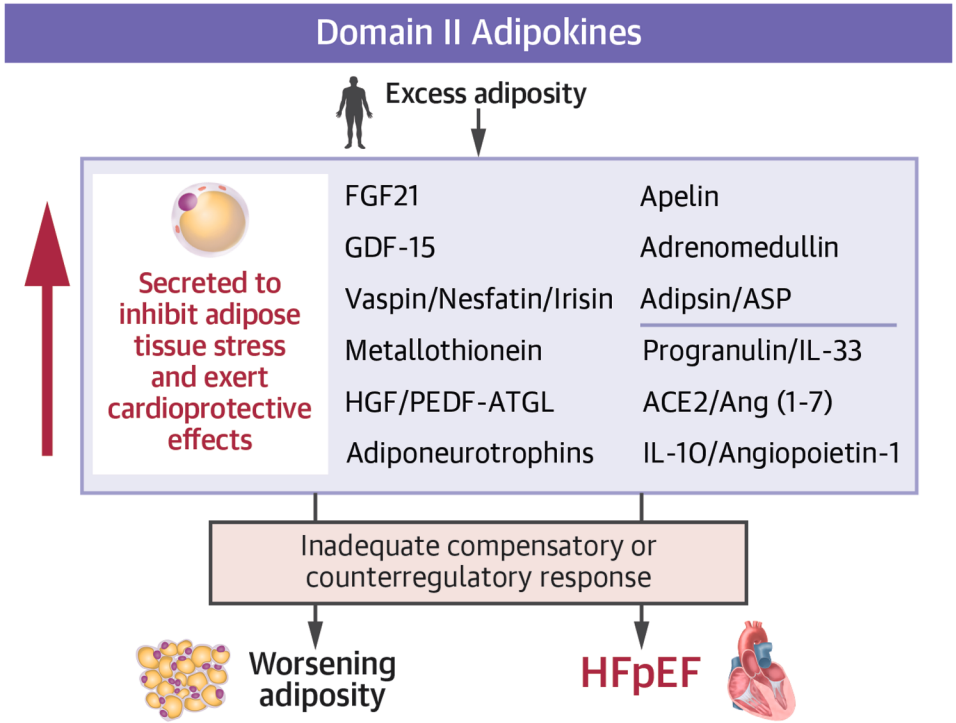
Domain II adipokines inhibit cellular stress, hypertrophy and inflammation in white adipose tissue and the heart (Table 3 and Figure 5). In lean individuals, adipocytes typically secrete only small quantities of Domain II adipokines. Consequently, their characterization has conventionally been linked to their synthesis in the liver, skeletal muscle, and central nervous system, thus explaining their classification as hepatokines, myokines, and neurotrophins.

TABLE 3 Domain II Adipokines

Protein or Signaling Axis	Adipocyte Source and Cellular Signaling	Biological Effects Relevant to Adipose Tissue and the Heart	Changes in Obesity, Visceral Adiposity, and Heart Failure
Signaling Through SIRT1/AMPK/PGC-1α and PI3K-Akt-mTOR			
Fibroblast growth factor 21 (FGF21)	Endocrine signaling, also epicardial secretion. FGF21 acts though adiponectin-dependent mechanisms.	FGF21 reduces visceral lipid overload. FGF21 from adipocytes (not cardiomyocytes) inhibits cellular stress and proinflammatory signaling.	Compensatory increases in serum FGF21 in obesity, visceral adiposity, and HFpEF.
Growth differentiation factor (GDF-15)	Secreted by adipocytes (and other cells) to suppress appetite/obesity.	GDF-15 mitigates myocardial apoptosis, inflammation, hypertrophy, and fibrosis.	Compensatory increases in obesity and HFpEF.
Vaspin	Endocrine signaling, vaspin enhances autophagy and suppresses NF-κB.	Vaspin inhibits proinflammatory adipokines and maladaptive hypertrophy, and it mitigates hypertension by promoting vasodilation.	Compensatory increase in obesity. Higher levels in patients with heart failure predict better outcome.
Nesfatin-1	Secreted by adipocytes to suppress food intake, enhance insulin secretion.	Cardioprotective effects in cardiomyocytes and in experimental cardiopathy.	
Irisin	Secreted by brown adipocytes to promote thermogenesis, irisin inhibits adipogenesis in white adipocytes.	Signals through SIRT1/PGC-1α to promote mitochondrial biogenesis, reduce cellular stress, and enhance autophagy. Irisin ameliorates maladaptive hypertrophy and fibrosis.	Irisin resistance leads to compensatory increases in obesity and HFpEF. High levels have better prognosis.
Metallothionein	Metallothionein is secreted by adipocytes (often within adipoexosomes) and exerts antioxidant effect.	Metallothionein prevents obesity-related cardiac hypertrophy and fibrosis in a PGC-1α–dependent manner.	Increased adipocyte expression in obesity. Undergoes endocytosis by failing heart.
Hepatocyte growth factor (HGF)	Secreted by adipose tissue, HGF promotes vascularization and antagonizes obesity.	HGF exerts cardioprotective effects. Elevated serum HGF levels identify patients with obesity-related LV hypertrophy prone to HFpEF.	Compensatory increases in serum HGF in obesity and HFpEF.
Pigment epithelium-derived factor/ adipose triglyceride lipase (PEDF/ATGL) signaling	Substantial synthesis of PEDF by adipocytes. PEDF promotes breakdown of fat depots through up-regulation of ATGL.	PEDF exerts broad range of cardioprotective effects and maintains vascular endothelial integrity. Modulation of ATGL influences the course of experimental HFpEF.	Compensatory increases in serum PEDF in obesity and heart failure.
Extraneuronal adiponeurotrophins	Secreted by adipocytes during adipogenesis to cause shrinkage of white adipose tissue.	Non-neuronal sources of adiponeurotrophins mitigate pressure-overload-induced cardiac hypertrophy and ameliorate heart failure.	Circulating levels increased in obesity. Cardiac expression reduced in heart failure.
Signaling Through G-Protein Coupled Receptors or β-Arrestin			
Apelin	Signals through APJ receptor, the effects of apelin are mediated by SIRT1 and AMPK.	Apelin promotes tolerance to pressure overload, ischemic injury, or obesity. It exerts positive inotropic, vasodilator, and diuretic effects.	Increased levels in obesity and HFpEF. Deficient cardiac synthesis in heart failure.
Calcitonin peptide family (adrenomedullin and calcitonin gene-related peptide [CGRP])	Diet-induced obesity leads to adipocyte-specific secretion of adrenomedullin, acting in an endocrine manner.	Adrenomedullin and CGRP attenuate cardiac hypertrophy, inflammation, and fibrosis in experimental HFpEF.	Serum levels of adrenomedullin are increased in obesity and in HFpEF.
Adipsin and acylation-stimulating protein (ASP)	Adipsin and ASP are secreted by adipocytes to regulate energy homeostasis.	Adipocyte-specific overexpression of adipsin exerts favorable effects on experimental HFpEF by alleviating microvascular injury.	Compensatory increase in obesity and heart failure.
Antagonists of Domain III Adipokines			
Progranulin	Progranulin acts a Wnt antagonist (when CTRP is deficient) as a compensatory response.	Heightened expression and release of progranulin in adipose tissue in obesity. Progranulin mitigates injury and age-related adverse ventricular hypertrophy.	Compensatory increase in obesity and heart failure (including HFpEF).
Angiotensin converting-enzyme-2 (ACE2)/ angiotensin (1-7) signaling	ACE2 and Ang(1-7) are secreted by adipocytes as natural antagonists of angiotensin II to inhibit adipogenesis and adipose tissue inflammation.	ACE2 and Ang(1-7) attenuate cardiac hypertrophy, inflammation and fibrosis. ACE2 silencing and overexpression aggravates and alleviates HFpEF, respectively.	ACE2 increased in obesity and ACE2/Ang(1-7) increased in HFpEF. High levels have better prognosis.
Interleukin-10 (IL-10) and angiopoietin-1 (Ang-1)	Secreted by adipocytes, Ang-1 and IL-10 antagonize effects of Domain III adipokines.	IL-10 and Ang-1 induce weight loss and ameliorate adipocyte stress, and they exert cardioprotective and vasculoprotective effects.	Compensatory increase in obesity and HFpEF. High Ang-1 has better prognosis.

ACE2 = angiotensin converting-enzyme 2; Ang = angiotensin; ASP = adipsin/acylation-stimulating protein; ATGL = adipose triglyceride lipase; FGF21 = fibroblast growth factor 21; GDF-15 = growth differentiation factor-15; HGF = hepatocyte growth factor; IL = interleukin; PEDF = pigment epithelium-derived factor; other abbreviations as in Tables 1 and 2.

FIGURE 5 Domain II Adipokines: Incomplete Compensatory or Counter-Regulatory Response in HFpEF



Domain II adipokines, secreted in response to visceral adiposity, are up-regulated to counteract metabolic, hypertrophic, and inflammatory stress, both in adipose tissue and the heart. These adipokines include molecules that activate sirtuin-1/adenosine monophosphate protein kinase/peroxisome proliferator-activated receptor-gamma coactivator-1alpha signaling, act through G-protein–coupled receptor pathways or function as direct antagonists of Domain III adipokines; interleukin-33 is discussed in the section on Domain III adipokines. Although this response is intended to exert cytoprotective and achieve homeostatic effects, it represents an insufficient or suboptimal compensatory or counter-regulatory response (often related to partial biological resistance). Consequently, worsening adiposity and heart failure with preserved ejection fraction (HFpEF) ensue, despite the action of Domain II adipokines. ACE2 = angiotensin converting-enzyme 2; Ang = angiotensin; ASP = adipsin/acylation-stimulating protein; ATGL = adipose triglyceride lipase; FGF21 = fibroblast growth factor 21; GDF-15 = growth differentiation factor-15; HGF = hepatocyte growth factor; IL = interleukin; PEDF = pigment epithelium-derived factor.

However, in obesity and visceral adiposity, the synthesis of Domain II adipokines is dramatically heightened, and adipocytes emerge as the major site of production, because adipose tissue comprises as much as 50% of body weight in people with obesity. The enhanced secretion of Domain II adipokines functions both as a mechanism to compensate for the loss of signaling of Domain I adipokines and as a means of counterbalancing the actions of Domain III adipokines. Although circulating levels of Domain II adipokines exert favorable effects on the myocardium, HFpEF still ensues, presumably because the compensatory or counter-regulatory responses are insufficient or overwhelmed. Despite their elevated circulating levels, the cellular responses to Domain II adipokines may be muted, because obesity induces biological resistance to the mechanisms that drive the cytoprotective effects of these adipokines (Box 6 and Box 7).

DOMAIN II ADIPOKINES THAT SIGNAL THROUGH NUTRIENT DEPRIVATION AND SURPLUS PATHWAYS. Many of the Domain II adipokines exert effects by through nutrient deprivation or surplus signaling pathways, acting to enhance SIRT1/AMPK/PGC-1α signaling or interfere with the PI3K-Akt-mTOR pathway, thus alleviating the cellular stresses that typically accompany states of nutrient excess.[85,93,94]

Fibroblast growth factor 21. Typically produced by the liver in lean individuals, fibroblast growth factor 21 (FGF21) is secreted by adipocytes in obesity, particularly within brown adipose tissue, exerting its

BOX 6. Key Features of Domain II Adipokines (Part 1)

1. Doman II adipokines include FGF21, GDF-15, vaspin, irisin, PEDF/ATGL, HGF, apelin, adrenomedullin, and adipsin. Several Domain II adipokines—ACE2/Ang(1-7), progranulin, interleukin 10, and angiopoietin-1—are direct antagonists of Domain III adipokines.
2. Domain II adipokines exert protective effects on both adipose tissue and the heart, muting adipose inflammation and cardiac hypertrophy and fibrosis. Many Domain II adipokines stimulate healthy thermogenesis in brown adipose tissue.
3. In lean people, adipocytes secrete only small quantities of Domain II adipokines, and other organs (eg, liver, skeletal muscle, central nervous system and others) represent the primary site of synthesis. However, as fat mass expands and adipocytes in visceral fat heighten their synthesis, adipose tissue emerges as the predominant site of production and of circulating levels.
4. The secretion of Domain II adipokines compensates for the loss of signaling of Domain I adipokines and counterbalances the actions of Domain III adipokines, but these responses appear to be insufficient to prevent HFpEF, often because obesity promotes resistance to their biological actions.

BOX 7. Key Features of Domain II Adipokines (Part 2)

1. Serum levels of Domain II adipokines are increased in people with obesity/visceral adiposity and with HFpEF, and they are associated with the severity of clinical symptoms and prognosis in heart failure. Increased circulating levels may be seen years before the onset of heart failure.
2. Consistent with the compensatory and counterregulatory actions of Domain II adipokines, patients with established heart failure who have elevated levels have a more favorable prognosis.
3. Domain II adipokines suppress the development of cardiac hypertrophy and fibrosis and alleviate the evolution of cardiomyopathy and HFpEF in experimental models. Many Domain II adipokines enhance vasodilation and inhibit vascular smooth muscle proliferation, thus acting to lower blood pressure.
4. Selective up-regulation of Domain II adipokine synthesis only in adipose tissue produces favorable effects on the course of experimental HFpEF. Transplantation of vaspin-expressing adipose tissue produces cardioprotective effects, and adipocyte-specific overexpression of adipsin ameliorates HFpEF.
5. Bariatric surgery and current drugs for HFpEF produce increases in FGF21, GDF-15, and ATGL. Drugs for HFpEF also increase circulating levels of other Domain II adipokines (e.g., irisin, apelin, HGF), whereas these are decreased by bariatric surgery, presumably because marked weight loss reduces the stimulus to secretion.

effects via the fibroblast growth factor receptor 1 and its coreceptor, β-*Klotho*.[240,241] Acting through SIRT1/AMPK and the release of adiponectin, FGF21 enhances insulin sensitivity, facilitates lipolysis and mitochondrial oxidative metabolism, augments energy expenditures, and shrinks visceral and hepatic fat depots. These effects of FGF21 protect against diet-induced obesity and diabetes.[242-246]

Cardiomyocytes are not an important source of FGF21, but intriguingly, cardiac injury is followed by the secretion of FGF21 from adipocytes,[247] which (acting through an endocrine mechanism) exerts a cardioprotective effect. Experimentally, enhanced FGF21 signaling in cardiomyocytes reduces oxidative stress and proinflammatory signaling, up-regulates autophagic flux, mitigates cardiac remodeling, and maladaptive hypertrophy and exerts a broad range of cardioprotective effects.[247-250]

However, obesity and diabetes reduce the expression of β-Klotho and fibroblast growth factor receptor 1, and this action interferes with the metabolic and cardiac response to FGF21, thus leading to FGF21 resistance.[251-253] As a compensatory response, serum FGF21 levels are elevated in adults with visceral adiposity.[254-257] Similarly, serum FGF21 levels are increased in patients with HFrEF and HFpEF in proportion to the severity of diastolic filling abnormalities, and these increased levels have adverse prognostic significance.[258,259] However, the expression of FGF21 in cardiomyocytes remains suppressed, thus demonstrating the importance of extracardiac production.[260]

Experimentally, dual GLP-1/glucagon receptor agonism increases adipose tissue expression and circulating levels of FGF21,[261] and SGLT2 inhibition increases myocardial FGF21 expression in experimental obesity.[262] Clinically, the FGF21 analogue pegozafermin has been shown to alleviate hepatic steatosis and fibrosis in patients with nonalcoholic fatty liver disease.[263]

Growth differentiation factor-15. Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor-β superfamily, is secreted by adipose tissue, liver, and heart under conditions of metabolic stress,[264-266] acting in an endocrine manner to restore tissue and whole-body homeostasis.

GDF-15 suppresses appetite[267] and promotes lipolysis and inhibits inflammatory responses in white adipose tissue.[267-271] It stimulates

thermogenesis in brown adipocytes[272] and enhances energy expenditure in skeletal muscles,[273] often coreleased with FGF21 to mediate an integrated AMPK-dependent mitochondrial stress response.[274,275] Heightened endocrine GDF-15 signaling leads to weight loss, and GDF-15 overexpression alleviates obesity.[265,276] Delivery of recombinant GDF-15 causes a catabolic state,[277] whereas experimental GDF-15 suppression promotes high-fat diet-induced obesity.[278] In the clinical setting, ponsegromab (a GDF-15 antibody) produces weight gain in patients with cachexia.[279]

However, as in the case of FGF21, obesity and visceral adiposity leads to resistance to the biological action of GDF-15,[280] perhaps related to down-regulation of its receptor or as a result of adipocyte-specific mitochondrial abnormalities,[281,282] and as with leptin, this resistance may be tissue-specific. Accordingly, serum GDF-15 levels are increased in patients with obesity and visceral adiposity.[283-286] Adipocyte secretion has been implicated in these heightened circulating levels GDF-15, because experimental obesity induces up-regulation of GDF-15 expression in adipocytes, but not in the liver.[287]

Adipocyte-specific secretion of GDF-15 exerts important systemic actions,[288] indicating that the endocrine actions of GDF-15 can yield cardioprotective effects. Treatment with or overexpression of GDF-15 induces autophagy and mitigates apoptosis and proinflammatory pathways[289,290] and alleviates cardiac hypertrophy, myocardial fibrosis,[290-292] and the diastolic filling abnormalities of HFpEF.[293] These actions may be mediated by an effect of GDF-15 to suppress endothelial inflammation.[294,295] Counter-regulatory up-regulation of GDF-15 may explain why circulating levels of GDF-15 are increased in patients who subsequently develop heart failure or cardiac fibrosis[296-298] or already have subclinical cardiac fibrosis or diastolic filling abnormalities.[299-301] Serum GDF-15 levels are increased and predict outcomes in patients with established heart failure, including those with HFpEF and obesity.[302-308] SGLT2 inhibitors further increase serum levels of GDF-15 in patients with heart failure.[309,310]

Vaspin. Vaspin (visceral adipose tissue-derived serine protease inhibitor) functions as an insulin-sensitizing adipokine,[311] which is minimally expressed in the visceral and subcutaneous fat of lean people. However, as body mass increases, the expression of vaspin increases strikingly in adipocytes.[311,312] Heightened adipocyte expression and secretion of vaspin (particularly from brown fat[313]) causes elevation of serum vaspin levels in obesity, visceral adiposity, and other insulin-resistant states.[314-316]

The heightened secretion of vaspin represents a counterbalancing endocrine response. Vaspin overexpresssion inhibits the development of diet-induced obesity,[317] and serum vaspin levels decline with weight loss.[318] Recombinant vaspin inhibits the expression of leptin, resistin, and proinflammatory cytokines in adipose tissue and enhances the expression of adiponectin.[319] The loss of visceral brown fat in experimental lipodystrophy is accompanied by impaired vaspin signaling, and importantly, transplantation of vaspin-expressing adipose tissue in this model produce cardioprotective effects.[320]

By activating AMPK and suppressing PI3K-Akt-mTOR signaling, vaspin enhances autophagy and reduces organellar stress,[321-326] while inhibiting maladaptive cardiac hypertrophy[321] and proinflammatory signaling[324,327] in the heart. It prevents cell death and preserves cardiac function in experimental cardiomyopathy and heart failure.[321,323,324] Vaspin also attenuates vascular smooth muscle proliferation,[328] and it suppresses the hypertensive responses to obesity by enhancing nitric-oxide-mediated vasodilation.[329,330]

Clinically, failure to trigger a compensatory increase in circulating vaspin levels appears to have adverse prognostic consequences,[331] because patients with low vaspin levels have an increased risk of heart failure hospitalizations.[332] Fenofibrate, which directly increases the expression of vaspin in adipocytes,[333] is accompanied by a decreased risk of heart failure hospitalization in patients with insulin resistance.[334]

Nesfatin-1. Originally described as an anorexigenic neuropeptide localized to the hypothalamus, nesfatin-1 is produced by adipocytes during differentiation and acts as a counter-regulatory adipokine.[335] Human obesity and visceral adiposity is accompanied by increased serum levels of nesfatin-1.[335,336] Nesfatin-1 reduces food intake,[337] promotes insulin secretion and insulin sensitivity,[338-340] inhibits adipocyte differentiation,[341] and suppresses adiposity-related inflammation and in oxidative stress.[342,343] Nesfatin-1 promotes expansion of brown fat,[344] mediated by enhanced SIRT1/PGC-1α signaling and inhibition of mTOR.

Although nesfatin-1 in the central nervous system may lead to sympathetic activation and hypertension,[345-347] blood-borne nesfatin-1 (eg, as from adipocytes[348]) produces cardioprotective effects in isolated cardiomyocytes,[349] in models of ischemic and postinfarction injury and in experimental cardiomyopathy.[350-354] In the clinical setting, failure to

trigger a compensatory increase in circulating nesfatin-1 levels appears to have adverse prognostic consequences, because patients with heart failure who have low nesfatin levels have an increased risk of adverse outcomes.[355]

Irisin. Originally described as a myokine released by skeletal muscle during exercise, irisin is a PGC-1α-dependent adipokine, which is formed by protease cleavage of the transmembrane protein, fibronectin type III domain containing 5.[356] When expressed and secreted by adipocytes,[357,358] irisin acts to ameliorate obesity by promoting thermogenesis in brown fat and by reducing adipogenesis (while enhancing browning) in white adipose tissue.[356,358-361]

Serum levels of irisin are related to its expression in adipocytes[357] and are increased in patients with obesity, especially those with visceral adiposity and systemic inflammation. These heightened levels act as a counter-regulatory response to the development of irisin resistance[357,359,362-366]; reports that patients with obesity have decreased serum irisin levels are related to the confounding influence of diabetes.[366,367] High preoperative levels of irisin predict the weight loss following gastric bypass surgery[368] (consistent with alleviation of irisin resistance), and irisin levels decrease following bariatric procedures.[369]

Acting by up-regulating SIRT1/PGC-1α,[356,370] irisin exerts a broad range of cardioprotective effects, promoting fatty acid oxidation and mitochondrial biogenesis,[371] reducing oxidative and endoplasmic reticulum stress[371-377] and proinflammatory signaling,[374] enhancing autophagic flux,[378,379] and preventing cardiomyocyte death.[375,376] Excessive levels may exerts deleterious effects,[380,381] a finding that parallels similar observations with SIRT1.[382] Irisin ameliorates maladaptive cardiac hypertrophy and fibrosis,[372,377,378,383] causes systemic vasodilation,[384] and mitigates the development of experimental heart failure.[372,373]

Serum levels of irisin are decreased following cardiac injury and in HFrEF,[385-387] indicating that up-regulation of cardiomyocyte synthesis during stress[388] is not likely to be an important source of circulating irisin. In marked contrast, serum levels of irisin are increased in patients with HFpEF,[389] presumably because the expanded adipose tissue mass emerges as the primary source of irisin production. Patients with HFpEF with higher levels are less likely to have clinical exacerbations and have a more favorable prognosis,[194,390,391] supporting the hypothesis that adipocyte-derived irisin exerts cardioprotective effects. Extracellular irisin can prime bone marrow mesenchymal cells to secrete cardioprotective exosomes,[392] and circulating irisin increases cardiac homing of adipose tissue-derived mesenchymal stem cells for repair.[393]

Metallothionein-1. Metallothioneins are a family of small cysteine-rich polypeptides, which function in energy transfer, act as heavy metal chelators, and exert antioxidant effects.[394] Adipocyte hypertrophy is accompanied by up-regulation of metallothionein synthesis, which (as a counterbalancing response) constrains adipogenesis and prevents diet-induced obesity.[395-397] Metallothioneins secreted by adipocytes contribute importantly to circulating levels,[398] potentially as a component of adipocyte-derived extracellular vesicles.[399] Metallothionein-1 promotes thermogenesis in healthy brown fat,[400] but experimental and clinical obesity induces the expression of metallothionein by adipocytes in white adipose tissue,[401-403] acting to limit adiposity.[397,404]

Silencing of metallothionein not only worsens obesity, but it also exacerbates obesity-related cardiac hypertrophy and fibrosis.[405,406] Metallothionein reduces cardiomyocyte oxidative and organellar stress,[407,408] promotes mitochondrial biogenesis and autophagy, and prevents apoptosis (all acting through PGC-1α).[409-412] Metallothionein also exerts cardioprotective effects across diverse cardiac injuries and metabolism-related cardiomyopathy,[406,413-415] and it ameliorates aging-associated ventricular diastolic dysfunction.[407] Patients with end-stage heart failure show the accumulation of metallothionein-containing lipovesicles in the subepicardial myocardium,[416] possibly a result of the endocytosis of epicardial adipoexosomes. Presumably triggered by hemodynamic stress, these dissipate following left ventricular assist device support.[416]

Hepatocyte growth factor. Originally identified by its actions within the liver, hepatocyte growth factor (HGF) is cleaved into a 2-chain active protein that signals through the c-Met tyrosine kinase receptor. Adipocytes secrete HGF during adipogenesis,[417-420] and as adipose mass expands during obesity, adipocyte-derived HGF mediates the vascularization that is needed to mitigate stress and inflammation in adipose tissue,[421,422] thus lessening the severity of diet-induced obesity.[423]

Acting through AMPK,[424-426] HGF functions as a counterbalancing response to fat mass accumulation, particularly in promoting pancreatic β-cell hyperplasia in response to insulin resistance.[427] However, the effectiveness of this compensatory mechanism is blunted, because obesity-related increases in plasminogen activator inhibitor (PAI) act as a natural antagonist of HGF activation.[428] Circulating levels of

HGF are increased in patients with obesity, visceral adiposity, and organ steatosis[429-432]; are primarily driven by adipose tissue synthesis[433,434]; and decline following bariatric surgery.[434,435]

Elevated serum levels of HGF identify patients likely to have new-onset heart failure (especially HFpEF) in the general community,[436,437] and obesity-related increases in circulating levels of HGF are associated with increases in left ventricular mass and progressive concentric remodeling years before the diagnosis of HFpEF.[438] Serum levels of HGF are also increased in patients with established heart failure, particularly in those with HFpEF, and have prognostic significance.[439-443]

Circulating HGF can signal through c-Met receptors in the heart to exert a broad range of cardioprotective effects, acting to attenuate myocardial injury, apoptosis, fibrosis, hypertrophy, and adverse ventricular remodeling.[444-447] Polymorphisms that up-regulate c-Met are accompanied by a decreased risk of heart failure.[448] Yet, the cardioprotective effects of HGF may depend on the delivery of measured levels from an extracardiac source,[444,449-451] because excessive cardiac-specific c-Met overexpression leads to maladaptive hypertrophy and cardiomyopathy.[452-454] Adenoviral intramyocardial HGF delivery has been evaluated in clinical trials of patients with postinfarction ventricular dysfunction,[455] but not in patients with obesity and HFpEF.

Pigment epithelium-derived factor and adipose triglyceride lipase. Originally described in the retina, pigment epithelium-derived factor (PEDF) is one of the most abundant proteins released by adipocytes, and it is secreted (often as a component of adipoexosomes) to reach circulating levels in the micromolar range, comparable to those achieved by adiponectin.[456] PEDF signals through several receptors[457] and primarily activates adipose triglyceride lipase (ATGL), leading to the breakdown of triglycerides and the release of fatty acids.[458] It also inhibits vascular endothelial growth factor receptor 2, leading to suppression of angiogenesis.[459]

ATGL signals through nutrient deprivation pathways, ie, AMPK, SIRT1, PGC-1α, and PPARα,[460-462] and changes in adipose tissue can modulate signaling at distant sites, ie, adipose-selective ATGL silencing abrogates PPARα activity in the liver.[461,462] In experimental obesity, mineralocorticoid receptor antagonism promotes AMPK-mediated ATGL signaling in brown adipose tissue.[463] PEDF is expressed during adipogenesis,[457] where it mediates triglyceride degradation in white adipose tissue and thermogenesis in brown fat.[464,465] PEDF ameliorates adipose tissue inflammation and oxidative stress,[466,467] but the ATGL-mediated release of free fatty acids leads to insulin resistance.[468] Adipocyte-specific overexpression of ATGL alleviates obesity.[469]

Serum levels of PEDF are elevated in patients with obesity,[470-475] where its lipolytic effects may act as a counterbalancing mechanism. Circulating levels of PEDF are also increased in patients with heart failure and have prognostic significance.[476] PEDF exerts a broad range of cardioprotective effects, including a reduction in oxidative stress, inflammation, and apoptosis and augmentation of autophagy in cardiomyocytes[477-480] as well as maintenance of the integrity of the vascular endothelium (with a reduction in leakage and cardiomyocyte edema)[481-484] and a decrease in ventricular hypertrophy, fibrosis, and remodeling.[485,486] ATGL produces similar favorable effects on stressed or injured heart.[487] Experimental systemic disruption of ATGL signaling leads to ventricular hypertrophy and HFpEF as well as to triglyceride overload and cardiomyopathy.[462,487,488]

Paradoxically, adipocyte-specific suppression of ATGL improves tolerance of hearts to catecholamine injury, mitigates hypertrophic responses to pressure overload, and prevents experimental HFpEF.[489-493] These effects that may be related to diminution of the proinflammatory actions of heightened serum levels of free fatty acids, triggered by ATGL-induced lipolysis.[490,493,494] Nevertheless, endocrine PEDF signaling appears to be important in obesity-related HFpEF, because myocardial steatosis is a characteristic feature of the disease,[495] and signaling through PEDF and ATGL mitigates lipid overload and improves diastolic filling abnormalities in metabolic HFpEF.[496]

Extraneuronal adiponeurotrophins. Originally characterized by their actions within the central nervous system, several neuronal growth factors—nerve growth factor (NGF), neutrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF), and ciliary neurotrophic factor (CNTF)—suppress appetite and enhance energy expenditure, an action attributed to sympathetic innervation-mediated transmutation of adipose tissue.[497,498] However, independent of these neuronal effects, these adiponeurotrophins are secreted by noninnervated adipocytes during adipogenesis and in response to proinflammatory signaling.[499-502] These extraneuronal forms play an important role in peripheral energy homeostasis,[503] while exerting cytoprotective paracrine and endocrine effects.[504-506]

Circulating levels of NGF, NT-3, and CNTF are increased in patients with obesity,[507-509] and BDNF gene polymorphisms are linked to obesity.[510] The increase in CNTF (along with obesity-related up-

regulation of the adipocyte CNTF receptor[502]) represents a counter-regulatory response. Extraneuronal CNTF induces thermogenesis in brown fat (by promoting PGC-1α),[503,511,512] reduces the mass of white adipose tissue,[513] and mitigates insulin resistance by promoting AMPK signaling in skeletal muscle.[514] Moreover, further augmentation of serum CNTF levels causes weight loss experimentally[515,516] and in patients with obesity in clinical trials.[517,518] NGF, BDNF, and NT-3 are also synthesized by adipocytes and produce extraneuronal effects similar to CNTF.[497,501,519,520]

NGF, BDNF, NT-3, and CNTF exert cardioprotective effects in experimental models. Their systemic overexpression ameliorates hypertrophy and cardiac remodeling, and their suppression leads to worsening cardiomyopathy.[521-530] Experimental and clinical hypertrophy and heart failure are accompanied decreased cardiac expression of NGF and NT-3,[531-533] suggesting that increased circulating levels of adiponeurotrophins and up-regulation of CNTF receptors in obesity[502,534] mediate a compensatory response.[535]

DOMAIN II ADIPOKINES ACTING THROUGH G PROTEIN-COUPLED RECEPTOR SIGNALING. Several domain II adipokines signal through G protein-coupled receptors linked to cyclic AMP (apelin, adrenomedullin, and calcitonin gene-related peptide) or through a β-arrestin-mediated inhibition of G-protein coupled receptor signaling (adipsin/acylation-stimulating protein [ASP]).

Apelin. Apelin acts as an agonist at the G-coupled APJ receptor.[536] Secreted by adipose tissue, apelin inhibits adipogenesis in white adipose tissue,[537] but enhances brown adipogenesis and browning of white adipocytes.[538] These effects appear to be related to its actions to improve glucose and lipid metabolism, promote mitochondrial oxidation and biogenesis, and mitigate oxidative stress and proinflammatory pathways.[539-542] As a result, overexpression of apelin confers resistance to obesity.[543] In nutrient surplus states, apelin expression within and secretion by adipocytes is enhanced, presumably as a counter-regulatory response.[536] Serum levels of apelin are increased in people with obesity and decline following weight loss.[536,544-546]

Apelin exerts positive inotropic effects in the healthy and failing heart and systemic vasodilator effects in patients with central obesity.[547,548] Apelin mitigates the development of maladaptive cardiac hypertrophy, inflammation, microcirculatory dysfunction, and fibrosis.[549] xperimental knockout of apelin undermines the ability of the heart to tolerate pressure overload, ischemic injury, or obesity.[550-552] Furthermore, apelin decreases the activity of the epithelial sodium channel and inhibits the actions of vasopressin on the renal medullary collecting tubule; both effects can promote a diuresis.[553,554]

In patients with HFrEF, serum apelin levels are decreased (and have adverse prognostic significance),[555-557] and apelin production in the failing heart is deficient.[558] However, although cardiac levels of apelin are also decreased in experimental obesity-related HFpEF,[559] serum levels of apelin are increased in patients with HFpEF (particularly if they have obesity),[560] consistent with enhanced production by the expanded adipose mass. Orally active apelin agonists have been evaluated for the treatment of patients with HFrEF,[561,562] but not for patients with HFpEF.

Calcitonin peptide family (adrenomedullin and calcitonin gene-related peptide). The calcitonin peptide family includes structurally similar polypeptides —adrenomedullin, calcitonin gene-related peptide (CGRP), and amylin—which signal through G protein-coupled receptors linked to cyclic AMP. Differential heterodimerization leads to differential agonism of the calcitonin receptor by adrenomedullin and CGRP.[563,564]

Circulating levels of adrenomedullin are increased in both experimental and clinical obesity (especially in states of visceral adiposity).[565-572] Dietary nutrient excess leads to adipocyte-specific expression of adrenomedullin, with adipocytes being the principal source of systemic adrenomedullin in obesity.[565-568] Adrenomedullin stimulates thermogenesis in brown fat, while inhibiting adipogenesis and inflammation, mitigating insulin resistance in white adipose tissue,[573-575] and suppressing hyperaldosteronemia.[576] Adipocytes also secrete CGRP,[577] and in response, CGRP exerts lipid mobilizing effects.[578] Serum levels of CGRP decline following bariatric surgery.[579]

Both adrenomedullin and CGRP act to attenuate myocardial hypertrophy, inflammation, and fibrosis in experimental models of pressure-overload HFpEF or obesity-related hypertension.[580-587] Achievement of supraphysiological levels of adrenomedullin and CGRP produces positive inotropic, lusitropic, and vasodilator effects in patients with heart failure.[588,589] Circulating levels of adrenomedullin (and its precursors) are related to increased left ventricular mass[590,591]; presage the onset of HFpEF in the general population[592]; and are increased in patients with HFpEF,[593] with higher levels being associated with increased pulmonary artery and left ventricular filling pressures, and worse functional capacity and prognosis.[593-597] Interestingly, both neprilysin inhibition

and mineralocorticoid receptor antagonism are accompanied by further increases in circulating adrenomedullin in HFpEF in the clinical setting.[598,599]

Adipsin and ASP. Adipsin (also known as complement factor D) leads to the production of ASP, a polypeptide that promotes the uptake and synthesis of triglycerides (while reducing the release of fatty acids) by adipocytes.[600-602] ASP exerts its metabolic effects by signaling through the C5L2 receptor,[602-604] which is coupled to a β-arrestin pathway that inhibits G protein-coupled receptor signal transduction.[605-607]

Adipsin and ASP are involved in the regulation of energy balance, acting to preserve pancreatic β-cell function and survival.[608,609] They promote lipid storage and adaptive adipogenesis, primarily in subcutaneous adipose tissue,[603,610] while promoting thermogenesis in brown fat.[611] Acting in concert, these effects minimize ectopic visceral fat depots. Silencing of the C5L2 receptor abrogates the benefits of adipsin and ASP, leading to adipose tissue inflammation, insulin resistance, and visceral adiposity.[612-614]

In states of nutrient excess, resistance to the actions of adipsin and ASP develops (caused by C5L2 down-regulation),[615-617] and compensatory augmentation of synthesis leads to heightened circulating levels of both adipsin and ASP in patients with central obesity.[226,618-622] Adipsin and ASP can exert endocrine effects as components of adipoexosomes.[623,624] Importantly, overexpression of adipsin specifically in adipocytes exerts favorable effects on experimental HFpEF or following myocardial infarction[624-626] —observations that directly support the adipokine hypothesis of HFpEF. This benefit appears to be mediated through an action to alleviate cardiac microvascular injury and improve mitochondrial health and fatty acid oxidation.[624-626] Circulating levels of adipsin and ASP are increased in patients with heart failure in proportion to the severity of systemic inflammation and diastolic filling abnormalities.[627,628]

DOMAIN II ADIPOKINES THAT DIRECTLY ANTAGONIZE DOMAIN III ADIPOKINES. Several Domain II adipokines are positioned as natural endogenous antagonists of Domain III adipokines, eg, progranulin, angiotensin converting-enzyme 2, angiotensin (1-7), interleukin (IL)-10, and angiopoietin-1 (Ang-1). IL-33 (discussed in the section on Domain III adipokines) can also be included in this category.

Progranulin. Progranulin acts an endogenous antagonist of Wnt-Frizzled signaling,[629] with a function similar to the CTRPs and SFRP5. Whereas CTRP and SFRP5 synthesis is deficient in obesity, progranulin is secreted by hypertrophied and inflamed adipose tissue, apparently to compensate for the obesity-related suppression of CTRP3 and CTRP9.[630,631] Serum levels of progranulin are increased in people with obesity or the metabolic syndrome, proportional to the magnitude of systemic inflammation.[632] Monocytes residing in adipose tissue are a primary source of progranulin, which antagonizes the effect of inflammation to promote adiposity.[633]

Progranulin prevents pathological hypertrophy and remodeling following experimental myocardial and pressure overload.[634,635] Depletion of progranulin causes mitochondrial dysfunction, thus undermining vascular health[636] and accelerating age-related progression of ventricular hypertrophy.[631] Serum levels of progranulin are elevated in patients with heart failure (including those with HFpEF), and these levels (and changes in these levels) precede the occurrence of worsening heart failure events and parallel the clinical course of heart failure.[637,638]

Angiotensin converting-enzyme 2/angiotensin (1-7) signaling. Acting as an endogenous antagonist to the effects of angiotensin II, angiotensin converting-enzyme 2 (ACE2) not only inactivates angiotensin II, but also converts it into angiotensin(1-7) (Ang[1-7]), which signals through the Mas receptor to oppose the biological actions of angiotensin II.[639] Activation of ACE2-Ang(1-7)-Mas signaling promotes thermogenesis in brown fat[640,641] and reduces diet-induced obesity and visceral fat expansion,[641-644] while attenuating lipogenesis and ameliorating inflammation in white adipose tissue.[640,644-649]

Additionally, ACE2 and Ang(1-7) exerts a broad range of cardioprotective effects, including a reduction in oxidative stress and suppression of prohypertrophic, proinflammatory, and profibrotic signaling in cardiac tissue, leading to alleviation of experimental hypertension and heart failure,[650-653] including HFpEF.[654,655] ACE2 silencing and overexpression aggravates and alleviates HFpEF, respectively.[652,656,657] Expressed in both adipocytes and endothelial cells, the cardioprotective effects of ACE2-Ang(1-7) may be mediated by a paracrine action of epicardial adipose tissue. Yet, an additional endocrine action seems plausible, because transgenic overexpression of Ang(1-7) in noncardiac tissue—yielding sustained increases in circulating Ang(1-7)—produces anti-inflammatory actions in adipose tissue and direct cardioprotective effects.[649,658]

Obesity is accompanied by increased adipocyte levels of ACE2[659] as well as increased circulating levels of ACE2 but decreased circulating levels of Ang (1-7),[660-662] raising the possibility that states of

adiposity may lead to resistance to the action of ACE2 to generate Ang(1-7). Epicardial adipocytes taken from mice or humans with obesity and HFpEF show increased expression of ACE2,[639,662] consistent with a compensatory response to ACE2 resistance. Yet, cytoprotective ACE2 signaling seems to be (at least partially) preserved in states of nutrient excess, because experimental global knockout of ACE2 in mice fed a high-fat diet results in epicardial adipose tissue inflammation and HFpEF.[662]

Clinically, circulating levels of soluble ACE2 are increased in patients with hypertrophy and diastolic filling abnormalities.[663] Circulating levels of both ACE2 and Ang(1-7) are increased in patients with HFpEF,[664,665] particularly those with a favorable prognosis.[666] Recombinant human ACE2 has been used to treat heart failure in clinical trials.[667]

IL-10 and Ang-1. Obesity is characterized by the activation of both inflammation and angiogenesis, and these pathways are constrained by the effect of Domain II counter-regulatory adipokines, which act as inhibitors of intracellular JAK/STAT, Wnt, and NF-κB signaling.[668-670] IL-10 is secreted by adipocytes to mute the deleterious effects of proinflammatory cytokines (TNF-α and IL-1β).[671] Ang-1 is secreted by adipocytes to interact with the Tie2 receptor, and this interaction is prevented by angiopoietin-2 (ANGPT2), a Domain III adipokine.[672,673]

Both IL-10 and Ang-1 inhibit adipogenesis and adipocyte stress,[674,675] and IL-10 and Ang-1 plasmids induce a reduction in body weight.[673,676] Serum levels of IL-10 and adipose tissue Ang-1 levels are increased in people with obesity and visceral adiposity,[677-679] consistent with a compensatory mechanism.

Both IL-10 and Ang-1 exert cardioprotective effects following myocardial injury, acting to reduce maladaptive hypertrophy, cardiomyocyte inflammation, and apoptosis.[680-684] IL-10 ameliorates obesity-related myocardial inflammation.[685] Up-regulation of Ang-1 maintains the structural integrity and quiescence of blood vessels[672] and ameliorates the evolution of experimental nephropathy in obese mice.[686,687]

Clinically, increases in circulating levels of Ang-1 presage a lower risk of heart failure events following kidney injury.[688] Serum levels of IL-10 are increased in patients with heart failure in proportion to increased levels of proinflammatory adipokines.[689-692] Increases in serum levels of IL-10 (or its receptor) are associated with inflammation-associated diastolic filling abnormalities in hypertrophic cardiomyopathy,[693] coronary artery disease,[694] and HFpEF.[695,696] Therapeutic up-regulation of IL-10 ameliorates the adverse cardiac remodeling seen in experimental HFpEF.[684]

COMPLEXITIES IN THE CHARACTERIZATION OF CARDIOPROTECTIVE ADIPOKINES. The observations summarized in the previous text (and in Tables 2 and 3 and in Figures 4 and 5) suggest that a robust crosstalk exists between adipocytes and cardiomyocytes, which determines the health of the heart and the development of cardiomyopathy, an effect that is modulated through suppression or augmentation of the synthesis and release of adipocyte-secreted cardioprotective molecules. Obesity may cause: 1) suppression of cardioprotective Domain I adipokines, leading to myocardial hypertrophy, inflammation and fibrosis, and thus, HFpEF, caused by unopposed action of Domain III adipokines; or 2) heightened adipocyte secretion of cardioprotective Domain II adipokines that act as an endogenous (yet often inadequate) compensatory response to the loss of Domain I adipokines or as a counterbalancing response to Domain III adipokines. The adipose-cardiac crosstalk may be bidirectional, ie, the predilection of cardiac injury to progress to cardiomyopathy may be mediated through or counteracted by an intermediary mechanism that involves the activation of a biological response within adipose tissue.[142,247] Conversely, relief of hemodynamic stresses in patients with cardiomyopathy may cause muting of inflammatory signaling within adipose tissue.[129]

It is intriguing that most of Domain II adipokines appear to stimulate thermogenesis in brown fat, suggesting that there may exist a special link between brown adipose tissue and the activation of counterbalancing mechanism that mediate cardioprotection (Figure 5). The heart is normally bathed in and nurtured by adipose tissue with features of brown fat, and both brown adipocytes and cardiomyocytes possess exceptional quantities of mitochondria. Brown fat thermogenesis requires the uncoupling of oxidative phosphorylation from ATP synthesis in healthy mitochondria, a mechanism that necessitates enhanced signaling through SIRT1 and PGC-1α,[697] and these are key mediators of cardioprotective pathways.[95]

However, not all proteins that both heighten brown adipocyte metabolism and alleviate cardiomyocyte stress are necessarily relevant to the development of adiposity-induced HFpEF. As an example, both bone morphometric proteins (BMPs) 7 and 9 stimulate brown fat thermogenesis,[698,699] and both BMP7 and BMP9 can alleviate obesity.[700,701] Serum levels of BMP9 are reduced in people with obesity or visceral adiposity,[702,703] and both BMP7

and BMP9 alleviate myocardial inflammation and fibrosis, thereby mitigating the effects of pathological ventricular remodeling and diabetic cardiomyopathy.[704-706] However, BMP7 levels are not reduced in obesity, and BMP9 is primarily secreted by hepatocytes, not adipocytes. Therefore, neither BMP7 nor BMP9 informs the adipokine hypothesis of HFpEF. Nonetheless, BMP7 and BMP9 mimetics may have therapeutic potential in adiposity-related HFpEF.[700,705,707-709]

Similarly, follistatin-like 1 (FSTL-1), an extracellular glycoprotein, acts as an endogenous antagonist of BMP4.[710] Typically described as a myokine, FSTL-1 is also produced by developing adipocytes and has been reported to participate in brown adipose tissue thermogenesis.[711,712] Serum levels of FSTL-1 are increased both in people with obesity and with heart failure (including HFpEF).[713,714] However, there is no evidence that FSTL-1 represents a counter-regulatory mechanism that inhibits obesity. In fact, FSTL-1 may be required for the development of adiposity[711] and may promote adipose tissue inflammation.[715] Furthermore, independent of a mediating influence of adipocytes, up-regulation of FSTL-1 in the heart suppresses hypertrophy and protects against cardiac injury,[716,717] and conversely, cardiac-specific abrogation of FSTl-1 worsens aldosterone-mediated HFpEF.[714] Taken collectively, it does not appear that adipocyte-secreted FSTL-1 participates in orchestrating crosstalk between adipose tissue and the heart in patients with obesity or heart failure.

PART VII: DOMAIN III ADIPOKINES: MOLECULES THAT ARE SECRETED BY DYSFUNCTIONAL HYPERTROPHIED ADIPOCYTES AND EXERT DELETERIOUS EFFECTS ON THE HEART

Obesity and visceral adiposity are accompanied by adipose tissue proliferation and inflammation. As stress within the fat depots escalates, the adipose secretome shifts to proteins that promote systemic inflammation, plasma volume expansion, coronary microvascular rarefaction, and myocardial hypertrophy, inflammation, and fibrosis. Unlike the cardioprotective Domain I and II adipokines, Domain III adipokines drive the pathogenetic mechanisms that lead to HFpEF. They may be synthesized primarily by hypertrophied and proliferating adipocytes. or alternatively, by adipose-resident inflammatory, stromal, or mesenchymal stem cells, which are stimulated by adipocyte-mediated paracrine signaling (triggered by nutrient excess). These proteins act by up-regulation of the PI3K-Akt-mTOR-PPARγ pathway, by promoting canonical and noncanonical Wnt signaling, and by activation of JAK/STAT and TGFβ-Smad signaling.

The Domain III adipokines, summarized in **Table 4** and **Figure 6**, are presented as 5 functional clusters: 1) major adipocyte-specific secreted proteins that act as endocrine mediators of adiposity-driven cardiomyopathy; 2) adipose-secreted growth factors and their binding proteins; 3) adipose-derived matricellular glycoproteins and other extracellular matrix glycoproteins; 4) adipose-secreted chemokines and angiopoietins; and 5) soluble endogenous antagonists and other proinflammatory proteins (including canonical proinflammatory cytokines).

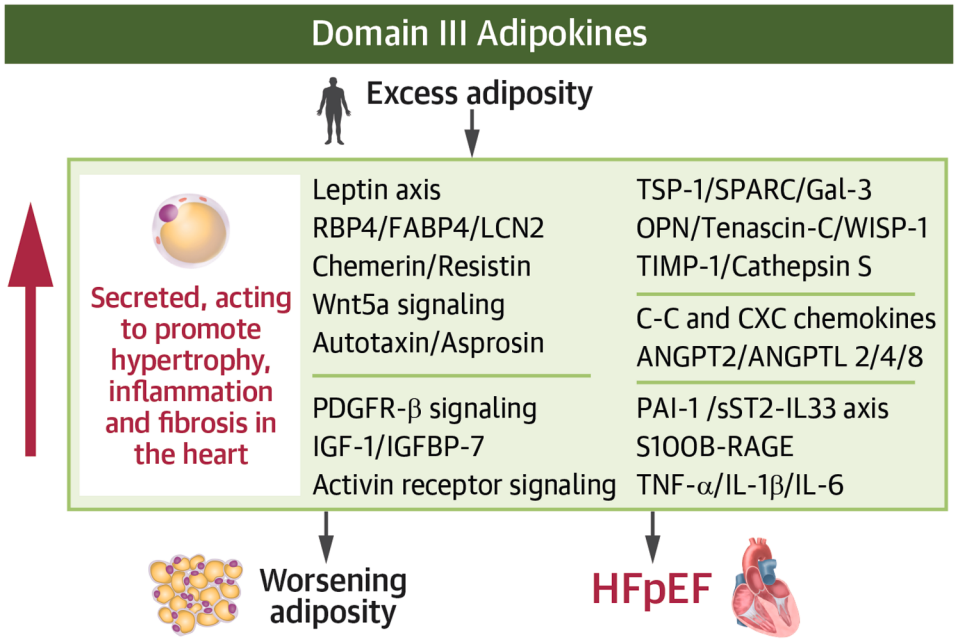
MAJOR ADIPOCYTE-SECRETED PROTEINS ACTING AS MEDIATORS OF ADIPOSITY-DRIVEN HFpEF.

These proteins are secreted primarily (if not exclusively) by adipocytes, and such secretion is the principal determinant of their circulating levels, with serum levels often in the high nanomolar or even micromolar range. These adipokines signal through the JAK/STAT pathway (eg, leptin, lipocalins), through G protein-coupled receptors (eg, chemerin, autotaxin, and asprosin), or through the Wnt/JNK pathway (eg, extracellular Wnt5a).

Leptin and the leptin-angiotensin II-aldosterone-neprilysin axis. The most studied Domain III adipokine is leptin, a master regulator of energy balance, which signals primarily through the JAK2/STAT3 pathway.[718] Serum levels of leptin are primarily driven by secretion from adipocytes and are closely correlated with percent body fat and epicardial fat mass.[718,719] The short-term actions of leptin in healthy individuals to promote satiety, lower blood pressure, and shield cardiomyocytes are transformed into maladaptive responses during chronic hyperleptinemia, as occurs in obesity.[20,720,721]

The secretion of leptin by adipocytes is a major driver of neurohormonal activation in obesity. Leptin stimulates adrenergic- and angiotensin-dependent mechanisms (including augmentation of renal sympathetic nerve traffic).[722,723] This adipokine (rather than angiotensin II) may be the major cause of aldosterone overproduction in obesity.[724,725] Experimentally, leptin directly augments sodium retention mediated by an action at multiple renal tubular sites.[20,726] Additionally, leptin triggers and potentiates systemic inflammatory responses[727,728] and contributes to ventricular hypertrophy,[729-731] impaired relaxation,[732] endothelial dysfunction and myocardial fibrosis.[733-735] Changes in left ventricular mass are correlated with changes in leptin after bariatric surgery.[731] The secretion of leptin from

FIGURE 6 **Domain III Adipokines That Drive the Central Mechanisms Underlying the Development of HFpEF**



Domain III adipokines represent the key pathological mediators of the adipose-heart axis in heart failure with preserved ejection fraction (HFpEF), acting to promote cardiac hypertrophy, inflammation, and fibrosis, as well as pulmonary and systemic hypertension. They are presented as 5 functional clusters: 1) major adipocyte-specific secreted proteins acting as endocrine mediators of adiposity-driven cardiomyopathy; 2) adipose-secreted growth factors and binding proteins; 3) adipocyte matricellular glycoproteins and other extracellular matrix glycoproteins; 4) adipocyte-secreted chemokines and angiopoietins; and 5) soluble endogenous antagonists and other proinflammatory proteins (including canonical proinflammatory cytokines). Unopposed signaling through Domain III adipokines further exacerbates adiposity and promotes the development of HFpEF. ANGPT2 = angiopoietin-2; ANPTL = angiopoietin-like protein; FABP4 = fatty acid binding protein 4; Gal-3 = galectin 3; IGF-1 = insulin-like growth factor-1; IGFBP-7 = insulin-like growth factor binding protein-7; IL = interleukin; LCN2 = lipocalin 2; OPN = osteopontin; PAI-1 = plasminogen activator inhibitor; PDGFRβ = platelet-derived growth factor receptor-β; RAGE = receptor for advanced glycation products; RBP4 = retinol binding protein 4; SPARC = secreted protein acidic and rich in cysteine; sST2 = soluble suppression of tumorigenicity 2; TIMP-1= tissue inhibitor of proteinase-1; TNF-α = tumor necrosis factor-α; TSP-1 = thrombospondin-1; WISP-1= Wnt1-induced secreted protein-1.

epicardial adipose tissue may be particularly likely to cause myocardial injury.[736]

Circulating levels of leptin presage the development of heart failure (particularly HFpEF) in elderly individuals in the general community.[737,738] In patients with established heart failure, levels of leptin are particularly identified with HFpEF (rather than HFrEF),[67,739] and they fully account for the influence of obesity to increase the risk of heart failure.[740] The magnitude of hyperleptinemia is correlated with symptom severity, exercise intolerance, clinical instability, and an adverse prognosis.[14,741,742]

Interestingly, many of the deleterious actions of leptin may be mediated (in part) by its effects to promote signaling through angiotensin II, aldosterone, and neprilysin, as components of the leptin-angiotensin II-aldosterone-neprilysin axis (Box 8).[20] The action of leptin to promote sodium retention and myocardial fibrosis may be related to the enhanced action of aldosterone.[38,743-745] Increased renal sympathetic nerve traffic caused by hyperleptinemia causes the release of neprilysin by the kidneys,[743] which (by degrading natriuretic peptides) can lead to additional cardiac hypertrophy and fibrosis.[744,745]

Independent of leptin, obesity leads to increased synthesis of angiotensin II, aldosterone, and neprilysin by adipocytes,[39,41,746,747] and this heightened activity contributes to further adipogenesis and worsening adiposity[748-750] and the development of HFpEF.[6,64,69,751] Importantly, increased adipocyte synthesis of angiotensin II promotes adipose tissue inflammation and changes in the adipocyte secretome, which can adversely influence adjoining cardiovascular structures.[752-755] Transplantation of perivascular adipose tissue in which angiotensin II signaling has been pharmacologically suppressed prevents vascular injury in recipient animals.[752] Adipocyte-specific angiotensinogen gene silencing is sufficient to mute adipose tissue inflammation,[756] and adipocyte-specific up-regulation of the

TABLE 4 Domain III Adipokines

Protein or Signaling Axis	Adipocyte Source and Cellular Signaling	Biological Effects Relevant to Adipose Tissue and the Heart	Changes in Obesity, Visceral Adiposity, and Heart Failure
Major Adipocyte-Specific and Adipocyte-Secreted Adipokines Driving Adiposity-Related Cardiomyopathy			
Leptin-angiotensin II-aldosterone neprilysin axis	Adipocyte secretion of leptin, angiotensin, aldosterone, and neprilysin. Mutual amplification of synthesis and actions, exerting endocrine effects.	Interplay promotes adipogenesis, systemic inflammation, neurohormonal activation, myocardial hypertrophy, and fibrosis.	Increased serum levels in obesity and heart failure. Interactions mediate obesity- and adiposity-related HFpEF.
Lipocalins (retinol binding protein 4 [RBP4], fatty acid binding protein 4 [FABP4]. lipocalin 2 (LCN2), chitinase-3 like-1 [YKL-40])	Lipocalins represent a major fraction of proteins secreted by adipocytes, often at part of adipoexosomes, and circulating in large quantities.	RBP4, FABP4, and LCN2 promote adipose tissue inflammation and end-organ steatosis, leading to hypertension, cardiac hypertrophy, and injury. YKL-40 mediates cardiac fibrosis.	Increased serum levels in obesity (particularly visceral adiposity) and HFpEF. Associated with diastolic filling abnormalities and adverse prognosis.
Chemerin	Secreted by adipocytes, disseminating adverse biology to end-organs. May mediate mineralocorticoid toxicity.	Chemerin promotes adipose tissue inflammation, hypertension, and cardiac hypertrophy, inflammation, and fibrosis.	Increased serum levels in obesity and heart failure (including HFpEF), presaging poor prognosis.
Resistin	Secreted by adipocytes to exert endocrine and paracrine effects.	Resistin promotes adipose tissue inflammation and maladaptive cardiac hypertrophy. Adipose-specific silencing has cardioprotective effects.	Increased serum levels in obesity, visceral adiposity, and heart failure. It presages heart failure and its prognosis.
Wnt5a-Frizzled 5 signaling	Adipocyte secretion of Wnt5a exerts endocrine effects through its receptor, Frizzled-5.	Wnt5a promotes adipose tissue inflammation. Adipocyte-derived Wnt5a can produce cardiac fibrosis.	Increased serum levels in obesity, visceral adiposity, and heart failure. It presages an adverse prognosis.
Autotaxin	Adipocyte secretion drives circulating levels of autotaxin and its catalytic end product, lysophosphatidic acid.	Adipocyte-derived autotaxin and lysophosphatidic acid cause mTOR-mediated maladaptive hypertrophy, fibrosis, and cardiomyopathy.	Serum levels of autotaxin and lysophosphatidic acid are increased in patients with obesity or heart failure.
Asprosin	Typically secreted by adipocytes during fasting, asprosin acts to increase blood glucose.	During nutrient excess, asprosin promotes adipogenesis and obesity. It promotes vascular endothelial inflammation and fibrosis.	Increased serum levels in obesity, heart failure, and in patients with adiposity and diastolic filling abnormalities.
Growth Factors and Their Binding Proteins			
Platelet-derived growth factor receptor (PDGFR)-β signaling.	Expansion of white adipose tissue through proliferation of PDGFRβ+ preadipocytes, leading to adipose tissue dysfunction.	Adipocyte-specific overexpression of PDGF-D (signaling through PDGFRβ) leads to PDGF-D-mediated cardiac fibrosis, exacerbated by obesity.	Serum and adipose tissue levels of PDGFRβ ligands are increased in obesity and adiposity. Up-regulated PDGFRβ signaling in HFpEF.
TGF-β superfamily—activin type I and type II signaling (GDF-3/ALK7 and activin A).	Adipocyte expression of GDF-3, ALK7, and activin A is enhanced by nutrient excess and drives obesity.	Activin A mediates epicardial adipose tissue cardiotoxicity. GDF3/ALK7 and activin A promote cardiac fibrosis. Activin type II receptor antagonism alleviates experimental HFpEF.	Serum levels of activin A are increased in obesity and HFpEF. Increased serum levels of GDF-3 in adverse cardiac remodeling.
Insulin-like growth factor-1 (IGF-1) receptor signaling.	Unlike other insulin-like growth factor binding proteins, IGFBP7 stimulates the IGF-1 receptor, with deleterious effects.	Signaling through IGFBP7 or IGF-1R leads to cardiac hypertrophy, fibrosis, and senescence, especially in the setting of aging and obesity.	Obesity increases IGF-1R expression and serum levels of IGFBP7. Serum IGFBP7 levels are linked to HFpEF.
Matricelllar Glycoproteins and Extracellular Matrix Modulators			
Thrombospondin-1	Adipocyte secretion, also as part of extracellular vesicles, signaling through Wnt/β-catenin.	Thrombospondin-1 (through CD47) leads to cardiac hypertrophy, fibrosis, pulmonary hypertension, and HFpEF.	Increased serum levels in obesity and heart failure. Circulating marker of cardiac hypertrophy.
Secreted protein acidic and rich in cysteine (SPARC)	Adipocyte secretion, also within extracellular vesicles, signaling through Wnt/β-catenin.	SPARC promotes adipose tissue inflammation and cardiac fibrosis, the latter effect mediated by extracardiac source.	Increased serum levels in obesity and heart failure and related to diastolic filling abnormalities.

Continued on the next page

mineralocorticoid receptor leads to vascular dysfunction.[757] The suppression of natriuretic peptides signaling in patients with obesity and HFpEF[42,758,759] can further promote aldosterone synthesis, impair renal sodium excretion and trigger myocardial inflammation and fibrosis, thus potentiating the actions of leptin.[20,760]

Sustained hyperleptinemia or hyperaldosteronemia is sufficient to recapitulate HFpEF experimentally.[751,761] The coordinated activation of leptin, angiotensin II, aldosterone, and neprilysin in obesity—together with their interplay to cause mutual amplification of their synthesis and actions—plays a seminal role in mediating the effect of obesity to cause HFpEF. Current drugs for HFpEF suppress the secretion or counter the actions of leptin and interfere with the actions of angiotensin II, aldosterone, and neprilysin.[762]

Lipocalins (retinol binding protein 4, fatty acid binding protein 4, lipocalin 2, and chitinase-3

TABLE 4 Continued

Protein or Signaling Axis	Adipocyte Source and Cellular Signaling	Biological Effects Relevant to Adipose Tissue and the Heart	Changes in Obesity, Visceral Adiposity, and Heart Failure
Matricellular lectins—extracellular galectin 3	Adipocytes secrete galectin-3 and are a primary source of circulating levels, thus enabling fibrosis at distant sites.	Mediates obesity-related cardiac lipotoxicity, fibrosis, and microvascular dysfunction. Adipose tissue activation leads to galectin-3–mediated stimulation of cardiac fibroblasts.	Increased serum levels in obesity, adiposity, and heart failure, especially HFpEF, with prognostic significance.
Osteopontin, tenascin-C, and Wnt1-induced secreted protein-1 (WISP1/CCN4])	Obesity leads to adipocyte secretion into extracellular matrix, signaling through Wnt/β-catenin.	Act to promote adipose tissue inflammation and cardiac hypertrophy and fibrosis, and cardiomyopathy.	Increased serum levels in obesity, adiposity, and heart failure, particularly HFpEF.
Tissue inhibitor of metalloproteinase 1 (TIMP1)	Obesity is accompanied by heightened adipocyte expression of TIMP1.	TIMP1 promotes maladaptive cardiac fibrosis. Adipocyte exosomes can stimulate TIMP1 in distant fibroblasts.	Increased serum levels in obesity, adiposity, and HFpEF, with prognostic significance.
Cathepsin S—protease-activated receptor 2 (PAR2) signaling	Cysteine protease, secreted by adipocytes and adipose tissue stromal cells, acting in paracrine and endocrine manner.	Signaling through PAR2, cathepsin S promotes adipogenesis, cardiac hypertrophy, and cardiomyopathy.	Increased serum levels in obesity and in heart failure, particularly HFpEF and in cardiac hypertrophy.
Chemokines and Angiogenesis Proteins			
C-C chemokine ligand 2 (CCL2) and C-C chemokine ligand 5 (CCL5, also known as RANTES)	Adipocytes secrete CCL2 and CCL5, which can (through paracrine or endocrine effects) promote inflammation in the heart.	CCR2 and CCR5 antagonists alleviate adipose inflammation and obesity. CCL2 antibodies prevent cardiac fibrosis and diastolic filling abnormalities. Extracardiac CCR2 suppression mitigates experimental cardiomyopathy.	Increased serum levels of both CCL2 and CCL5 in obesity, visceral adiposity, and heart failure. Decreased cardiac expression of CCL2 in the failing human heart.
CXC chemokine ligand 8 (CXCL8) and CXC chemokine 12 (CXCL12)	Adipocytes secrete CXCL8 and CXCL12, which (by signaling through CXCR2 and CXCR4, respectively) promote local and systemic inflammatory responses.	Signaling through CXCL8/CXCR2 and CXCL12/CXCR4 is implicated in adverse remodeling and fibrosis in models of HFpEF, effects muted by CXCR2 and CXCR4 antagonism.	Increased serum levels of both CXCL8 and CXCL12 in obesity, adiposity and heart failure, especially HFpEF.
Angiopoietin-2 (ANGPT2)	Normally secreted by endothelial cells and adipocytes to promote vascular stability and metabolic homeostasis.	Inflammation causes ANGPT2 to act as Tie2 receptor antagonist, thereby promoting vascular fragility, endothelial apoptosis, and microvascular rarefaction.	Serum levels are increased in obesity and heart failure, especially in HFpEF.
Angiopoietin-like protein-2, -4, and -8 (ANGPTL2, ANGPTL4 and ANGPTL8)	Sustained heightened secretion of ANGPTL2, ANGPTL4 and ANGPTL8 by adipocytes promotes local and systemic inflammation.	Adipocyte-specific genetic ablation of ANGPTL4 prevents vascular injury. ANGPTL2 has deleterious effects on cardiomyocytes and activates fibroblasts in diet-induced HFpEF.	Serum levels of ANGPTL2, ANGPTL4 and ANGPTL8 are increased in obesity. Serum ANGPTL2 and ANGPTL4 are increased in HFpEF.
Soluble Endogenous Antagonists and Other Proinflammatory Proteins			
Plasminogen activator inhibitor (PAI-1)	Obesity causes marked increase in PAI-1 secretion from adipocytes, promoting further obesity.	Increased circulating PAI-1 leads to cardiac fibrosis. Transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet.	Increased serum levels in obesity, adiposity, and HFpEF, especially with their coexistence, with prognostic significance.
Soluble suppression of tumorigenicity 2 (sST2) and the interleukin-33/ST2 axis	Adipose tissue secretes sST2. sST2 acts as a decoy to prevent IL-33 from exerting cardioprotective and anti-inflammatory effects.	Inflamed adipose tissue is the source of circulating sST2. sST2 promotes fat inflammation and augments vascular hyperplasia and myocardial fibrosis.	Increased serum levels of sST2 in obesity, adiposity, and HFpEF, with prognostic significance, driven by extracardiac source.
Calgranulin (S100B)-RAGE (receptor for advanced glycation endproduct) signaling	Adipocytes secrete S100B in proportion to fat mass. Obesity up-regulates RAGE cell-surface expression on cardiomyocytes.	S100B-RAGE signaling promotes cardiomyocyte apoptosis, myocardial hypertrophy and fibrosis, and cardiomyopathy, alleviated by RAGE silencing.	Increased in S100B and RAGE obesity and heart failure. The decoy function of soluble RAGE decreased in obesity. RAGE may mediate cardiomyopathy.
Canonical proinflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin-1β [IL-1β]. interleukin 6 [IL-6])	Adipose tissue production of TNF-α, IL-1β, and IL-6 in obesity is likely related to production by infiltrating inflammatory cells.	Studies of the effect of inhibition of TNF-α, IL-1β, and IL-6 on the evolution of experimental HFpEF have produced inconsistent results.	Increased serum levels in obesity and HFpEF, but also increases in levels of receptor decoys and endogenous antagonists.

HFpEF = heart failure with preserved ejection fraction.

BOX 8. Domain III: Leptin-Angiotensin II-Aldosterone-Neprilysin Axis

1. In obesity, adipose tissue secretes heightened quantities of leptin, angiotensin II, aldosterone, and neprilysin, with the magnitude of hyperleptinemia being directly proportional to the increase in fat mass. The secretion of leptin by adipocytes is as a major driver of renal sympathetic nerve traffic angiotensin II and aldosterone production, and it causes sodium retention in patients with obesity or visceral adiposity.
2. The mutually reinforcing interplay of leptin, angiotensin II, aldosterone, and neprilysin promotes systemic inflammatory responses, plasma volume expansion and redistribution, and ventricular hypertrophy and myocardial fibrosis. Sustained hyperleptinemia or hyperaldosteronemia is sufficient to recapitulate HFpEF experimentally.
3. Circulating levels of leptin precede and predict the development of heart failure (particularly HFpEF, but not HFrEF) in elderly individuals, and they fully account for the influence of obesity to increase the risk of heart failure. The magnitude of hyperleptinemia is correlated with symptom severity and exercise intolerance and is associated with an adverse prognosis.
4. Adipocyte-specific up-regulation of the mineralocorticoid receptor leads to vascular dysfunction. Transplantation of perivascular adipose tissue in which angiotensin II signaling has been suppressed prevents vascular injury in recipient animals.
5. Bariatric surgery and GLP-1 receptor agonism reduce circulating levels of leptin, angiotensin II, aldosterone, and/or neprilysin. Current drugs for HFpEF suppress the secretion or counter the actions of leptin and interfere with the actions of angiotensin II, aldosterone, and neprilysin.

BOX 9. Domain III: Major Non-Leptin Adipocyte-Secretory Mediators of HFpEF

1. In obesity and visceral adiposity, adipocytes drive the secretion of a suite of prohypertrophic, proinflammatory, and profibrotic adipokines, including the lipocalins (RBP4, FABP4, and LCN2), chemerin, resistin, Wnt5a, autotaxin, and asprosin.
2. These Domain III adipokines promote maladaptive cardiac remodeling and fibrosis, and they also impair vascular function, augment arterial stiffness, and enhance the evolution of systemic and pulmonary hypertension. Their experimental suppression ameliorates HFpEF.
3. Circulating levels of these Domain III adipokines are increased in people with obesity and visceral adiposity, and they are associated with left ventricular hypertrophy and diastolic filling abnormalities in the general population and predict the subsequent development of HFpEF. Serum levels are increased in patients with HFpEF, identifying patients with more severe disease and a poor prognosis.
4. Adipocyte secretion plays the central role in mediating the cardiac and vascular injury produced by these adipokines. Adipocyte-specific secretion of chemerin promotes vascular injury. Adipocyte-specific silencing of autotaxin blocks the deleterious effects of obesity on the heart, preventing the development of cardiac hypertrophy, cardiomyopathy and heart. Genetic silencing of resistin—specifically in adipose tissue—reduces circulating levels of resistin and acts to preserve cardiac function during experimental pressure overload, despite having no influence on the cardiac expression of resistin. Mice with selective deletion of LCN2 in adipose tissue—but not those with selective deletion of LCN2 in the kidney—are protected from aldosterone-induced renal injury.
5. Bariatric surgery, GLP-1 receptor agonists, and SGLT2 inhibitors reduce circulating levels of RBP4, FABP4, LCN2, chemerin, resistin, Wnt5a, autotaxin, and/or asprosin.

like-1). Lipocalins are glycoproteins with an antiparallel beta-barrel structure, of which 3 act as transporters of lipophilic molecules—retinol binding protein 4 (RBP4), fatty acid binding protein 4 (FABP4), and lipocalin 2 (LCN2) (also known as neutrophil gelatinase-associated lipocalin [NGAL]). These adipokines comprise a substantial proportion of the total production of proteins by adipocytes[763-765] (with RBP4 circulating in the micromolar range), exerting an important influence on lipid metabolism, insulin sensitivity, and cardiac and vascular health (Box 9).

During nutrient excess, adipocytes secrete RBP4, FABP4, and LCN2 into the bloodstream,[765-770] and LCN2 further facilitates the release of RBP4 and enhances the action of retinoic acid to promote thermogenesis in brown fat.[771,772] Through an endocrine action (often within extracellular microvesicles[773]), the secretion of RBP4, FABP4, and LCN2 by adipocytes promotes lipolysis,[767,768,774] insulin resistance,[766,767,770,775] macrophage activation and adipose tissue inflammation,[776-778] and end-organ steatosis.[779-781] Lipocalins signal through the JAK/STAT pathway, and RBP4 primes the NLRP3 inflammasome, allowing its activation by proinflammatory interleukins.[782] FABP4, RBP4, and LCN2 are also linked to PPARγ signaling.[766,783,784] Obesity (particularly visceral adiposity) is accompanied by increased circulating levels of RBP4, FABP4, and

LCN2,[785-791] which drive end-organ steatosis, inflammation, and fibrosis.[779-781,792,793]

Acting in concert, RBP4, FABP4, and LCN2 exert deleterious effects on the heart by impairing cardiac contractility and enhancing myocardial injury, maladaptive remodeling and fibrosis.[794-800] The lipocalins also increase blood pressure, promote vascular smooth muscle cell proliferation, impair endothelial function, and enhance arterial stiffness.[801-807] Increased circulating levels of RBP4, FABP4, and LCN2 are associated with left ventricular hypertrophy and diastolic filling abnormalities in the general population or in people with obesity,[795,808-811] and their serum levels are increased in patients with heart failure (including HFpEF), where they presage a poor prognosis.[795,812-816] Mendelian randomization studies have linked RBP4 to an increased risk of heart failure.[817]

Importantly, mice with selective deletion of LCN2 in adipose tissue—but not those with selective deletion of LCN2 in the kidney—are protected from aldosterone-induced renal injury.[818] This finding is consistent with evidence that this adipocyte-secreted molecule with deleterious endocrine effects is an important mineralocorticoid receptor target.[818-820] Conversely, pressure overload-induced cardiac hypertrophy leads to increased expression of RBP4 in adipocytes (but not in cardiomyocytes),[796] and serum levels of RBP4 in patients with advanced heart failure decline following left ventricular assist device implantation.[821] These observations indicate mutual lipocalin-mediated endocrine crosstalk between adipocytes and cardiomyocytes in the pathogenesis of cardiac stress.

Chitinase-3 like-1 (known as YKL-40) also has an antiparallel beta-barrel structure (but without transporter activity), but it is characterized as a proinflammatory glycoprotein that modulates the remodeling of the extracellular matrix.[822] Secreted from adipocytes in visceral fat during states of inflammation,[823] YKL-40 acts to inhibit collagen degradation,[824] thus promoting fibrosis within adipose tissue and at adjacent and distant sites.[825] Obesity is accompanied by increased expression of YKL-40 in adipocytes, leading to an increase in serum levels,[823] which decline following bariatric surgery.[823,826] The expansion of epicardial adipose tissue in states of excess adiposity leads to the secretion of YKL-40 and to fibrosis in the underlying myocardium.[825]

YKL-40 suppression mitigates myocardial inflammation and remodeling following experimental myocardial infarction[827]; but unloading of the failing heart does not lower the expression of YKL-40.[828] Clinically, heightened circulating levels of YKL-40 are associated with an elevated risk of incident heart failure,[829] and they are indicative of myocardial involvement in systemic inflammatory states.[830] Serum levels of YKL-40 are increased in patients with heart failure and have prognostic significance,[831-833] and elevated levels are also associated with clinical pressure-overload states and HFpEF, especially in those with cardiac hypertrophy, diastolic filling abnormalities, and poor outcomes.[834-837] Treatment with sacubitril/valsartan and tirzepatide lowers serum levels of YKL-40 in patients with heart failure and diabetes, respectively.[838,839]

Chemerin. Originally described as the product of a retinoid-responsive gene known as retinoic acid receptor responder 2 (Rarres2),[840,841] chemerin is secreted during adipocyte differentiation.[841,842] Activated by PPARγ and signaling through G protein-coupled receptors, chemerin directs bone marrow mesenchymal stem cells towards adipogenesis.[843] Experimental sustained increases in chemerin promote visceral adiposity and glucose intolerance,[844-847] and diet-induced obesity is accompanied by increased circulating levels of chemerin.[840,846] Chemerin enhances the recruitment of macrophages to adipose tissue to promote inflammation.[848,849]

Clinically, Rarres2 mRNA expression in visceral adipose tissue is increased in obese individuals,[850] and chemerin expression in visceral (not subcutaneous) fat contributes to the elevated systemic levels of chemerin.[851] Enhanced adipose tissue processing of chemerin in obesity results in heightened circulating levels of bioactive chemerin.[852]

Adipocyte secretion of chemerin exerts important cardiovascular effects. Chemerin promotes hypertension by mediating vasoconstriction and enhancing vascular smooth muscle cell proliferation.[853,854] These effects can be mediated by the secretion of chemerin from perivascular fat.[855] Additionally, chemerin triggers endothelial and myocardial inflammation,[852,856] cardiomyocyte apoptosis,[856,857] and the migration of cardiac fibroblasts,[858] potentially related to the secretion of chemerin by epicardial adipocytes.[859] Chemerin may mediate the adverse cardiac effects of mineralocorticoid receptor signaling[860] and contribute to pulmonary hypertension.[861] Importantly, adipocyte-specific secretion of chemerin adversely affects vascular function.[862]

Increased serum levels of chemerin presage the development of heart failure[863,864] and are correlated with both left ventricular hypertrophy and diastolic filling abnormalities.[864,865] Serum chemerin levels are also increased in patients with established heart

failure (including HFpEF), where elevated levels identify those with impaired functional capacity and a poor prognosis.[815,866-869] Metabolic reprogramming by SGLT2 inhibition can attenuate adipocyte chemerin signaling and organ steatosis, despite minimal weight loss.[870,871] Chemerin receptor antagonism ameliorates the adverse end-organ consequences of metabolic disorders.[872,873]

Resistin. Resistin is a cysteine-rich polypeptide that is released by adipocytes and by adipose tissue resident mesenchymal stem cells and inflammatory cells.[874-876] Adipogenesis is accompanied by increased synthesis of resistin by human adipocytes, and the secretion of resistin by adipose tissue attenuates its responsiveness to insulin and promotes regional inflammation.[877-879]

Obesity (especially central adiposity) is accompanied by increased serum levels of resistin and augmented resistin expression in abdominal adipose tissue.[880-882] Heightened circulating resistin levels presage the development of heart failure,[592,883-886] are associated with left ventricular hypertrophy and diastolic filling abnormalities,[887-889] and identify patients with HFpEF.[890] Patients with heart failure have elevated levels of resistin, especially if they have impaired exercise tolerance, limited functional capacity, and an unfavorable prognosis.[14,741,891,892]

Systemic administration or cardiac-specific upregulation of resistin causes deleterious cardiovascular effects, including proliferation of vascular smooth muscle and enhanced endothelial cell inflammation and oxidative stress,[893-895] impaired function of cardiomyocytes,[896,897] and adverse remodeling and fibrosis.[897-900] Conversely and importantly, genetic silencing of resistin—specifically in adipose tissue—reduces circulating levels of resistin and acts to preserve cardiac function during experimental pressure overload, despite having no influence on the cardiac expression of resistin[901]—exemplifying adipokine-mediated dissemination of adipose tissue biology to the heart.

Wnt5a-Frizzled-5 receptor signaling. The wingless-type integration site (Wnt) protein family typically signals through β-catenin, but unlike other Wnt proteins, Wnt5a utilizes a noncanonical mechanism to activate JNK and other downstream pathways.[902] Wnt5a plays an essential role in embryonic cardiac morphogenesis, and its expression subsides postnatally.[902-904] However, in patients with obesity, the synthesis and secretion of Wnt5a by adipocytes (particularly within visceral fat) is heightened.[905,906] Extracellular Wnt5a enhances adipocyte differentiation and augments lipid accumulation,[674,907-909] and it promotes adipose tissue inflammation independent of fat mass expansion.[10] SFRP5 acts as a decoy receptor for extracellular Wnt5a, thus preventing its interactions with the Wnt5a receptor (Frizzled-5).[164,905,910]

Adipocytes are the primary source for circulating Wnt5a,[911] and thus, serum Wnt5a levels are increased in patients with obesity, especially those with visceral adiposity and systemic inflammation.[906,911-913] Circulating levels of WNT5a exert important endocrine effects, especially in patients with obesity, in whom levels of the SFRP5 decoy are simultaneously suppressed.[910] An increase in the ratio of Wnt5a to SFRP5 in the bloodstream or adipose tissue in patients with obesity is accompanied by increased oxidative stress within the arterial wall and enhanced vascular calcification,[914] and the secretion of Wnt5a from epicardial adipocytes is associated with the presence of coronary artery disease.[915] Furthermore, adipocyte-derived extracellular vesicles can direct mesenchymal stem cells toward adipogenic differentiation (through Wnt5a) and can promote the expression of Wnt5a in cardiac fibroblasts.[916,917]

Extracellular Wnt5a signals through fibroblast Frizzled-5 receptors to promote myocardial fibrosis during pressure overload,[918] and following hemodynamic stress, extracellular Wnt5a enhances cardiomyocyte Wnt5a expression, pathological hypertrophy and heart failure.[919-921] Interference with extracellular Wnt5a suppresses the myocardial expression of Wnt5a in the failing heart,[922] and pharmacological Wnt5a inhibition mitigates the cardiac hypertrophy and fibrosis and alleviates experimental HFpEF.[923]

Serum and cardiac levels of Wnt5a are increased in experimental and clinical heart failure,[922,924,925] being associated with pulmonary hypertension and an adverse prognosis.[926,927] Therapeutic abrogation of Wnt5a signaling—by inhibition of Wnt5a secretion or by Frizzled-5 antagonism—prevents the development of experimental postinfarction heart failure and HFpEF.[922,928,929]

Autotaxin. Autotaxin (known as ectonucleotide pyrophosphatase/phosphodiesterase 2) is a secreted lysophospholipase D, which acts extracellularly to catalyze the formation of lysophosphatidic acid,[930] a bioactive lipid that (via endocrine signaling) exert effects on diverse organs, particularly the heart (Box 9).

Autotaxin is synthesized during adipogenesis and activates the proliferation of white adipose tissue.[930,931] Adipocytes are the principal source of circulating autotaxin,[932] and diet-induced obesity induces the expression of autotoxin by adipocytes.[933,934] Accordingly, serum levels of autotaxin

and lysophosphatidic acid are increased in experimental and clinical obesity[934-939] and lead to further obesity.[940,941]

Once in the bloodstream, lysophosphatidic acid signals through G protein-coupled receptors in the heart (which are up-regulated in obesity) to promote maladaptive myocardial hypertrophy, cardiac fibrosis, and cardiomyopathy through up-regulation of Akt-mTOR and PPARγ signaling and suppression of autophagy.[931,942,943] Inhibition of autotaxin mitigates postinfarction ventricular remodeling.[944] Serum levels of autotaxin are increased in patients with cardiac hypertrophy, left ventricular dysfunction, or with heart failure and have prognostic significance.[938,945,946]

Importantly, adipocyte-specific silencing of autotaxin blocks the deleterious effects of obesity on the heart, preventing the development of cardiac hypertrophy, cardiomyopathy, and heart failure, thus exemplifying the central premise of adipokine hypothesis.[943] Adipocyte-derived autotaxin has been proposed as one of the key mediators of obesity-driven cardiomyopathy.[938,943] Inhibition of the interaction of lysophosphatidic acid and its receptors in the heart alleviates cardiac hypertrophy and heart failure.[946,947] Ziritaxestat, an autotoxin inhibitor, has been developed for the treatment of pulmonary fibrosis.[948]

Asprosin. Directly transcribed from the fibrillin gene, asprosin typically acts as a fasting-induced glucogenic polypeptide.[949-951] During nutrient deprivation, asprosin is released by adipocytes to maintain blood glucose, acting in an endocrine manner to increase appetite, promote the hepatic release of glucose, and impair glucose uptake in skeletal muscle.[950-952] However, during nutrient excess, sustained synthesis of asprosin by white adipose tissue promotes lipid deposition and contributes to adipose tissue and skeletal muscle inflammation.[952-954] Adipocyte expression and serum levels of asprosin are increased in patients with obesity,[955-957] particularly those with marked visceral adiposity,[956-959] and these levels decline with weight loss produced by incretin-based drugs and gastric bypass surgery.[960,961] Experimental asprosin gene silencing and the administration of asprosin antibodies alleviate obesity and the metabolic syndrome.[962,963]

Asprosin has been proposed as a key mediator of obesity-related cardiovascular disease[964] by its actions to promote the development of the vascular endothelial dysfunction that characterizes obesity and HFpEF. Asprosin enhances vascular smooth muscle oxidative stress, inflammation, and proliferation, and it induces the endothelial-to-mesenchymal transition that leads to cardiac fibrosis.[965-969] Serum levels of asprosin are increased and have prognostic significance in patients with heart failure and dilated cardiomyopathy,[970,971] and they are also increased in elderly diabetic patients who have central obesity and abnormal diastolic filling dynamics.[972]

BOX 10. Domain III: Adipose Tissue Secretion of Growth Factors, Matricellular Proteins and Extracellular Matrix Glycoproteins

1. In states of excess adiposity, adipose tissue secretes heightened quantities of several growth factors—platelet-derived growth factors (especially PDGF-D), transforming growth factor superfamily members (especially activin A), and insulin-like growth factors and their binding proteins (especially IGFBP7)—as well as matricellular proteins (eg, thrombospondin-1, SPARC, and galectin-3) and canonical extracellular matrix glycoproteins (eg, TIMP1 and cathepsin S).
2. These Domain III adipokines play a major role in vascular dysfunction and cardiac fibrosis, often leading to pulmonary hypertension. Both IGF-1 and IGF-1 receptors are up-regulated in the aging heart and predispose to cardiac injury. IGFBP7 (which prolongs the action of IGF-1) and activin A promote cardiac senescence. Thrombospondin-1 enhances vasoconstrictor responses and leads to hypertrophy, fibrosis, and microvascular rarefaction in experimental HFpEF.
3. Adipocyte-specific overexpression of PDGF-D leads to PDGF-D-mediated cardiac fibrosis through an endocrine mechanism. Activin A appears to mediate the adverse paracrine effects of expanded and inflamed epicardial adipose tissue on the adjoining myocardium. Galectin-3 acts as an intermediary in obesity-related cardiac lipotoxicity, myocardial fibrosis, and microvascular endothelial dysfunction, the hallmarks of HFpEF.
4. Serum levels of these Domain III adipokines are increased in patients with obesity and visceral adiposity and are reduced following bariatric surgery. Increased serum levels presage the development of heart failure, and circulating levels are elevated in patients with established HFpEF, where they identify a poor prognosis.
5. Sotatercept, a fusion protein that traps and sequesters ligands of activin type II receptors (particularly activin A) is approved for use in patients with pulmonary arterial hypertension, and it ameliorates the development of experimental HFpEF.

ADIPOSE-SECRETED GROWTH FACTORS AND THEIR BINDING PROTEINS RELEVANT TO HEART FAILURE.

Certain growth factors (not exclusively secreted by adipose tissue) play a major role in obesity-driven

adipose biology and its cardiovascular consequences, because their adipose synthesis is heightened by an expanding adipocyte mass (Box 10).

Platelet-Derived Growth Factor Receptor-β Signaling. Platelet-derived growth factors (PDGFs) and their receptors, PDGFRα and PDGFRβ, play a central role in the response of adipose tissue to the development of obesity,[973,974] while simultaneously activating cardiac fibroblasts that lead myocardial fibrosis.[975]

PDGFRα+- and PDGFRβ+-preadipocytes represent different progenitor lineages.[976] In obesity, the pool of PDGFRβ+-preadipocytes expands greatly, leading to growth of white adipose tissue, PDGF-mediated insulin resistance, and PDGFRβ+-mediated angiogenesis, while PDGFRα+-preadipocytes are directed toward the formation of adipose tissue fibroblasts.[976-982] The imbalance in PDGFRβ+/PDGFRα+ adipocytes is seminal to the development of adipose tissue dysfunction in obesity.[976,980] Genetic knockout of PDGFRβ restores healthy adipocyte biology[983] and ameliorates obesity.[981]

Importantly, the biological consequences of PDGFRβ+ preadipocyte dominance can be disseminated from adipocytes to the heart. Adipocyte-specific overexpression of PDGF-D (an endogenous agonist of PDGFRβ receptors) promotes PDGF-D-mediated maladaptive cardiac remodeling, whereas adipocyte-specific silencing of PDGF-D decreases circulating PDGF-D levels and attenuates deleterious cardiac hypertrophic and fibrotic responses in experimental obesity.[984] The consequences of these effects may be further enhanced by up-regulation of PDGFRβ in the injured heart.[985] The failing heart exhibits proliferation of PDGFRβ+-mesenchymal stem cells, along with augmented expression of the PDGFRβ ligands, PDGF-BB and PDGF-D.[986] Genetic overexpression of PDGF-D leads to cardiac fibrosis, cardiomyopathy, and heart failure,[987,988] and PDGFRβ signaling promotes myocardial hypertrophy.[975,989] Experimental obesity-related augmented expression of PDGF-BB and PDGFRβ mediates pulmonary hypertension,[990] and is linked to increases in left atrial volume[991] and the end-organ fibrosis seen in HFpEF.[992]

Clinically, circulating and adipose tissue levels of PDGF-BB and PDGF-D (agonists of PDGFRβ receptors) are increased in people with obesity or insulin resistance,[993-996] and elevated serum levels of PDGFs are seen in patients with HFpEF.[997] Interestingly, adiponectin appears to bind directly to and inhibit PDGF-BB.[998] Anticancer tyrosine kinase inhibitors (eg, imatinib), acting as PDGFRβ antagonists, ameliorate cardiac fibrosis, and pulmonary hypertension.[986,999,1000] The cardiotoxicity of imatinib and other tyrosine kinase inhibitors in the clinical setting is not related to their effect to inhibit PDGFRβ, but to off-target effects.

TGF-β superfamily and activin type I and II receptor signaling. The TGF-β superfamily includes families of mutually reinforcing and antagonistic polypeptides (including bone morphogenetic proteins and growth differentiation factors), which signal through activin type I and II receptors. Stimulation of activin type I and II receptors and downstream Smad 2/3 transcription factors leads to both adipose expansion and cardiac fibrosis.[1001,1002] Although TGF-β1 represents the canonical link between obesity and the Smad2/3-mediated activation of cardiac fibroblasts,[1003,1004] 2 key activin ligands are of particular interest in understanding the link between obesity and heart failure: 1) growth differentiation factor 3 (GDF-3), which signals through activin-like receptor 7 (ALK7), a type I receptor[1005]; and 2) activin A (which signals through the type II receptor).

ALK7 is predominantly expressed in adipocytes,[1006,1007] and ALK7 is up-regulated during adipogenesis.[1008] Obesity and nutrient excess enhances the expression of activin A and GDF-3 in adipocytes.[1002,1007,1009] Genetic overexpression of GDF-3 leads to a profound expansion of fat mass,[1009] and adipocyte-specific up-regulation of activin signaling enhances adipogenesis.[1010] Conversely, pharmacological inhibition or genetic disruption of GDF-3, ALK7, or type II receptor signaling ameliorates experimental obesity.[1011-1014] Obesity-driven up-regulation of GDF-3 mediates adipose tissue inflammation,[1015,1016] whereas experimental or clinical ALK7 loss-of-function polymorphisms are accompanied by reduced adiposity.[1017,1018] Serum levels of activin A are increased in patients with obesity and visceral adiposity[1019,1020] and are reduced by bariatric surgery.[1021,1022]

Activin A has been identified as a key intermediary of the adverse effects of epicardial adipose tissue dysfunction on the adjoining myocardium.[1023] GDF-3/ALK7 and activin A/type II receptor signaling can promote cardiac fibrosis and apoptosis,[1024-1027] and ALK7 silencing alleviates myocardial fibrosis and ventricular dysfunction.[1028] ALK7 promotes vascular smooth muscle proliferation,[1029,1030] and activin A mediates deleterious pulmonary vascular changes.[1031] Heightened serum levels of GDF-3 and activin A are associated with postinfarction ventricular remodeling.[1024,1032]

Clinically, elevated serum levels of activin A identify patients with diabetes who have left ventricular hypertrophy.[1033] Circulating levels of activin

A are increased and have prognostic significance in patients with pulmonary arterial hypertension.[1034] A clinical gain-of-function ALK7 polymorphism is associated with both central obesity and left ventricular hypertrophy.[1035] Circulating levels of activin A are also increased in patients with HFpEF, particularly those with obesity,[1036] in proportion to the severity of diastolic filling abnormalities, and have prognostic significance,[1037] and activin type II receptor antagonism alleviates experimental HFpEF.[1026] Sotatercept, a fusion protein that traps and sequesters ligands of activin type II receptors (particularly activin A) also ameliorates experimental HFpEF,[1026,1031] and it is a U.S. Food and Drug Administration (FDA)-approved treatment for patients with pulmonary arterial hypertension.[1038] Bimagrumab, an activin type II inhibitor, is being developed for the treatment of patients with obesity.[1039]

Insulin-like growth factor-1 receptor signaling. Insulin-like growth factor-1 (IGF-1), the key mediator of the effects of growth hormone, signals through its cognate receptor, insulin growth factor-1 receptor (IGF-1R). The interactions of IGF-1 and IGF-1R are attenuated by a family of insulin-like growth factor binding proteins (IGFBPs), which typically act to limit IGF-1R activation.

Adipocytes secrete IGF-1 into the circulation.[1040] IGF-1 promotes adipogenesis and adipose hypertrophy,[1041,1042] and the expression of IGF-1R in adipocytes is up-regulated in diet-induced obesity.[1043] Pharmacological antagonism of the IGF-1R with cixutumumab mitigates against the development of diet-induced obesity,[1044] and suppression of endothelial IGF-1R ameliorates adjoining adipose tissue dysfunction.[1045] Serum levels of IGFBP1 (an endogenous antagonist of IGF-1R in adipocytes[1046]) are decreased by obesity.[1047-1049] The resulting unrestrained IGF-1R signaling contributes to obesity-related cardiac hypertrophy[1050] and to angiotensin II-mediated cardiac fibrosis.[1051] IGF-1R expression is up-regulated in the aging and the failing human heart;[1052,1053] and experimental suppression of IGF-1R signaling prolongs cardiac survival.[1052,1054]

Interestingly, in contrast to other IGFBPs, IGFBP7 has a low affinity for IGF-1, and it acts to accentuate (rather than inhibit) IGF-1R signaling.[1055-1057] Adipose tissue is a significant source of IGFBP7,[1058] and serum levels of IGFBP7 are increased in patients with central obesity and organ steatosis.[1059,1060]

Importantly, IGFBP7 signals through IGF-1R to promote cardiomyocyte senescence, leading to adverse ventricular remodeling and cardiac fibrosis; these derangements can be ameliorated by IGFBP7 silencing.[1061-1063] The effect of IGFBP7 to induce senescence is intertwined with a similar action of activin A.[1064] IGFBP7 and activin A appear to inhibit each other, suggesting an interplay that prevents excessive senescence.[1064]

Clinically, serum levels of IGFBP7 are associated with left ventricular hypertrophy in the general population,[301] and they are consistently elevated in patients with HFpEF, in proportion to the severity of diastolic filling abnormalities and left atrial enlargement, and have prognostic significance.[1065-1070] Interestingly, the failing heart is not a source of either circulating IGF-1 or IGFBP7 in HFpEF, since it extracts both proteins from the circulation.[1071,1072] The role of IGFBP7-mediated IGF-1R signaling in linking adiposity and HFpEF warrants further investigation.

ADIPOSE TISSUE MATRICELLULAR GLYCOPROTEINS AND OTHER EXTRACELLULAR MATRIX GLYCOPROTEINS. Obesity can drive adipocytes to secrete certain adipokines into the extracellular matrix, where they can promote adipogenesis and adipose tissue inflammation, while signaling to the myocardium to promote cardiac inflammation and fibrosis. These adipokines can be grouped into 2 broad categories: 1) matricellular proteins; and 2) canonical extracellular matrix glycoproteins (Box 10).

Despite their localization in the extracellular matrix, matricellular proteins do not have scaffolding functions, and they are grouped together[1073] because 1) they are expressed during embryonic development and in response to injury; 2) they play a key role in the extracellular matrix to promote cell counter-adhesion, in contrast to most matrix proteins (which promote adhesion); and 3) following their secretion into the extracellular matrix, they can exert effects on adjoining tissues or be released into the circulation, often as components of adipoexosomes.[1074] This mechanism allows matricellular proteins to function as signaling molecules, generally acting through the Wnt/β-catenin pathway.

Canonical extracellular matrix glycoproteins (eg, tissue inhibitor of proteinase-1 and cathepsin S) directly modulate the degradation of scaffolding proteins (collagen and elastin), but additionally, they drive crosstalk between adipocytes and fibroblasts, thus being positioned to exert adverse effects on both adipose and cardiac tissue biology. YKL-40 (discussed earlier) can also be classified into this group.

Wnt/β-catenin signaling matricellular glycoproteins. These include thrombospondin-1, secreted protein acidic rich in cysteine (SPARC) (osteonectin), galectin-3, Wnt1-induced secreted protein-1/cellular

communication network factor 4 (WISP1/CCN4), osteopontin, and tenascin-C.

Thrombospondin-1. Acting through its receptor CD47, thrombospondin-1 promotes remodeling of the extracellular matrix to stimulate adipocyte proliferation and amplify adipose tissue inflammation.[1075-1079] Thrombospondin-1 is preferentially expressed in visceral adipocytes (rather than subcutaneous fat) in obese subjects,[1080,1081] and it is shed from human white adipose tissue as a key component of extracellular vesicles.[1082] Experimentally, the release of thrombospondin-1 into the circulation mediates high fat diet-induced insulin resistance and skeletal muscle fibrosis,[1083] and signaling through CD47 promotes further obesity.[1084] Circulating levels of thrombospondin-1 are increased in patients with obesity.[1085,1086]

Signaling through CD47 receptors on cardiomyocytes, thrombospondin-1 promotes hypertrophy and heart failure.[1087] Silencing of CD47 signaling promotes autophagic cellular housekeeping and prevents hypertrophy and apoptosis in cardiomyocytes following injury.[1088-1091] Thrombospondin-1 is a key mediator of cardiac fibrosis,[1092-1094] acting to modulate extracellular matrix remodeling in heart failure.[1095] Additionally, thrombospondin-1 enhances vasoconstrictor responses[1096] and has been implicated in experimental systemic and pulmonary hypertension.[1096,1097] It mediates the development of hypertrophy, fibrosis, and microvascular rarefaction in experimental HFpEF, an effect that is blocked by thrombospondin-1 antagonists.[1098-1100]

In the clinical setting, circulating thrombospondin-1 is a marker for the identification of cardiac hypertrophic states.[1101] Thrombospondin-1/CD47 signaling is up-regulated and mediates vasoconstrictor responses in the pulmonary arteries of patients with pulmonary arterial hypertension.[1102] Endocrine activation of CD47 may be particularly important, because patients with heart failure have increased circulating levels (but low cardiac expression) of thrombospondin-1.[1103-1105]

Secreted protein acidic rich in cysteine. Acting on collagen and metalloproteinases, SPARC regulates the assembly and organization of the extracellular matrix, thereby playing a key role in cellular growth.[1106] In response to dietary excess, SPARC is secreted during adipocyte differentiation and proliferation,[1107,1108] leading to its up-regulation in human adipocytes in obesity.[1109] Serum levels of SPARC are correlated with adipocyte expression, body mass index, and visceral fat mass,[1107,1109,1110] and they decline following bariatric surgery.[1111] SPARC modulates adipose tissue remodeling by enhancing the postsynthetic maturation of collagen[1112] and proinflammatory signaling,[1113,1114] leading to adipose and visceral organ inflammation and fibrosis.[1115,1116]

As a result of its effects in the extracellular matrix, SPARC contributes to the development of cardiac inflammation, myocardial fibrosis, and diastolic filling abnormalities during aging and hemodynamic stress.[1117-1121] SPARC impairs vascular endothelial function, predisposing to systemic and pulmonary hypertension.[1122-1124] SPARC is packaged in circulating extracellular vesicles, whose numbers are increased in patients with hypertension.[1125] Serum levels of SPARC are elevated and have adverse prognostic significance in patients with heart failure.[1126,1127]

Importantly, extracardiac sources of SPARC mediate cardiac fibrosis. Transplantation of SPARC-expressing bone marrow mesenchymal stem cells taken from mice with pressure overload recapitulates the cardiac fibrosis and myocardial stiffness phenotype in recipient mice that are not under hemodynamic stress.[1128] These observations support crosstalk between extracardiac sources and the heart, akin to other adipokines.[129,134,143,821]

Matricellular lectins (galectin-3). Extracellular galectin-3 is a pentameric ligand for the β-galactoside residues of numerous glycoproteins, driving their crosslinking and the formation of higher order lattices that bind to integrins, thus playing a critical role in signaling between fibroblasts and the extracellular matrix.[1129,1130]

Galectin-3 is up-regulated and secreted during adipogenesis[1131-1133] and promotes adverse adipose tissue remodeling and organ steatosis, effects that are prevented by galectin-3 inhibition.[1134,1135] Adipocytes represent an important source of circulating galectin-3, explaining the strong parallelism between visceral adipose tissue expression and serum levels of galectin-3 during the evolution of obesity-related heart disease.[1136] Circulating levels of galectin-3 are increased in patients with obesity, particularly those with visceral adiposity and systemic inflammation.[1137-1143]

Experimental studies have implicated galectin-3 in the pathogenesis of obesity-related cardiac lipotoxicity, microvascular dysfunction, and myocardial fibrosis[1137,1144-1147]—the hallmarks of HFpEF. Enhanced expression of galectin-3 in the failing heart is localized to cardiac fibroblasts and macrophages.[1148] Infusions of galectin-3 stimulate fibroblast proliferation and collagen deposition,[1149] and knockout or suppression of galectin-3 alleviates cardiac fibrosis.[1137,1149] Importantly, neurohormonal stimulation of white adipose tissue leads to galectin-

3-mediated activation of cardiac fibroblasts,[491] demonstrating a role for adipose tissue-cardiac signaling in the pathogenesis of HFpEF.

Clinically, galectin-3 is an indicator of the presence of latent heart failure or the future risk of heart failure in the general community,[1143,1150] and particularly, of diastolic filling abnormalities, left atrial enlargement or HFpEF in patients with obesity or diabetes.[1137,1150-1152] Circulating levels of galectin-3 are increased in patients with heart failure, are related to the severity of ventricular remodeling, and have prognostic significance.[1153-1155] Serum levels of galectin-3 are particularly increased in those with HFpEF,[1156-1158] in whom circulating levels are correlated with obesity,[1159] diastolic filling abnormalities,[1160] and fibrosis.[1146,1161] Cardiac stress is not the source of circulating galectin-3, since it is not reduced by mechanical cardiac support or heart transplantation,[1162,1163] thus reinforcing the importance of extracardiac production.

Osteopontin, tenascin-C, and Wnt1-induced secreted protein-1. Three additional matricellular proteins—osteopontin, tenascin-C, and WISP1/CCN4—have been implicated as mediators of obesity-related heart failure.

The adipocyte expression of all 3 glycoproteins is up-regulated in obesity.[1164-1167] All 3 play a role in promoting adipogenesis and adipose tissue inflammation[1165-1170] and are secreted into the extracellular matrix and released at heightened levels into the circulation, particularly in patients with obesity and organ steatosis.[1171-1175] As with other matricellular proteins, these adipokines are involved in the deposition of collagen, the postsynthetic collagen processing and remodeling of the extracellular matrix.[1167,1176]

Experimentally, all 3 matricellular proteins promote myocardial hypertrophy and fibrosis.[1177-1181] Overexpression of osteopontin in cardiomyocytes leads to cardiomyopathy,[1182] and silencing of tenascin C alleviates experimental HFpEF.[1181] Clinically, epicardial adipocytes may be an important source of osteopontin,[1183] and serum levels of tenascin-C and osteopontin are increased and have prognostic significance in patients with heart failure,[1184,1185] including those with HFpEF.[1186] Elevated serum levels of tenascin-C are associated with cardiac hypertrophy and ventricular remodeling[1187,1188] and with diffuse cardiac fibrosis in patients with HFpEF.[1189]

Canonical extracellular matrix glycoproteins. Exemplified by tissue inhibitor of metalloproteinase 1 (TIMP1) and cathepsin S, these are secreted by adipocytes and act as regulators of the extracellular matrix, thereby acting to modulate adipose biology and mediate the development of cardiac fibrosis.

TIMP1 and CD63 signaling. There exists a delicate balance between a family of metalloproteinases (MMPs) (which act to degrade components of the extracellular matrix) and a family of tissue inhibitors of metalloproteinases (TIMPs), which oppose the effects of MMPs.[1190] Unlike matricellular proteins, these proteins do not counter cellular adhesion or modulate cellular morphology. Nevertheless, MMPs and TIMPs influence the biology of both adipocytes and cardiac fibroblasts.[1190,1191]

TIMP1 is particularly noteworthy, because it not only inactivates most MMPs, but it also exerts MMP-independent effects by interacting with the CD63 receptor and signaling through integrin β1.[1192] Obesity augments the expression of TIMP1 in adipocytes,[1193,1194] and in turn, TIMP1 up-regulation promotes the expansion of fat mass in high fat diet-induced obesity by promoting adipocyte hypertrophy, leading to organ steatosis.[1195-1197]

In parallel, TIMP1 expression is increased in the hypertrophied and fibrotic myocardium of experimental and clinical pressure overload.[1198,1199] Persistence of fibrosis following alleviation of the hemodynamic stress is related to continued myocardial TIMP1 expression,[1200] and TIMP1 silencing ameliorates cardiac fibrosis.[1201] In replacement fibrosis following major cardiac tissue loss, up-regulation of TIMP1 causes adaptive collagen deposition to stabilize ventricular structure, and such an action is antagonized by MMPs.[1202-1204] In contrast, in states of pressure overload or HFpEF, TIMP1 causes maladaptive fibroblast activation that is mediated through CD63, is exacerbated by aldosterone, and is not reversed by MMPs.[1200,1205]

In the clinical setting, serum levels of TIMP1 are increased in people with obesity, particularly those with central adiposity or organ steatosis.[1206-1208] Heightened serum levels presage those with obesity who are likely to develop heart failure during follow-up.[1209] Increased serum levels (often with increased cardiac expression) of TIMP1 are seen in patients with hypertension,[1210] left ventricular hypertrophy,[1211] and chronic pressure overload and are related to the severity of interstitial fibrosis and diastolic filling abnormalities.[1198,1212,1213] Serum levels of TIMP1 levels are increased in HFpEF and have prognostic significance.[80,1214,1215]

Intriguingly, circulating levels may represent important biological mediators of TIMP1 signaling, since adipose tissue can release TIMP1 and CD63 as components of secreted extracellular microvesicles.[1216] Endocytosis of these TIMP1-carrier

adipoexosomes by recipient fibroblasts induces their own production of TIMP1,[1217] explaining why adipocyte-secreted exosomes can induce TIMP1 at distant sites.[1218]

Cathepsin S/protease-activated receptor 2 signaling. Cathepsins are cysteine proteases that typically function under acidic conditions in the lysosome, but cathepsin S is adapted to a neutral pH, allowing it to be biologically active when secreted. Cathepsin S has elastase activity, but more importantly, cathepsin S cleaves and activates protease-activated receptor 2 (PAR2), which has potent proinflammatory effects.

Cathepsin S is expressed by adipocytes and promotes adipogenesis,[1219,1220] explaining why adipose-tissue expression and serum levels of cathepsin S are increased in parallel in patients with obesity (and visceral adiposity) and are reduced by weight loss.[1221-1224] In diet-induced obesity, cathepsin S inhibition alleviates adipogenesis, inflammatory infiltration, and organ lipid accumulation.[1219] Simultaneously, PAR2 is up-regulated in adipose tissue stromal cells in experimental obesity[1225,1226] and promotes adipogenesis and adipose tissue inflammation, effects that are muted by PAR2 antagonism.[1227,1228]

Experimentally, the elastase activity of cathepsin S may undermine the ability of the heart to tolerate hemodynamic and metabolic stresses.[1229,1230] Additionally, cathepsin S signaling through PAR2 promotes the development of cardiomyopathy by enhancing oxidative stress and proinflammatory signaling in cardiomyocytes and endothelial cells.[1231,1232] Suppression or antagonism of PAR2 alleviates cardiac hypertrophy, myocardial inflammation, fibrosis, and apoptosis.[1233-1236]

Clinically, serum levels of cathepsin S are increased in patients with cardiac hypertrophy and are correlated with left ventricular mass and diastolic filling abnormalities.[1237] Circulating levels of cathepsin S are also increased and have prognostic value in patients with heart failure, particularly with HFpEF.[1238,1239] Yet, paradoxically, cardiac PAR2 expression may be suppressed in patients with HFpEF,[1240] being regarded a maladaptive response that may induce further cardiac fibrosis and diastolic dysfunction.[1240]

ADIPOSE TISSUE-SECRETED CHEMOKINES AND ANGIOPOIETINS.

Obesity can drive adipocyte synthesis and secretion of chemokines and angiopoietins, which not only promote cell migration to induce inflammation and vasculogenesis, but also have important effects on lipid metabolism and cardiac remodeling (Box 11).

BOX 11. Domain III: Adipose Tissue-Secreted Chemokines and Angiopoietins

1. Obesity is accompanied by enhanced adipose tissue secretion of several chemokines—CCL2, CCL5, CXCL8, CXCL12—and several angiopoietins or angiopoietin-like proteins—ANGPT2, ANGPTL2, ANGPTL4, and ANGPTL8.
2. Chemokines are chemoattractants for inflammatory cells that promote adverse ventricular remodeling. Angiopoietins and angiopoietin-like proteins target the vascular endothelium to cause inflammation, which is transmitted to the adjacent myocardial tissue. Chemokines, angiopoietins, or angiopoietin-like proteins are important mediators of cardiac fibrosis and microvascular rarefaction, thereby playing a role in experimental diet-induced HFpEF.
3. Serum levels of these Domain III adipokines are increased in patients with obesity. Increases in serum levels precede and presage the development of HFpEF, and they are increased in patients with established HFpEF in proportion to its severity. Adiposity-related enhanced secretion by epicardial adipocytes exerts adverse effects on the underlying myocardium.
4. Adipocyte-specific ablation of ANGPTL4 abrogates its effects to inhibit lipoprotein lipase, thereby promoting vascular injury. Suppression of CCR2 in bone marrow inflammatory cells ameliorates experimental cardiomyopathy. CCL5/CCR5 signaling may mediate aldosterone-induced end-organ injury.
5. Weight loss produced by bariatric surgery and incretin receptor agonists reduces circulating levels of adipose tissue-secreted chemokines, angiopoietins, and angiopoietin-like proteins.

Adipocyte-secreted C-C and CXC chemokines. Chemokines are chemoattractant polypeptides that promote cell migration and enhance proinflammatory responses. Chemokines are grouped based on the spacing of the first 2 of 4 conserved N-terminal cysteine residues, ie, those with 2 adjacent cysteines are named C-C chemokines, and those where the 2 cysteines separated by 1 amino acid are named CXC chemokines. Chemokines are further identified as ligands or receptors and designated with an L or R; hence, CCL refers to a C-C chemokine ligand (ie, agonist) and CXCR refers to a CXC receptor.

Chemokine (C-C) motif ligands (CCL2 and CCL5). The 2 most well-characterized C-C chemokines are CCL2 (also known as monocyte chemoattractant protein-1) and CCL5 (RANTES). CCL2 and CCL5 signal through their respective receptors, CCR2 and CCR5, to mobilize inflammatory cells from the bone marrow into the bloodstream.

Obesity causes increased expression of both CCL2 and CCL5 in adipocytes,[1241,1242] thereby evoking adipose tissue inflammation, suppression of lipolysis and adaptive thermogenesis, and further obesity.[1243-1245] Enhanced adipocyte-specific expression of CCL2 leads to insulin resistance and visceral adiposity,[1246] and serum CCL2 levels are increased in patients with visceral adiposity and decreased by weight loss.[1247-1249] CCR2 antagonism mitigates against the development of obesity and organ steatosis produced by a high-fat diet.[1250] Endogenous NAMPT is a natural antagonist of CCR5,[181] and dual CCR2/CCR5 antagonists alleviate adipose tissue inflammation and insulin resistance.[1251,1252] In obesity, epicardial adipocytes heighten their secretion CCL2 and CCL5 onto the adjoining myocardium in proportion to the expansion of fat mass.[1253-1255]

Cardiac-specific overexpression of CCL2 promotes adverse ventricular remodeling and myocardial fibrosis,[1256,1257] but the relevance of this observation is uncertain since (in contrast to experimental models) the failing human heart shows down-regulation of the ligand CCL2, but up-regulation of the receptor CCR2,[1258-1260] pointing to enhanced sensitivity to an extracardiac source. It is therefore noteworthy that serum CCL2 levels are elevated in patients with hypertension who are at increased risk of diastolic filling abnormalities.[1261] Serum levels of both CCL2 and CCL5 are increased in heart failure in proportion to the severity of disease and prognosis.[1262-1265]

Importantly, adipose tissue-specific suppression of CCL2 has favorable effects at distant sites,[1266] and suppression of CCR2 in inflammatory cells residing in the bone marrow acts to ameliorate experimental cardiomyopathy.[1267] Knockout of CCR2 alleviates obesity-related end-organ injury;[1245] and antibodies to CCL2 prevent cardiac fibrosis and diastolic filling abnormalities following experimental pressure overload.[1268] CCL5/CCR5 signaling mediates aldosterone-induced end-organ injury,[1269] and systemic CCR2 or CCR5 antagonism alleviates pressure-overload hypertrophy,[1258] pulmonary and systemic vascular hypertrophy and proliferation,[1270,1271] and postinfarction heart failure.[1272,1273]

Chemokine (CXC) motif ligands (CXCL8 and CXCL12). Although many CXC chemokines are linked to obesity and heart failure, the 2 most studied are 1) CXCL8 (also known as IL-8, signaling through the CXCR2 receptor); and 2) CXCL12 (also known as stromal cell-derived factor-1, signaling through the CXCR4 receptor). CXCL8 and CXCL12 interact synergistically to regulate inflammatory responses.[1274,1275]

Obesity leads to heightened adipocyte secretion of both CXCL8 and CXCL12, which act to promote insulin resistance and recruit inflammatory and bone marrow mesenchymal stem cells to adipose tissue, especially visceral fat,[1276-1282] effects that are blocked by CXCR2 antagonism.[1283,1284] Obesity (especially central adiposity) is accompanied by increased serum levels of both CXCL8 and CXCL12,[1278,1285-1288] with adipocytes in white adipose tissue being a primary source of circulating levels.[1289] Obesity enhances the number of circulating CXCR4-positive bone marrow mesenchymal stem cells and their recruitment to visceral fat.[1277]

CXCL8 and CXCL12 signaling has also been implicated in the pathogenesis of adverse ventricular remodeling and myocardial fibrosis seen in angiotensin II or aldosterone-excess models of HFpEF,[1290,1291] effects that are blocked by CXCR2 and CXCR4 antagonism.[1292-1295] Serum levels of both CXC chemokines are increased in patients at risk of and with established heart failure, especially with HFpEF.[1296-1301]

Experimentally, enhanced signaling through CXCL12/CXCR4 has been linked to cardiac repair if it takes place immediately following cardiac injury.[1302-1305] These observations have led some investigators to propose that CXCL12 overexpression could cause circulating mesenchymal stem cells to target the myocardium and mature into cardiomyocytes.[1306] However, trials have not confirmed this hypothesis,[1307,1308] and instead, sustained CXCL12 signaling (continuing beyond the early phase of injury) promotes cardiac fibrosis rather than regeneration.[1309] Because CXCL12 is degraded by dipeptidyl peptidase 4,[1310] dipeptidyl peptidase 4 inhibitors potentiate CXCL12 signaling and promote cardiac fibrosis,[1311] possibly explaining why their use has been accompanied by an increased risk of heart failure in certain large-scale clinical trials in type 2 diabetes.[1312,1313]

Angiopoietins and angiopoietin-like proteins. Originally recognized for their action to modulate angiogenesis, angiopoietins and angiopoietin-like proteins are structurally similar families have important effects on lipid metabolism and systemic inflammation. The 2 families are distinguished by the fact that angiopoietins are ligands for the Tie-2 receptor tyrosine kinase, whereas angiopoietin-like proteins are not. Both angiopoietins and angiopoietin-like proteins also signal through cell adhesion molecules.

Angiopoietin-2. Ang-1 is secreted by adipocytes to interact with the Tie2 receptor, and this action is opposed by angiopoietin-2 (ANGPT2), which is expressed primarily in vascular endothelial cells.[672,673] ANGPT2 is also expressed in adipocytes to promote thermogenesis in brown fat and to enhance

fatty acid storage in subcutaneous adipose tissue.[1314,1315] The expansion of adipose tissue requires an adequate blood supply,[1316] and physiological levels of adipocyte- or endothelium-derived ANGPT2 promote healthy vascular proliferation and metabolic homeostasis, signaling through α5β1 integrin (rather than Tie2) as its primary receptor.[1314,1317-1319]

However, following inflammatory stress or collagen deposition,[1320-1323] the actions of ANGPT2 (or a spliced variant[1324]) are directed away from α5β1 integrin and toward Tie2 as its primary receptor.[1322,1325] This redirection coerces ANGPT2 to act as an antagonist of Ang-1.[1320] Because Ang-1/Tie2 signaling promotes vascular stability, the effects of heightened ANGPT2 signaling are transformed from an action that facilitates the healthy growth of blood vessels to an effect that enhances endothelial cell apoptosis, vascular fragility and leakiness, and angiotoxicity.[1322,1326-1328]

These pathophysiological relationships may explain why obesity and visceral adiposity are accompanied by increased adipose tissue and serum levels of ANGPT2 and soluble Tie2.[435,1329] Levels of ANGPT2 parallel those of other Domain III adipokines (leptin, thrombospondin-1, and CCL2).[1103,1327,1328] Epicardial adipose tissue secretes ANGPT2, leading to inflammation in the adjoining myocardium.[1023] Heightened serum levels of ANGPT2 are linked to the genesis of myocardial and vascular inflammation,[1320,1329,1330] particularly in patients with metabolic disorders.[1331,1332] The vasculotoxic effects of ANGPT2 may underlie the pathogenesis of microvascular rarefaction[1328,1333]—a hallmark of HFpEF—often accompanied by end-organ fibrosis.[1326,1334]

Clinically, serum levels of ANGPT2 are increased in patients with hypertensive vascular disease[1335] and are associated with visceral adiposity and obesity.[1336,1337] Heightened levels presage the development of heart failure in the general community.[1338] Serum ANGPT2 levels are elevated in patients with established heart failure in parallel with the severity of disease and prognosis,[1339-1342] particularly in HFpEF.[836,1343]

Angiopoietin-like proteins 2, 4, and 8. Angiopoietin-like proteins comprise a family of 8 polypeptides, with ANGPTL2, angiopoietin-like 4 (ANGPTL4), and angiopoietin-like 8 (ANGPTL8) being the most relevant to obesity and heart failure.

Although typically linked to endothelial cells, ANGPLT2, ANGPTL4, and ANGPTL8 are robustly synthesized in adipocytes and promote adipogenesis and lipid accumulation, signaling through cell adhesion molecules.[1344-1350] Additionally, ANGPTL4 and ANGPTL8 modulate the activity of lipoprotein lipase to promote triglyceride storage into adipose tissue.[1351,1352] Whereas physiological levels of ANGPTL2 and ANGPTL8 maintain healthy adipose homeostasis,[1353] obesity is accompanied by sustained up-regulation of ANGPTL2, ANGPTL4, and ANGPTL8,[1354-1356] which acts to promote adipose tissue inflammation.[1347,1354] Conversely, ANGLPTL2, ANGPTL4, and ANGPTL8 silencing alleviates obesity, ectopic fat deposition, and adipose tissue dysfunction.[1345,1356-1358]

Serum levels of ANGPLT2, ANGPTL4, and ANGPTL8 are increased in patients with obesity and visceral adiposity.[1359-1362] In addition, ANGPTL2, ANGPTL4, and ANGPTL8 are released by epicardial adipose tissue to exert paracrine effects,[1363-1365] and ANGPLT2 can be up-regulated within injured cardiac tissue and lead to autocrine effects.[1366] Obesity-driven elevation of ANGPTL2 expression in human adipose tissue is associated with systemic insulin resistance.[1344] Importantly, adipocyte-specific genetic ablation of ANGPTL4 promotes the action of lipoprotein lipase, thereby minimizing the development of organ steatosis and atherosclerotic vascular injury,[1358,1367] another example of signaling between adipose tissue and the cardiovascular system.

ANGPTL4 induces angiogenesis,[1368] and ANGPTL2 enhances vascular inflammation[1369,1370] and high-fat-diet-induced endothelial dysfunction,[1371] and impairs cardiac tolerance to injury.[26,1372] ANGPTL2 augments adverse ventricular remodeling in experimental HFpEF,[1373] and ANGPTL4-mediated fibroblast activation has been implicated in HFpEF induced by nutrient excess.[1374] Circulating ANGPTL2 levels are increased in experimental HFpEF, and serum ANGPTL2 and ANGPTL4 levels are elevated in patients with HFpEF, especially in those with obesity, systemic inflammation and worse exercise performance.[1375-1378] Elevated urinary levels of ANGPTL2 in patients with HFpEF presage an increased risk of adverse heart failure events.[1379]

SOLUBLE ENDOGENOUS ANTAGONISTS AND OTHER PROINFLAMMATORY ADIPOKINES. Obesity can trigger the adipose tissue synthesis of certain adipokines that 1) act as natural endogenous antagonists of cytoprotective proteins; or 2) can accentuate adipose tissue inflammation and myocardial injury (Box 12).

Plasminogen activator inhibitor. Urokinase plasminogen activator exerts adipoprotective effects because it generates plasmin (promoting proteolysis of the extracellular matrix), and it activates certain adipokines (eg, hepatocyte growth factor) that maintain healthy adipocyte biology in a plasmin-

BOX 12. Domain III: Soluble Endogenous Antagonists and Other Proinflammatory Proteins

1. This grouping of Domain III adipokines includes plasminogen activator inhibitor-1 (PAI-1), endogenous inhibitors of the ST2/interleukin-33 axis, calgranulin-RAGE signaling, and canonical proinflammatory cytokines (TNF-α, IL-1β, IL-6).
2. PAI-1 is a major adipocyte-derived proinflammatory adipokine and acts as an endogenous antagonist of HGF (a Domain II adipokine). It exerts profibrotic effects in the heart and is a marker of cardiac aging. A soluble form of ST2 (sST2) acts a decoy molecule to prevent IL-33 from interacting with ST2 and exerting its cardioprotective effects. Canonical proinflammatory cytokines signal through the NF-κB inflammasome.
3. With the expansion of fat mass, adipose tissue is transformed into a major organ for the production of PAI-1, sST2, RAGE ligands, and canonical cytokines, whose circulating levels are increased in obesity. Increased circulating levels precede the development of heart failure, and they are increased in established HFpEF and presage an adverse prognosis.
4. Transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet, demonstrating adipose-cardiac adipokine signaling.
5. Circulating levels of PAI, sST2 and canonical cytokines are reduced by bariatric surgery, incretin receptor agonists and current drugs for HFpEF. However, inhibition of canonical cytokines has not been demonstrated to have favorable effects in experimental HFpEF.

independent manner.[428,1380,1381] PAI-1 is the endogenous suppressor of urokinase plasminogen activator, thus promoting adipose tissue dysfunction and fibrosis.[1382]

Obesity is accompanied by heightened expression of PAI, particularly in white adipose tissue residing in visceral fat.[1383,1384] With obesity, adipose tissue is transformed into a major PAI-1 producing organ, because adipocytes acquire the ability to respond to inducers of PAI-1 transcription.[1385] The secretion of PAI-1 by adipocytes parallels the degree of adipocyte hypertrophy and represents the principal driver of circulating PAI-1.[1385,1386] PAI-1 silencing alleviates adipose tissue inflammation and diet-induced obesity.[1383,1387,1388]

Clinically, serum PAI-1 levels are elevated in patients with central obesity,[1389,1390] are correlated with visceral mass fat, and decline following bariatric surgery.[1391-1393] Increased circulating levels of PAI-1 presage the development of the metabolic syndrome in the general population[1394] and are correlated with the degree of clinically measured cardiac fibrosis.[1395] They are a marker of aging-related heart failure,[1396] and predict the subsequent development of HFpEF.[1397] Serum levels of PAI are increased in patients with established heart failure, particularly those with obesity or HFpEF,[1398] and have prognostic significance.[1399] PAI-1 levels are lowered by SGLT2 inhibition, GLP-1 receptor agonists, angiotensin receptor blockers, and mineralocorticoid antagonism.[1400-1403]

Interestingly, in the heart, low physiologic levels of PAI-1 are cardioprotective,[1404-1407] but sustained elevated levels are profibrotic.[1408-1411] Fibrosis in experimental HFpEF is paralleled by increased PAI-1 expression in the myocardium.[1404] Obesity itself has only a modest effect on expression of PAI-1 in the myocardium.[1412] Yet, importantly, transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet[105]—demonstrating that PAI-1 secreted from adipocytes is capable of influencing the function of the heart.[105,1413]

Soluble suppression of tumorigenicity (sST2) and the ST2/IL-33 axis. Tissue injury leads to the extracellular release of IL-33, which exerts compensatory cytoprotective effects (typically in an autocrine or paracrine manner) by interacting with the cell-surface ST2 (suppression of tumorigenicity 2) receptor. In inflammatory states, a soluble form of ST2 (referred to sST2) lacking its cell-penetrating domains is secreted into the extracellular space and acts as a decoy receptor, binding to IL-33 and preventing its homeostatic effects.[1414]

In obesity and visceral adiposity, adipose tissue is the primary secretory site for sST2, which acts to disrupt the functionality of the IL-33/ST2 axis at distant sites.[1414-1418] During nutrient excess, enhanced IL-33/ST2 signaling[1419] initially serves to attenuate adipose tissue inflammation and aldosterone-induced adipogenesis,[1420] thus positioning IL-33/ST2 as a Domain II adipokine. Silencing of ST2 exacerbates diet-induced adiposity.[1421]

However, as obesity advances and is sustained, the expanded and inflamed adipose tissue mass expresses and drives heightened circulating levels of sST2.[1418,1422] By diverting IL-33 away from ST2, enhanced sST2 signaling promotes fat accumulation, insulin resistance, and inflammatory responses.[1418] Serum sST2 levels are reduced by bariatric surgery[1423] and GLP-1 receptor agonism.[1424] sST2 can also be released by epicardial adipocytes and act in a paracrine manner to suppress the activity of IL-33 and cause fibrosis in the adjoining myocardium.[1417,1425,1426]

Signaling through the IL-33/ST2 axis attenuates adverse ventricular remodeling, prevents heart failure and improves survival after myocardial injury or mechanical stress.[1427-1431] Conversely, disruption of IL-33/ST2 signaling by sST2 promotes adverse cardiac remodeling, vascular hyperplasia, and myocardial fibrosis.[1430-1433] sST2 may enhance collagen deposition by an effect that is independent of its actions as a IL-33 decoy.[1434]

Clinically, circulating levels of sST2 presage the onset of heart failure[1435] and are increased in patients with established heart failure,[1436] including those with HFpEF. They reflect the severity of ventricular hypertrophy, diastolic filling abnormalities, and prognosis,[303,1157,1436,1437] and they decline following treatment with sacubitril/valsartan or liraglutide.[80,1424] Of note, the heart is not a source of circulating sST2. Heightened circulating sST2 levels are driven by extracardiac synthesis and are linked to systemic inflammation,[1438-1442] presumably triggered by visceral adiposity.[1417,1422] As further evidence of adipose-cardiac mutual crosstalk, changes in the IL-33/ST2 axis triggered by cardiac diastolic stress can produce a peripheral inflammatory response.[1440,1443]

Calgranulin-receptor for advanced glycation products signaling. S100B is the best studied member of a family of 20 calcium-binding proteins (known as calgranulins) that are released from injured tissues and signal through the membrane-bound receptor for advanced glycation products (RAGE).[1444]

Low physiological levels of S100B promote intracellular homeostasis,[1445] but with heightened extracellular levels, S100B acts as a damage-associated molecular pattern molecule,[1446] signaling through RAGE to promote deleterious inflammatory reactions.[1447] Originally described as being restricted to astrocytes and a marker of neuronal stress, S100B is synthesized during adipogenesis,[1448] and the secretion of S100B from adipocytes is the primary source of the blood-borne protein.[1449-1451] Enhanced expression of S100B or RAGE by hypertrophied adipocytes in visceral white adipose tissue[1452-1454] leads to adipose tissue expansion and inflammation.[1451,1455-1459] As a result, serum levels of S100B are increased in patients with obesity and visceral adiposity[1452-1454,1460,1461] and decrease following prolonged starvation.[1462] RAGE antagonism alleviates diet-induced obesity.[1463]

Circulating S100B can interact with cardiac membrane-bound RAGE, whose expression in cardiomyocytes is up-regulated by diet-induced obesity[1464] and by aging and cardiac hypertrophy.[1465,1466] Enhanced S100B-RAGE signaling can promote derangements in calcium handling, cellular stress, mitochondrial abnormalities and apoptosis,[1467-1470] as well as cardiac hypertrophy and fibrosis and cardiomyopathy.[1466,1471,1472] Genetic or pharmacological suppression of RAGE ameliorates adverse ventricular remodeling in pressure-overload HFpEF.[1473,1474] Serum levels of S100B and RAGE are increased in patients with heart failure in parallel with its severity and prognosis, especially those with diastolic filling abnormalities.[1475-1478]

Interestingly, the circulating form of RAGE (ie, soluble RAGE) is a decoy molecule that is cardioprotective, because it binds to RAGE ligands (eg, S100B) and prevents the deleterious effects of RAGE in the heart.[1479,1480] However, serum levels of soluble RAGE are decreased in patients with obesity,[1481] thus attenuating its ability to interfere with RAGE signaling. Of note, advanced glycation end products (prominent in patients with type 2 diabetes) and beta-amyloid (prominent in cardiac amyloidosis) also act as extracellular ligands for deleterious RAGE signaling.[1482,1483]

Canonical NF-κB-linked proinflammatory cytokines. The canonical proinflammatory cytokines—TNF-α, IL-1β, and IL-6—play a prototypical role in mediating inflammatory responses. Although they are secreted by hypertrophied adipocytes,[1484,1485] the recruitment of inflammatory cells to adipose tissue is the primary driver of the increased expression of canonical cytokines in visceral fat in diet-induced obesity.[1486]

Early studies suggested that TNF-α might worsen obesity,[1487] but subsequent work has shown that TNF-α, IL-1β, and IL-6 signaling does not increase body weight or impair insulin resistance.[1488-1491] Serum levels of TNF-α, IL-1β, and IL-6 are increased in patients with obesity in proportion to visceral fat, but these changes are also accompanied by a parallel increase in their decoy receptors and antagonists.[1485,1492-1497]

Experimentally, TNF-α, IL-1β, and IL-6 are capable of exerting both favorable and adverse cardiac effects, and suppression of these cytokines have yielded inconsistent effects on the evolution of experimental HFpEF.[1498-1505] Serum levels of TNF-α, IL-1β, and IL-6 are increased in patients with heart failure,[1506,1507] especially with HFpEF and obesity.[1378,1508] However, these patients also show increased levels of soluble TNF-α receptors and IL-1β receptor antagonists,[836,1509,1510] and the net effect of potential agonist-antagonist interactions in states of excess adiposity is not known. TNF-α antagonists increase the risk of worsening heart failure in patients with HFrEF,[1511,1512] but in these studies, reverse TNF-α signaling may have led to unintended

agonist effects.[1510,1513] Therefore, in contrast to the other adipokines discussed in this paper, the role of canonical proinflammatory cytokines in the genesis of adiposity-related HFpEF remains unclear.

PART VIII. TESTING THE ADIPOKINE HYPOTHESIS OF HFpEF: UNDERSTANDING THE EFFECT OF CURRENT AND FUTURE TREATMENTS ON VISCERAL ADIPOSITY AND THE SECRETION OF ADIPOKINES

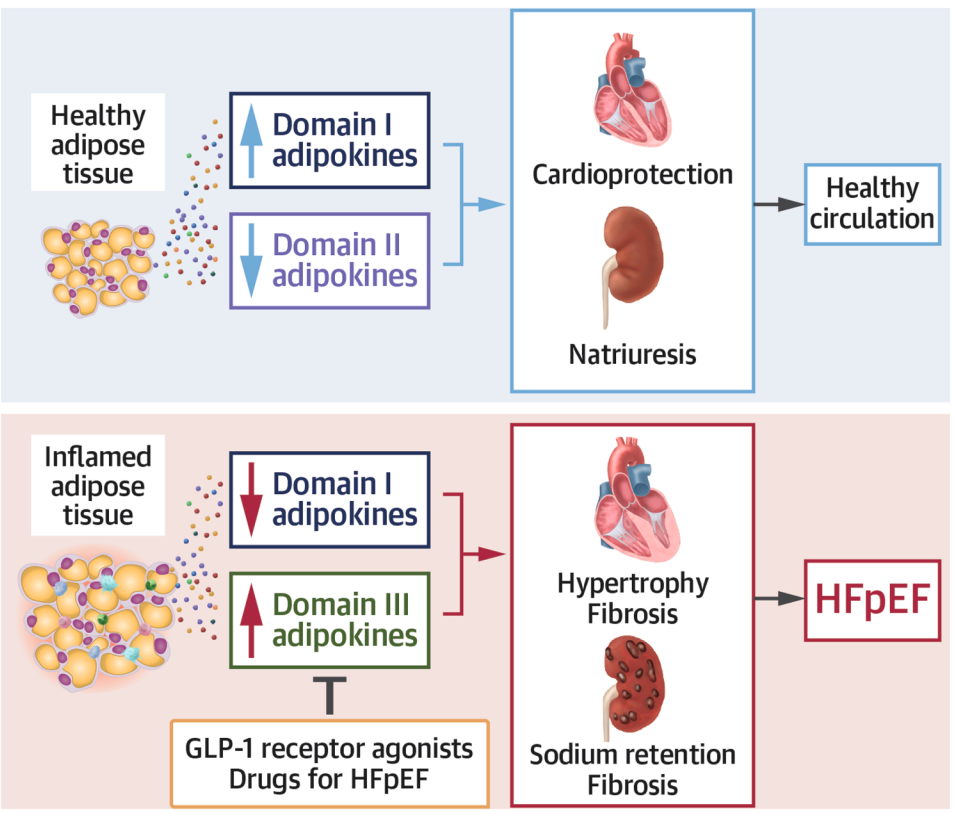
A sound and useful conceptual framework should not only reflect the findings of pathophysiological studies, but it should also align with and contribute to an explanation of the available evidence for current treatments. Additionally, a worthwhile paradigm should define a roadmap for the potential repurposing of available drugs and for the development of novel molecules to be tested in clinical trials in HFpEF (Central Illustration 2).

The adipokine hypothesis proposes that an expansion and dysfunctional transformation of visceral adipose tissue drives the pathogenesis of HFpEF through the altered secretion of bioactive molecules that influence the health of the heart, vasculature, and kidneys. Therefore, it is important to understand whether current interventions for HFpEF act to ameliorate visceral adiposity and restore a healthy adipokine balance. The findings of studies that address these issues are summarized in Box 13.

BARIATRIC SURGERY AS AN EXEMPLAR OF THE ADIPOKINE HYPOTHESIS OF HFpEF. The most persuasive evidence that dietary caloric excess and visceral adiposity drive the adipokine derangements seen in HFpEF is provided by the distinctive pattern of physiological and clinical responses seen following bariatric surgery.

Gastric bypass surgery results in dietary nutrient deprivation and profound weight loss, which is accompanied by a disproportionately larger reduction in visceral fat mass and alleviation of adipose tissue inflammation.[1514-1517] Bariatric surgery does

CENTRAL ILLUSTRATION 2 Shifts in the Balance of Adipokines in the Healthy Circulation and in HFpEF



Packer M, JACC. 2025;■(■):■-■.

GLP-1, glucagon-like peptide-1; HFpEF = heart failure with preserved ejection fraction.

BOX 13. Biological and Clinical Effects of Bariatric Surgery and Current HFpEF Treatments Are Aligned With the Adipokine Hypothesis

1. Bariatric surgery, incretin receptor agonists, MRAs, SGLT2 inhibitors, and angiotensin receptor neprilysin inhibitors act to shrink visceral adipose tissue depots. The magnitude of this reduction is disproportionately larger than the decrease in body weight.
2. The suppression of systemic inflammation following bariatric surgery in people with obesity is not related to an effect on circulating inflammatory cells (eg, monocytes), but instead, it is related to suppression of inflammation-related genes in adipose tissue.
3. Bariatric surgery, incretin receptor agonists, MRAs, SGLT2 inhibitors, and angiotensin receptor neprilysin inhibitors act to increase Domain I adipokines, while decreasing Domain III adipokines, thus ameliorating the adipokine derangement seen in patients with visceral adiposity.
4. The responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a new set point that would be expected to produce strikingly favorable biological effects in the heart.
5. In people with obesity, adipocytes represent the major source of circulating aldosterone, angiotensin II, and neprilysin. The central role of adiposity in driving neurohormonal activation explains 1) why bariatric surgery leads to decreases in circulating aldosterone, angiotensin II, and neprilysin; and 2) why patients with HFpEF who have obesity and visceral adiposity show particularly favorable responses to treatment with current drugs for HFpEF.
6. Metformin and fenofibrate have favorable effects on adipokine biology, reduce visceral fat mass, and improve the balance of circulating adipokines in obesity. Experimental and clinical observations support the potential for a benefit of these drugs in HFpEF.

not merely reduce the number and size of adipocytes, but it radically alters the biology of adipose tissue so as to fundamentally change the profile of its secretory state.[1515,1518] Most importantly, the suppression of systemic inflammation following surgery in people with obesity is not related to an effect on circulating inflammatory cells (eg, monocytes), but instead, it is linked to the suppression of inflammation-related genes in adipose tissue.[1519]

Surgical weight loss is accompanied by increases in serum levels or adipose tissue expression of Domain I adipokines (ie, adiponectin)[1111,1520] and nearly universal decreases in serum levels or adipose tissue expression of Domain III adipokines (leptin,[546,622,731] aldosterone,[1521] angiotensin,[1522] neprilysin,[1522] FABP4,[1523] RBP4,[1524] YKL-40,[826] chemerin,[848] resistin,[1525,1526] Wnt5a,[905] asprosin,[961] activin A,[1021,1022] thrombospondin-1,[1527] SPARC,[1111] TIMP1,[1528] cathepsin S,[1224] CCL2,[826,1249] ANGPTL2,[435] PAI,[1393,1525] sST2,[1423] TNF-α,[1525] IL-1β,[1519] and IL-6),[1520] although serum levels of IGF-1 increase.[1529,1530] Additionally, obesity surgery generally results in a decline in serum levels of Domain II adipokines (ie, vaspin,[318,1531] irisin,[368,369] HGF,[435] apelin,[546] acyl-stimulating protein,[622] and IL-10[1519]), presumably because the need for their compensatory and counterbalancing actions diminishes. Soluble RAGE (a counter-regulatory decoy molecule that is deficient in obesity[1481]) declines further.[1532] However, when obesity underlies the development of biological adipokine resistance (as appears to be the case of FGF21, GDF-15, ATGL, and progranulin), levels of these adipokines increase following gastric bypass surgery,[1533-1536] and this increase may help to drive postoperative weight loss and metabolic improvements.[1533]

These responses to bariatric surgery demonstrate that *dietary nutrient deprivation is sufficient* to produce a decisive shift in the balance of circulating adipokines to a new set point that would be expected to produce strikingly favorable biological effects in the heart. As a result of the selective suppression of inflammation-related genes in adipose tissue,[1519] the amelioration of systemic inflammation following bariatric surgery is likely related to heightened signaling of anti-inflammatory Domain I adipokines, coupled with suppression of proinflammatory Domain III adipokines.

Accordingly, bariatric surgery ameliorates left ventricular hypertrophy (in patients with and without HFpEF),[1512,1537] while improving coronary microvascular function and diastolic filling abnormalities.[1538] These beneficial effects are correlated with changes in the adipokine profile and visceral fat mass[731,1514,1539] and may be independent of weight loss.[1540] As a result of these favorable mechanistic actions, gastric bypass surgery is accompanied by a profound decrease in the risk of new-onset heart failure, and in particular, a reduction in hospitalizations for HFpEF.[1541,1542]

APPLICABILITY OF THE ADIPOKINE HYPOTHESIS TO CURRENT TREATMENTS FOR HFpEF. To date, studies of the actions of MRAs, GLP1-receptor agonists, SGLT2 inhibitors, sacubitril/valsartan have focused on the effects of these drugs on the heart and

kidney, but these drugs also have well-characterized favorable effects on adipocyte biology.

Therefore, key questions include:

1. Does the obesity-driven transformation of adipose tissue contribute meaningfully to the activation of angiotensin II, aldosterone, and neprilysin in HFpEF?
2. Do MRAs, GLP1-receptor agonists, SGLT2 inhibitors, and sacubitril/valsartan shrink visceral fat mass and ameliorate adipose tissue dysfunction?
3. Do these drugs act to normalize the adiposity-driven imbalance of Domain I and III adipokines?
4. Is the magnitude of the clinical benefit of these drugs in HFpEF is influenced by the pretreatment severity of obesity and visceral adiposity?

Mineralocorticoid receptor antagonists. Aldosterone is a Domain III adipokine, and adipocytes are a major source of aldosterone in patients with obesity, both because adipocytes secrete aldosterone directly and because adipokines (eg, leptin) act to stimulate the secretion of aldosterone from the adrenal gland.[38-41]

There is a mutual reinforcing link between excess visceral adiposity and circulating levels of aldosterone.[1543] Adipocyte-specific up-regulation of the mineralocorticoid receptor leads to the metabolic syndrome and underlies aldosterone's adverse effects on the cardiovascular system.[757] Conversely, the marked reduction in visceral fat mass produced by bariatric surgery reduces circulating levels of aldosterone.[1521] Mineralocorticoid receptor antagonism inhibits adipocyte expansion and alleviates proinflammatory signaling in adipose tissue.[463,1544]

Spironolactone and eplerenone act to reduce visceral fat mass in patients with elevated circulating levels of aldosterone.[1545] As a result, eplerenone reduces waist circumference (ie, central obesity) in patients with hypertension and diabetes[1546] (disproportionately more than the effect on body weight), and spironolactone prevents weight gain in patients with HFpEF.[1547] Subantihypertensive doses of mineralocorticoid receptor antagonists ameliorate the abnormalities of ventricular diastolic filling in obesity.[1548]

In experimental studies and in clinical trials of patients with metabolic abnormalities or HFpEF, MRAs have been observed to increase serum levels or adipose tissue expression of Domain I adipokines (ie, adiponectin and eNAMPT[1549,1550]) and Domain II adipokines (ie, GDF-15, adrenomedullin, apelin, HGF, and ATGL[463,599,1543,1551,1552]), while reducing serum levels of Domain III adipokines (ie, leptin, chemerin, and PAI[1550,1553-1556]), with LCN2 and chemerin representing specific aldosterone targets that are mitigated by MRAs.[818-820,863] These changes represent a major shift in adipokine balance to a state of reduced adipose tissue and myocardial stress.

Consistent with these mechanistic observations, eplerenone appears to be particularly effective in patients with HFrEF who have central obesity.[1557] Furthermore, in patients with HFpEF, there exists a linear relationship between body mass index and the magnitude of the reduction in cardiovascular death or worsening heart failure events with finerenone, with a benefit of the drug being apparent only in patients with obesity.[1558] Similar findings with respect to the influence of obesity have been observed in patients with HFpEF treated with spironolactone.[1559]

GLP1- and dual GLP1/GIP receptor agonists. Agonism of GLP-1 and GIP receptors on adipocytes contributes to the weight loss produced by incretin-based drugs.[1560,1561] Signaling through these receptors reduces adipocyte hypertrophy, organellar stress, and inflammation, while promoting mitochondrial energetics and brown fat thermogenesis (through up-regulation of SIRT1).[1562-1566] GIP agonism provides an additional lipolytic effect[1567] and drives futile calcium cycling in white adipose tissue.[1568] Sustained stimulation of the GIP receptor in *adipocytes* contributes importantly to the incremental effect of dual agonists on weight loss.[1560]

In clinical trials, incretin receptor signaling produces a profound reduction in visceral fat,[1569,1570] including the shrinkage of epicardial adipose tissue (which expresses both GLP-1 and GIP receptors[1571]) and of the fat depots surrounding the heart.[27,1572] The reduction in visceral fat following incretin receptor agonism is disproportionately larger than its effect on body weight.[27] GLP-1 receptor agonists alleviate experimental dysmetabolism-related HFpEF, potentially by reducing the accumulation of lipid droplets and adjacent fibrosis within the heart.[1573-1575]

In experimental studies and in clinical trials of patients with diabetes or obesity, incretin-based agonists increase serum levels or adipocyte/adipose tissue expression of Domain I adipokines (ie, adiponectin, CTRP3, omentin-1, SFPR5, eNAMPT, and ZAG),[146,159,174,214,839,1576-1583] while they simultaneously act to reduce levels of most Domain III adipokines (ie, leptin, aldosterone, RBP4, FABP4, resistin, asprosin, galectin-3, PAI, sST2, YKL-40, CCL2, RAGE, and canonical proinflammatory cytokines),[463,838,1401,1424,1563,1565,1577-1579,1584-1590] although serum Wnt5a and ANGPTL-8 levels

increase.[1591,1592] With respect to Domain II adipokines, experimental GLP-1 receptor agonism induces FGF21,[1593] and FGF21 up-regulation may be required for the its effect to produce weight loss.[1594] Additionally, GLP-1 receptor agonism increases adipose expression of irisin,[1595] metallothionein,[1596] and ATGL[1597]; however, GDF-15 is unchanged by liraglutide[1598] and is reportedly decreased by trizepatide.[839]

Taken collectively, the pattern of these changes reflects a major reduction in visceral adipose tissue mass, which is accompanied by a consistent shift in the balance of adipokines to a new state of reduced adipose tissue and myocardial stress. The amelioration of systemic inflammation following incretin receptor agonism[26,1599] is likely related to heightened signaling of anti-inflammatory Domain I adipokines, coupled with suppression of proinflammatory Domain III adipokines.

Incretin-based agonists improve the clinical status and outcomes of patients with HFpEF and obesity,[26,1599] and the effects of tirzepatide on health status and exercise tolerance are most marked in those with the highest pretreatment body mass index.[1600] Additionally, the clinical benefits of semaglutide and tirzepatide in HFpEF are related to the magnitude of weight loss.[1601] Importantly, the reduction in visceral fat (particularly, epicardial and paracardiac adipose tissue) is paralleled by amelioration of left ventricular hypertrophy and left atrial enlargement.[27,1602] These observations suggest that changes in the mass and biology of visceral adipose tissue may act as mediators of the cardioprotective effect of incretin-based drugs.

SGLT2 inhibitors. SGLT2 inhibitors induce a system-wide state of starvation mimicry,[1603,1604] as evidenced by the induction of ketogenesis, the augmentation of autophagic flux, and the up-regulation of AMPK/SIRT1/PGC-1α signaling in diverse tissues.[93,95,1605] The expression of SGLT2 in the proximal renal tubule is increased in patients with obesity and diabetes,[1606] but the action of SGLT2 inhibitors to up-regulate nutrient deprivation signaling and inhibit adipogenesis does not depend on the induction of renal glycosuria,[2] because these effects are seen in isolated cultured adipocytes.[1607-1611] Human epicardial adipose tissue exhibits abundant expression of SGLT2, especially in developing adipocytes.[1612,1613]

In experimental obesity, SGLT2 inhibitors reduce adipocyte hypertrophy, inflammation and cellular stress in white adipose tissue, while acting to decrease visceral fat mass. They also promote brown fat thermogenesis through enhanced AMPK/SIRT1/PGC-1α signaling.[1606-1616] In clinical trials, SGLT2 inhibitors decrease visceral adiposity and waist circumference and alleviate organ steatosis,[1617-1620] acting to reduce epicardial adipose tissue mass.[1620-1623] Yet, in clinical studies, these benefits on visceral adiposity are accompanied by only modest changes in body weight, perhaps caused by compensatory hyperphagia.[1624,1625] The incremental dietary calories do not appear to be stored in visceral fat, which is disproportionately reduced by SGLT2 inhibition. (Long-term changes in weight are not influenced by a diuretic effect because SGLT2 inhibitor-induced natriuresis is truncated by renal tubular counterregulatory mechanisms.[1626] The decline in body weight with SGLT2 inhibitors is related to a decrease in fat mass, not water.[1627])

With the induction of starvation mimicry, in a manner similar to that seen with incretin receptor agonists, SGLT2 inhibitors have been observed to increase serum levels or adipose tissue expression of Domain I adipokines (ie, adiponectin and ZAG[213,1628,1629]) and Domain II adipokine (ie, FGF21, GDF-15 and apelin[310,1614,1630-1632]), while they simultaneously act to reduce serum levels of a broad range of Domain III adipokines (ie, leptin, RBP4, chemerin, asprosin, PAI, CCL2, CXCL8, RAGE, TNF-α and IL-6),[870,1400,1613,1614,1628,1633-1637] with minimal changes in IGF-1, IGFBP7, sST2, and galectin-3.[1638-1640] Serum FABP4 levels do not change consistently,[1635,1641] but SGLT2 inhibition decreases the expression of FABP4 in epicardial adipocytes.[1613] These changes, considered together, represent a meaningful shift in adipokine balance to a set point of reduced adipose tissue and myocardial stress.

As further evidence of the relevance of this shift, epicardial adipocytes pretreated with empagliflozin exert cytoprotective effects when cocultured with cardiomyocytes in vitro.[1613] Similarly, transplantation of fat tissue that is pretreated with an SGLT2 inhibitor acts to ameliorate the vascular abnormalities in recipient mice with experimental diet-induced obesity.[1642]

SGLT2 inhibition alleviates experimental obesity-related HFpEF,[1643] and in patients with HFpEF, the reduction in body weight is paralleled by decreases in left ventricular filling pressures at rest and exercise.[1644] Accordingly, the pretreatment body mass index influences the magnitude of the effect of SGLT2 inhibitors on weight loss and on health status,[1645-1647] with weight reduction and symptomatic benefits being seen primarily in patients with morbid obesity. The magnitude of SGLT2 inhibitor-related decreases in the risk of hospitalizations for heart failure is greater in patients with type 2 diabetes who have obesity.[1647] These observations, taken

collectively, support an important role of pretreatment (and treatment-related changes in) the mass and biology of visceral adipose tissue in influencing the benefits of SGLT2 inhibitors.

Angiotensin receptor neprilysin inhibition. Both angiotensin II and neprilysin are considered Domain III adipokines, and in patients with obesity, the expansion of visceral adipocyte mass represent an important causal mechanism for activation of the renin-angiotensin system and for heightened circulating levels of neprilysin, both because adipocytes secrete angiotensin II and neprilysin directly and because the effect of Domain III adipokines (eg, leptin) to activate renal sympathetic nerves stimulates both angiotensin II and neprilysin.[20,41,746,747,752] The marked reduction in fat mass produced by bariatric surgery reduces circulating levels of angiotensin II and neprilysin.[1521,1522]

Both angiotensin II and atrial natriuretic peptide play opposing roles in adipogenesis and modulating adipocyte biology. Experimentally, interference with angiotensin II receptor signaling reduces adipocyte size, suppresses proliferation, oxidative stress and inflammation, and promotes thermogenesis in white adipose tissue.[1648-1654] In clinical trials, angiotensin receptor blockade shrinks visceral fat mass[1655] and ameliorates adipocyte hypertrophy,[754] with a treatment effect that is disproportionally larger than the effect on body weight. In experimental models or the clinical setting, angiotensin receptor blockers increase serum levels or adipocyte synthesis of Domain I adipokines (eg, adiponectin[1656,1657]) and Domain II adipokines (eg, apelin)[1658,1659] while simultaneously diminishing serum levels or the adipose expression of Domain III adipokines (CCL2, cathepsin S, FABP4, YKL-40, PAI, CCL2, TNF-α, and IL-6).[754,838,1652,1654,1660-1663]

Neprilysin inhibition potentiates these adipokine shifts. Its augmentation of atrial natriuretic peptide signaling inhibits adipogenesis and adipocyte proliferation,[1618] and enhances white adipose lipolysis (an effect attenuated in obesity),[1664-1666] while heightening brown fat thermogenesis[1666-1669] and promoting weight loss.[1670] Of note, augmented natriuretic peptide signaling alleviates obesity only if it takes place in adipocytes (and not in skeletal muscle)[1671]—perhaps because atrial natriuretic peptide directly enhances the release of adiponectin and suppresses the secretion of leptin from adipocytes.[1672-1675] Essentially, natriuretic peptide receptor signaling acts as an adipokine switch, which is biased toward adiposity by the suppressed circulating levels of natriuretic peptides that are characteristic of patients with obesity or HFpEF.[42,759] Sacubitril/valsartan reduces visceral fat mass in experimental obesity-related HFpEF.[1676]

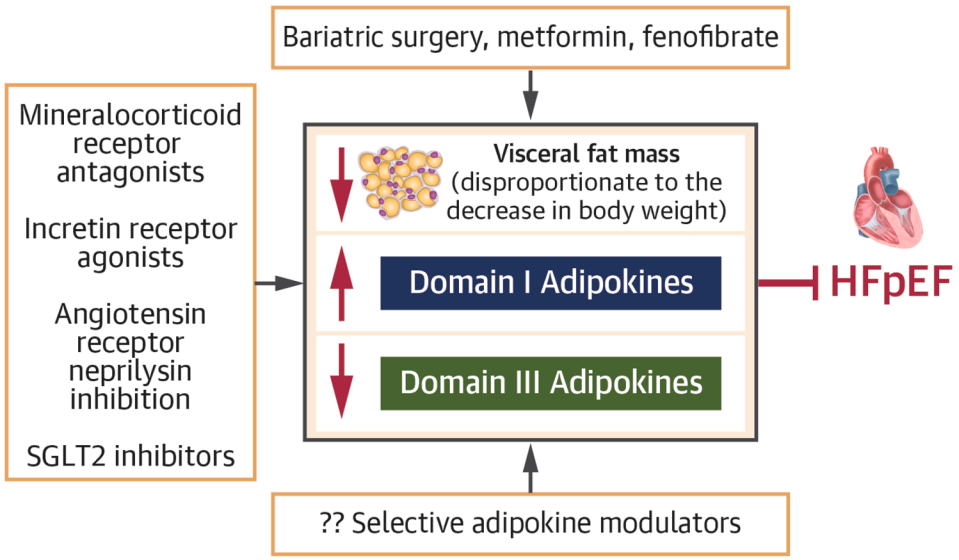
Clinically, atrial natriuretic peptide delivery increases serum levels of adiponectin in patients with or without heart failure,[1672,1677] while reducing serum levels or adipose tissue expression of leptin, RBP4, CCL2, TNF-α, and IL-6.[1673,1676] Neprilysin not only degrades atrial natriuretic peptide, but it also promotes the breakdown of several Domain II adipokines (ie, adrenomedullin, apelin, and ang[1-7]), and thus, neprilysin inhibition increases their serum levels.[1677-1683] Sacubitril/valsartan reduces serum levels of sST2, TIMP1, and YKL-40 in patients with HFpEF.[80,1682]

Consistent with these observations, the benefits of angiotensin receptor blockade in patients with HFpEF seem to be limited to patients with the lowest pretreatment levels of natriuretic peptides (indicative of obesity).[1684] At the same time, neprilysin inhibition appears to produce greater clinical improvement and effects on heart failure outcomes in patients with HFpEF who have obesity or central adiposity.[12,1685] Phosphodiesterase 9 (PDE9) inhibition can potentiate natriuretic peptides beyond that produced by neprilysin inhibition.[1686] PDE9 inhibition alleviates experimental obesity,[1687] and it may lead to additional favorable adipokine shifts that are relevant to patients with HFpEF.[1688]

Perspective and synthesis. These findings, taken collectively, indicate that MRAs, incretin-based agonists, SGLT2 inhibitors and angiotensin receptor neprilysin inhibitors exert favorable effects on adipocyte biology, which is manifest experimentally and clinically, by a reduction in visceral adipose tissue mass that is disproportionate to any change in body weight. The shrinkage of visceral fat is accompanied by up-regulation of Domain I adipokines and suppression of Domain III adipokines, experimentally and clinically (**Figure 7**). These drugs also cause up-regulation of many Domain II adipokines, which may allow for their cardioprotective effects, because the opposing action of Domain III adipokines has been simultaneously minimized.

It is understood that patients with HFrEF respond favorably to treatment with angiotensin receptor neprilysin inhibitors, MRAs, and SGLT2 inhibitors, presumably because the failing heart triggers the activation of neurohormonal systems related to ventricular distension or renal hypoperfusion. However, these conventional hemodynamic triggers are muted in patients with HFpEF, raising questions about the identity of the mechanisms that cause up-regulation of aldosterone, neprilysin, and angiotensin II in this disorder. The near-universal

FIGURE 7 Effect of Current and Potential Drugs for HFpEF on Visceral Adiposity and the Secretion of Adipokines



Bariatric surgery, incretin-based drugs, and current drugs for heart failure with preserved ejection fraction (HFpEF) act to reduce visceral mass (disproportionate to changes in body weight), which is accompanied by a favorable shift in the balance of cytoprotective and proinflammatory adipokines (Domain I and III, respectively) and to beneficial effects in HFpEF. The responses to bariatric surgery demonstrate that nutrient deprivation—by itself—is sufficient to produce a decisive shift in the balance of circulating adipokines to a new set point that would be expected to produce strikingly favorable biological effects in the heart. A reduction in systemic inflammation following bariatric surgery is related to a reduction in inflammatory signaling in adipocytes, rather than in circulating inflammatory cells. Repurposing of certain drugs and the development of specific adipokine modulate may act through a similar mechanism.

prevalence of central obesity in HFpEF points to the expansion of visceral adipose tissue as the candidate driving force. When fat mass comprises 50% of body weight in people with obesity, adipocytes emerge as the major source of circulating aldosterone, angiotensin II, and neprilysin,[39,41] which decline following bariatric surgery.[1521,1522] The central role of adiposity in driving neurohormonal activation may explain why patients with HFpEF who have greater obesity and visceral adiposity show particularly favorable responses to neurohormonal antagonists.

POTENTIAL FOR REPURPOSING OF DRUGS APPROVED FOR NON-HFpEF INDICATIONS. Several currently available drugs have actions that improve the biology and secretory profile of adipose tissue and produce cardioprotective effects in experimental models, and thus, present an opportunity for being repurposed for the treatment of HFpEF.

Metformin. Although often regarded as an antihyperglycemic agent that reduces glucose production in the liver, metformin is an AMPK activator that has direct effects on adipocytes to modulate energy homeostasis. In states of dietary excess, metformin inhibits adipogenesis and lipid droplet accumulation and fusion,[1689] suppresses adipose tissue inflammation and fibrosis,[1690,1691] and minimizes the obesity-related secretion of extracellular vesicles,[1692] while restoring healthy brown fat function.[1690,1693]

As a result of these actions, metformin inhibits the development of experimental diet-induced obesity,[1693] and shrinks visceral fat depots and produces weight loss in patients with obesity.[1694,1695] Many of the Domain I adipokines (eg, adiponectin, CRTP3/9, and omentin-1) and Domain II adipokines (eg, FGF21, GDF-15, and vaspin) signal through AMPK, and thus, metformin mimics the downstream effects of these adipokines and normalizes the adipocyte AMPK deficit that is seen in diet-induced obesity.[1696]

Additionally, metformin acts directly on adipocytes to up-regulate Domain I adipokine signaling (ie, enhanced adiponectin gene expression, protein secretion, and receptors[1697,1698]; increased serum omentin-1 and NRG-4 levels[1699,1700]; and augmented adipocyte expression of CRTP3 and eNAMPT[1696,1701]),

while suppressing adipocyte secretion and serum levels of Domain III adipokines (ie, leptin, FABP4, RBP4, resistin, CCL2, thrombospondin-1, and PAI).[1078,1694,1702-1710] With respect to Domain II adipokines, metformin up-regulates FGF21 and GDF-15,[1693,1711] but it decreases serum levels of vaspin, irisin, and PEDF.[1712-1714]—a pattern similar to that seen with bariatric surgery.

Interestingly, the only clinical trial evidence that metformin has reduced the risk of diabetic complications is derived from a subgroup analysis of the UKPDS (UK Prospective Diabetes Study), and the patients who showed beneficial effects of metformin in that study were specifically those who were overweight.[1715] Metformin reduces epicardial adipose tissue mass in people with obesity,[1715,1716] and it alleviates left ventricular stiffness, diastolic filling abnormalities, and pulmonary hypertension and mitigates against the development of experimental HFpEF, including that produced by obesity.[1717,1718] Its use in hypertensive patients with diabetes is accompanied by a reduced risk of new-onset symptomatic HFpEF,[1719] and in patients with established HFpEF, its use is associated with a lower risk of death.[1720]

Fenofibrate and pioglitazone. PGC-1α is a convergence point for nutrient surplus and deprivation signaling, and the interactions of PGC-1α with PPARα and PPARγ lead to opposing effects on adipose and cardiac biology, which are both context- and duration-dependent.[1721] Enhanced PPARα signaling (as with fenofibrate) reduces adipocyte hypertrophy and adipose tissue inflammation,[1722-1724] promotes brown fat thermogenesis,[1725] shrinks visceral fat mass and organ adiposity,[1724,1726] and ameliorates diet-induced obesity.[1724-1726] In contrast, augmented PPARγ signaling (as with pioglitazone) promotes lipogenesis, adipocyte hypertrophy, and stress[1727-1730]; inhibits fat mobilization and brown fat thermogenesis[1731,1732]; causes weight gain and tissue fat accumulation[1733,1734]; and worsens central obesity.[1734]

Importantly, several Domain I and II adipokines (eg, adiponectin, CTRP3, ZAG, FGF21, irisin, ATGL) enhance PPARα or diminish PPARγ signaling in adipose and nonadipose tissues.[462,1735-1744] Specifically, the secretion of ATGL from adipocytes can activate PPARα signaling in the liver and heart.[460-462] Furthermore, the cardiomyopathy seen in ATGL-deficient mice is rescued by PPARα (but not PPARγ) agonism.[1745] Therefore, although the favorable changes in serum levels of adipokines produced by fenofibrate are notable, they may be inconsequential,[1746-1749] because the drug acts directly on their downstream targets.

The opposing effects of PPARα and PPARγ signaling in adipose tissue are paralleled by their mutually antagonistic actions in the heart. The expression of PPARα in the heart is suppressed in experimental pressure overload,[1750] and PPARα silencing promotes and PPARα agonism with fenofibrate ameliorates maladaptive hypertrophy and experimental cardiomyopathy.[1751-1754] In contrast, prolonged up-regulation of PPARγ leads to mitochondrial oxidative dysfunction, lipid accumulation, maladaptive hypertrophy, and cardiomyopathy.[1755,1756] Experimental cardiomyopathy produced by high-fat diet-induced obesity is alleviated by PPARγ silencing.[1733]

The parallelism between PPARα/PPARγ signaling in adipose and cardiac tissues appears to be causal, rather than coincidental. For example, the effect of PPARγ agonism with rosiglitazone to induce cardiac hypertrophy is mediated by the drug's effect on *adipose tissue,* because the prohypertrophic action is attenuated by adipocyte-specific (but not by cardiomyocyte-specific) silencing of PPARγ.[1756,1757] The rosiglitazone-mediated cardiac hypertrophic signal appears to be driven by the secretion of microRNA200a from adipocytes. PPARα and PPARγ also exert mutually opposing effects on renal tubular sodium reabsorption, with PPARα agonism favoring sodium excretion and PPARγ agonism causing sodium retention.[1758,1759]

In clinical trials of patients with dyslipidemia or diabetes, PPAR-α agonism with fenofibrate reduces the risk of hospitalizations for heart failure,[334] whereas both selective PPARγ and dual PPARα/PPARγ agonists increase the risk of adverse heart failure outcomes.[1760-1764]

TNF-α inhibitors, IL-1/IL-1β antagonists and colchicine. Drugs that directly antagonize canonical proinflammatory cytokine signaling—TNF-α antagonists (eg, etanercept and infliximab), IL-1/IL-1β inhibitors (eg, anakinra and canakinumab), and NLRP3 inflammasome antagonists (eg, colchicine)—mitigate systemic inflammatory responses and might seem appealing for the treatment of adiposity-related HFpEF.

Although etanercept exerted favorable effects on adipose tissue in experimental dietary excess[1765] and colchicine inhibited cardiac fibrosis in experimental obesity,[1766] studies in the clinical setting have not supported these observations. TNF-α antagonism in

patients with or without the metabolic syndrome does not improve their adipokine profiles. Treatment with etanercept and infliximab is accompanied by weight gain, increases in muscle fat mass, and worsening of visceral adiposity.[1767-1771] Furthermore, pretreatment obesity or visceral adiposity attenuates (rather than accentuates) the clinical responses to the anti-inflammatory effects of these drugs.[1772-1775]

Similarly, interference with IL-1 signaling in obesity may not produce favorable effects,[1776] perhaps because excess adiposity leads to enhanced synthesis of an endogenous soluble IL-1 receptor antagonist,[1493] thus predisposing to weight gain[1493,1777] and potentially minimizing the benefits of anakinra and canakinumab. Furthermore, colchicine inhibits (rather enhances) lipolysis,[1778] and does not appear to have benefits on adipose tissue inflammatory cell infiltration or insulin sensitivity.[1779,1780] Similarly, IL-1 antagonism does not exert favorable effects on leptin or adiponectin in patients with visceral adiposity or diabetes.[1776,1781]

Taken together, these observations do not suggest that antagonism of canonical proinflammatory cytokines is likely to be beneficial in the treatment of adiposity-related HFpEF. TNF-α receptor antagonists cause worsening of heart failure in patients with an HFrEF,[1511,1512] but their effects in HFpEF have not been explored. Long-term IL-1β antagonism with canakinumab is accompanied by a decrease in heart failure events in patients with atherosclerotic heart disease,[1782] but the effect of the drug in patients with established heart failure (and particularly HFpEF) is not known. Anakinra does not improve functional capacity in patients with HFpEF and obesity,[1783] and colchicine does not produce symptomatic benefits or prevent worsening heart failure events in patients with established heart failure, despite reduced systemic inflammation.[1784-1786]

These findings suggest that canonical proinflammatory cytokines may not play an important role in adiposity-related HFpEF. Nevertheless, because it decreases systemic inflammation in patients with obesity and chronic kidney disease,[1787] ziltivekimab (an IL-6 antagonist) is being evaluated in a large-scale trial of patients with HFpEF.[1788]

SELECTIVE ADIPOKINE TARGETING: A ROADMAP FOR NOVEL THERAPEUTIC APPROACHES. The proposed adipokine hypothesis identifies imbalances in Domain I, II, and III adipokine signaling that might be ameliorated by specifically targeted interventions. Interestingly, many of these adipokines have already been earmarked in the development of new drugs, although such development has largely focused on disorders other than HFpEF. Examples of novel therapeutic approaches are noted below.

- Adiponectin receptor agonists, AdipoRON and ADP355, have been developed for the treatment of a broad range of conditions, including diabetic nephropathy, neurodegenerative diseases, and nonalcoholic fatty liver disease.[127,1789,1790]
- Several long-acting FGF21 analogues—pegozafermin, efruxifermin, and zalfermin—have been shown to alleviate organ steatosis and are being developed for nonalcoholic fatty liver disease.[263,1791,1792]
- A long-acting recombinant GDF-15 dimer (MBL949) and a GDF-15/GFRAL receptor agonist (LY346325) are being developed for the treatment of obesity.[1793,1794]
- AMG 986, an orally active apelin agonist that stimulates the APJ receptor,[561,562] has been evaluated in patients with HFrEF. No studies have been performed in patients with HFpEF.
- Phosphodiesterase 9 inhibitors—CRD-733, osoresnontrine, tovinontrine, and PF-04447943—can potentiate the natriuretic peptide augmentation produced by neprilysin inhibition. CRD-733 is being developed for HFpEF,[1688] but the others have been developed for schizophrenia and sickle cell disease.
- HGF has been developed for intramyocardial adenoviral delivery, and an engineered bioactive HGF fragment can be delivered in an extracellular matrix-derived hydrogel.[1795] Both have been directed towards the treatment of myocardial infarction.
- LPrA-2, Allo-aca, LDFI, and 9F8 are leptin antagonists—formulated as peptides or antibodies—which are being developed for the treatment of neovascularization-related eye diseases, obesity, and chronic kidney disease.[1796-1798]
- BMS309403, a small molecule inhibitor of FABP4, is being developed for the treatment of cancer.[1799]
- Rosazumab, a humanized monoclonal antibody inhibitor of YKL-40, is currently approved for the treatment of osteoporosis.[1800]
- Antagonists of the chemerin receptor (CCX832 and α-NETA) have been primarily developed for the treatment of diabetic nephropathy.[872,1801]
- Drugs that inhibit Wnt5a secretion or act as Frizzled-5 antagonists can prevent the development of experimental postinfarction heart failure and HFpEF.[922,928,929] Clinically, Wnt5a antagonists—such as Box5, Wnt5a/FZD2 siRNA, and RNF43—have been developed for the treatment of melanoma and other cancers.[1802]

- Ziritaxestat—an orally active inhibitor of autotaxin—is being developed for the treatment of idiopathic pulmonary fibrosis.[948]
- Asprosin-neutralizing antibodies are being developed for the treatment of the metabolic syndrome.[963]
- Sotatercept, a trap for activin type II receptor ligands (targeting activin A), is effective (and FDA-approved) for the treatment of pulmonary arterial hypertension,[1038] and it has yielded promising results in experimental HFpEF.[1038] Bimagrumab, an activin type II inhibitor, is being developed for the treatment of obesity.[1039]
- Cixutumumab, an antagonist of the IGF-1 receptor,[1044] has been developed for the treatment of solid tumors.
- LY3000328, a selective cathepsin S inhibitor, has cardioprotective effects and is being investigated for the treatment of abdominal aortic aneurysm.[1803,1804]
- LSKL peptide—a selective thrombospondin-1 antagonist—has been developed and tested for hypertrophic scar formation,[1805] and potentially, for the treatment of cancer.
- Selvigaltin, a small-molecule galectin-3 inhibitor, is being developed for the treatment of hepatic cirrhosis and idiopathic pulmonary fibrosis.
- Azeliragon (TTP488)—a small molecule RAGE inhibitor—is being evaluated for the treatment of cancer.[1806] Another RAGE inhibitor, FPS-ZM1, is being investigated for the treatment of pain.[1807] Small-molecule disruptors of advanced glycation product crosslinks have been evaluated in clinical HFpEF.[1483]
- Ziltivekimab, a humanized monoclonal antibody against the IL-6 ligand, reduces a systemic inflammation in patients with obesity and chronic kidney disease[1787] and is being evaluated in a large-scale trial of patients with HFpEF.[1788]
- Pirfenidone is an orally active antifibrotic agent that is FDA-approved for the treatment of idiopathic pulmonary fibrosis. It has been regarded as a TGF-β1 suppressor,[1808] but it may act as a PPARα agonist, similar to fenofibrate.[1809] Pirfenidone alleviates experimental obesity (while up-regulating adiponectin and down-regulating resistin),[1806] while mitigating obesity-related cardiac steatosis and fibrosis.[1810] Pirfenidione has produced a reduction in extracellular volume by cardiac magnetic resonance imaging in a small short-term trial in patients with HFpEF (largely with obesity).[1811]
- Amycretin and CagriSema act as dual agonists of the GLP-1 and amylin receptors, producing substantial weight loss.[1812] However, even though amylin is a member of the calcitonin peptide family, amylin is not meaningfully produced by adipocytes. Furthermore, experimental hyperamylinemia causes proteotoxic effects, pathological cardiomyocyte remodeling, and diastolic dysfunction.[1813] The possibility that amylin agonism may simultaneously produce both weight loss and cardiotoxic effects underscores the lessons learned from large-scale trials that some weight loss interventions can have serious off-target adverse effects.[1814,1815]

Whenever newly developed drugs have the capacity to interfere with a mechanism that underlies a broad range of inflammation-driven disorders, the direction of their development often reflects the acceptability of surrogate endpoints in short-term trials to support regulatory approval and/or with the ability to achieve premium pricing in the marketplace. In contrast with cancer, neurodegenerative disease, and rare disorders, the return on investment for a drug that is directed to the treatment of HFpEF may be viewed unfavorably by corporate sponsors.

Nevertheless, new ways of understanding the pathogenesis of HFpEF should logically motivate a change in the direction of drug development toward HFpEF. This opportunity may be particularly relevant for the long list of adipokine-targeting agents (enumerated above) that are currently being advanced for the treatment of obesity or nonalcoholic fatty liver diseases—disorders of visceral adiposity that are closely intertwined with the pathogenesis of HFpEF.

PART IX. THE ADIPOKINE HYPOTHESIS OF HFpEF: SYNTHESIS OF THE EVIDENCE

Adipose tissue, often comprising ≡ 50% of body weight in people with obesity, is the body's largest secretory organ, and the adipocyte secretome represents the transducer that translates dietary nutritional signals into the release of messenger molecules from adipose tissue—adipokines—that are transmitted to and influence biological responses in other organs. Excess visceral adiposity triggers a state of heightened adipose tissue stress, characterized by cellular growth and inflammation, which is paralleled by a dramatic shift in the biological secretory profile of adipose tissue. As the mass of visceral fat expands, adipose tissue abandons the nurturing cytoprotective profile that is dominant in lean people, and it produces an altered suite of secreted molecules that act to promote hypertrophy and inflammation in neighboring cells (via a

paracrine effect) and at distant sites following release into the bloodstream (via an endocrine effect).

ADIPOSE TISSUE IS THE MAJOR SYNTHESIS SITE FOR CIRCULATING ADIPOKINES, AND THESE ADIPOKINES (ACTING BY AN ENDOCRINE OR PARACRINE MECHANISM) TARGET THE HEART. Many of the key adipokines are principally synthesized by adipocytes, but others are normally produced in the liver, skeletal, or cardiac muscle and other organs in healthy lean people, and therefore, have been commonly regarded as hepatokines, myokines, or cardiokines. Yet, given the enormity of the expanded fat mass in people with obesity, if the biology of the secretome is transformed, adipose tissue emerges as a principal source of synthesis of these adipokines and is the primary determinant of circulating blood levels. Furthermore, adipose tissue (including adipocytes in the bone marrow or lipid accumulation in organs) not only synthesizes numerous proteins, but it is also a source of eicosanoids, metabokines, lipokines, microRNAs, and reprogrammed progenitor and inflammatory cells that migrate to and are taken up by the other tissues, allowing adipose tissue dysfunction to be transmitted beyond the confines of the fat mass, thus igniting the emergence of a systemic disorder that promotes widespread tissue inflammation and growth.

Inflamed and hypertrophied adipose tissue transmits its deranged biology to all organs in the body, explaining why obesity is a major exacerbating factor for cancer, nonalcoholic fatty liver disease, inflammatory arthritic disorders, and chronic kidney disease. Yet, the heart represents a particularly vulnerable target for the dissemination of deranged adipokine signals from the expanded visceral fat mass. The myocardium is not only exposed to the changes in the circulating adipokine profile, but it is bathed in epicardial adipose tissue, which—as the most biologically active visceral fat depot—secretes adipokines directly onto the heart, both in lean adults and in people with obesity. The secretions from healthy epicardial adipocytes exert nurturing and cardioprotective functions, but with visceral adiposity, epicardial fat transmits prohypertrophic, proinflammatory, and profibrotic signals (as part of an altered secretome) onto the adjoining myocardium. Furthermore, the adipokine-mediated expansion of plasma volume places hemodynamic stresses on the heart, which may enhance its susceptibility to the paracrine and endocrine effects of prohypertrophic, proinflammatory, and profibrotic adipokines.

AN EXPANSION OF VISCERAL FAT MASS DRIVES A SYNCHRONIZED TRANSFORMATION OF ADIPOSE TISSUE SECRETION OF DOMAIN I, II, AND III ADIPOKINES THAT INFLUENCES THE EVOLUTION OF HFpEF. Although visceral adiposity can adversely influence coronary atherogenesis, the primary cardiovascular consequence of deranged adipokine signaling is HFpEF, a state of myocardial inflammation, coronary microvascular dysfunction, and fibrosis that limits chamber distensibility, and thus, the ability of the ventricles to tolerate adipokine-related hypervolemia. In fact, the clinical, physiological and molecular features of obesity/visceral adiposity and HFpEF are strikingly parallel and substantially superimposable (Table 1).

Accordingly, the exercise intolerance of patients with obesity can often be explained by elevated left ventricular filling pressures at rest or exercise. At the same time, central obesity and visceral adiposity consistently precedes and predicts the development of HFpEF, and they are characteristic features of nearly every patient with HFpEF, being closely associated the hemodynamic and clinical severity of the disease and its prognosis in individual patients. Among the visceral fat depots of interest, patients with HFpEF are particularly likely to have an expanded or proinflammatory epicardial adipose tissue mass. The altered balance in the circulating adipokines that characterizes patients with obesity also characterizes patients with HFpEF. The mechanistic and clinical overlap between visceral adiposity and HFpEF is so substantial that it is logical to conclude that one disorder causes the other.

This paper proposes that an expansion of visceral fat mass precedes and is the primary cause of HFpEF, ie, HFpEF results from an adiposity-driven derangement of adipose secretion that yields an altered suite of signaling adipokines, allowing for the heightened adipocyte stress to be disseminated to the heart. This paper presents a novel organization for key adipokine proteins: 1) Domain I adipokines are cardioprotective proteins whose secretion is suppressed and whose adaptive functions are lost in obesity; 2) Domain II adipokines are cardioprotective proteins that are up-regulated by adiposity as a suboptimal compensatory or counter-regulatory response; and 3) Domain III adipokines (whose secretion is heightened in obesity) promote systemic inflammation, sodium retention, and cardiac hypertrophy and fibrosis. Adipokines that belong to the same domain change with a striking degree of parallelism, whereas Domain I and III adipokines demonstrate a consistent inverse relationship, both in healthy individuals and

across a broad range of chronic metabolic and inflammatory disorders.

KEY LINES OF EVIDENCE THAT VISCERAL ADIPOSITY AND THE RESULTING CHANGE IN THE ADIPOKINE SECRETORY PROFILE REPRESENT THE PRINCIPAL CAUSE OF HFpEF. The evidence to support the adipokine hypothesis of HFpEF is based on the following 12 well-supported and mutually reinforcing lines of evidence:

1. Epidemiological parallelism between obesity and HFpEF

The surge of HFpEF in clinical practice has closely followed the global epidemic of obesity in the clinical community.

2. Role of dietary nutrient excess in experimental and clinical HFpEF

In both experimental models and in the clinical setting, dietary nutrient excess represents the key originating and causal event in the evolution of HFpEF.

3. Adiposity and adipokine derangements precede and presage HFpEF

In epidemiological studies, changes in adiposity and in circulating adipokines are observed years before the diagnosis of HFpEF and predict its development.

4. Near-universal prevalence and relevance of central obesity in HFpEF

Central obesity and visceral adiposity are present in nearly every patient with HFpEF and are closely related to the hemodynamic and clinical severity of the disease. Among the visceral fat depots of interest, patients with HFpEF are particularly likely to have an expanded or proinflammatory epicardial adipose tissue mass.

5. Biological and clinical parallelism and overlap in obesity and HFpEF

Obesity and HFpEF exhibit striking similarities and parallelism and substantial overlap in their clinical, pathophysiological, and molecular features.

6. Adipocytes are the primary site of adipokine synthesis in obesity

Adipocytes (not cardiomyocytes) typically synthesize and secrete cardioactive adipokines. In people with visceral adiposity or obesity (where fat mass comprises as much as 50% of body weight), adipose tissue is the dominant source of proinflammatory adipokines.

7. Parallelism of adipokines in obesity and heart failure and with disease severity

Serum levels or adipose tissue expression of adipokines change in parallel in obesity and heart failure. The magnitude of the increase and decrease of circulating adipokines is accompanied by parallel changes in the clinical and hemodynamic severity and prognosis of heart failure.

8. Adipokines have established biological effects on the heart

Adipokines have well-characterized effects on cardiac structure and function that are relevant to HFpEF, and they have been directly implicated in the pathogenesis of HFpEF in experimental studies.

9. Dietary nutrient deprivation ameliorates adiposity, adipokines, and HFpEF

Bariatric surgery cause shrinkage of visceral fat depots (disproportionate to the change in body weight), while simultaneously increasing circulating Domain I adipokines and decreasing in circulating Domain III adipokines. The responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a cardioprotective profile. Changes in systemic inflammation following bariatric surgery are related to changes in inflammatory signaling within and disseminating from adipose tissue.

10. Current HFpEF drugs ameliorate adiposity, adipokines, and HFpEF

Current drug treatments for HFpEF cause shrinkage of visceral fat depots (disproportionate to the change in body weight), while simultaneously increasing circulating Domain I adipokines and decreasing in circulating Domain III adipokines.

11. Adiposity may identify patients who benefit most from neurohormonal antagonism

An expanded adipose tissue mass is the primary driver of neurohormonal activation, explaining why adiposity may identify patients most likely to respond to MRAs, SGLT2 inhibitors, and angiotensin receptor neprilysin inhibitors in clinical trials.

12. Selective targeting of adipokines in adipose tissue influences cardiac structure and function

Experimental interventions that target only adipose tissue so as to selectively increase or decrease its secretion of specific adipokines can lead (typically in an endocrine manner) to changes in cardiac or vascular structure and function and can influence the development of cardiomyopathy.

ADIPOSE-SPECIFIC INTERVENTIONS THAT TARGET THE SECRETION OF SPECIFIC ADIPOKINES EXERT EFFECTS ON THE HEART, KIDNEYS AND VASCULATURE THAT ARE RELEVANT TO HFpEF. Experimental studies have confirmed that signaling from adipose tissue to the heart and kidney drives changes in organ health that are relevant to HFpEF (Box 14).

BOX 14. Adipose-Specific Interventions That Target the Secretion of Specific Adipokines Exert Endocrine Effects on the Heart, Kidneys and Vasculature

The responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a new set point that would be expected to produce favorable biological effects in the heart.

Domain I Adipokines
Adipocyte-specific suppression of eNAMPT induces a systemic multiorgan metabolic dysfunction.

Domain II Adipokines
Adipocyte-specific overexpression of adipsin produces favorable effects on the evolution of HFpEF, and transplantation of vaspin-expressing adipose tissue produces cardioprotective effects.

Domain III Adipokines
Adipocyte-specific secretion of chemerin exerts adverse vascular effects. Adipocyte-specific overexpression of PDGF-D promotes maladaptive cardiac remodeling, whereas adipocyte-specific silencing of PDGF-D decreases circulating PDGF-D levels and attenuates deleterious cardiac hypertrophic and fibrotic responses in experimental obesity.

Neurohormonal stimulation of white adipose tissue leads to galectin-3-mediated activation of cardiac fibroblasts. Conversely, adipocyte-specific silencing of autotaxin blocks the deleterious effects of obesity on the heart, preventing the development of cardiac hypertrophy, cardiomyopathy, and heart failure. Transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet.

Genetic silencing of resistin—specifically in adipose tissue—reduces circulating levels of resistin and acts to preserve cardiac function during experimental pressure overload, despite having no influence on the cardiac expression of resistin.

Mice with selective deletion of LCN2 in adipose tissue—but not those with selective deletion of LCN2 in the kidney—are protected from aldosterone-induced renal injury. Adipocyte-specific up-regulation of the mineralocorticoid receptor leads to vascular dysfunction. Transplantation of perivascular adipose tissue in which angiotensin II signaling has been pharmacologically suppressed prevents vascular injury. Adipocyte-specific ablation of ANGPTL4 prevents vascular disease.

The suppression of systemic inflammation following bariatric surgery in people with obesity is not related to an effect on circulating inflammatory cells (e.g., monocytes), but instead, it is related to suppression of inflammation-related genes in adipose tissue.

Transplantation of bone marrow mesenchymal cells and adipocytes from mice with HFpEF leads to recapitulation of HFpEF in healthy recipient mice, but knockout of SPARC in transplanted bone marrow taken from mice with pressure overload prevents transmission of the cardiac fibrosis phenotype to recipient mice. Suppression of CCR2 in bone marrow-resident inflammatory cells ameliorates experimental cardiomyopathy. Transplantation of fat tissue (that is pretreated with an SGLT2 inhibitor) into recipient mice with experimental diet-induced obesity ameliorates their vascular abnormalities.

Nutrient Surplus and Deprivation Signaling
Selective SIRT1 up-regulation in adipose-derived stem cells alleviates diabetes-induced HFpEF.

Adipocyte-specific up-regulation of heme oxygenase-1 improves the biological profile of cardiac and vascular tissues in experimental obesity.

The effect of PPARγ agonism with rosiglitazone to induce cardiac hypertrophy is mediated by the drug's effect on adipose tissue rather than the heart, because the prohypertrophic action of the drug is attenuated by adipocyte-specific (but not by cardiomyocyte-specific) silencing of PPARγ.

For Domain I adipokines, adipocyte-specific suppression of eNAMPT induces a systemic multiorgan metabolic dysfunction.[186-188]

For Domain II adipokines, adipocyte-specific overexpression of adipsin produces favorable effects on HFpEF.[624-626] Transplantation of vaspin-expressing adipose tissue produces cardioprotective effects in recipient mice.[320]

For Domain III adipokines, adipocyte-specific secretion of chemerin adversely affects vascular function.[862] Adipocyte-specific overexpression of PDGF-D promotes maladaptive cardiac remodeling, whereas adipocyte-specific silencing of PDGF-D decreases circulating PDGF-D levels and attenuates deleterious cardiac hypertrophic and fibrotic responses in experimental obesity.[984] Neurohormonal stimulation of white adipose tissue leads to galectin-3-mediated activation of cardiac fibroblasts.[491]

Experimental silencing of resistin—specifically in adipose tissue—reduces circulating levels of resistin and preserves cardiac function during pressure overload, but without any influence on cardiac expression of resistin.[901] Adipocyte-specific silencing of autotaxin blocks the deleterious effects of obesity on the heart, preventing the development of cardiac hypertrophy, cardiomyopathy, and heart failure.[943] Transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet.[105]

Mice with selective deletion of LCN2 in adipose tissue—but not those with selective deletion of LCN2 in the kidney—are protected from aldosterone-induced renal injury.[818] Adipocyte-specific up-regulation of the mineralocorticoid receptor leads to vascular dysfunction.[757] Transplantation of perivascular adipose tissue in which angiotensin II signaling has been pharmacologically suppressed prevents vascular injury.[752] Adipocyte-specific ablation of ANGPTL4 prevents vascular disease.[1358]

The transplantation of bone marrow adipocytes from mice with HFpEF leads to recapitulation of HFpEF in healthy recipient mice,[104] but knockout of SPARC in transplanted bone marrow extracted from mice with pressure overload prevents the transmission of the cardiac fibrosis phenotype to recipient mice.[1128] Adipose tissue-specific suppression of CCL2 has favorable effects at distant sites,[1266] and suppression of CCR2 in inflammatory cells residing in the bone marrow acts to ameliorate experimental cardiomyopathy.[1267] Transplantation of fat tissue that has been pretreated with an SGLT2 inhibitor acts to ameliorate the vascular abnormalities in recipient mice with experimental diet-induced obesity.[1642]

With respect to the balance of intracellular nutrient deprivation and surplus signaling, selective SIRT1 up-regulation in adipose-derived stem cells alleviates diabetes-induced HFpEF.[101] Adipocyte-specific up-regulation of heme oxygenase-1 (which reinforces SIRT1 signaling[102]) improves the biological profile of cardiac and vascular tissues in experimental obesity.[103] The effect of PPARγ agonism with rosiglitazone to induce cardiac hypertrophy is mediated by the drug's effect on adipose tissue rather than the heart, because the prohypertrophic action of the drug is attenuated by adipocyte-specific (but not by cardiomyocyte-specific) silencing of PPARγ.[1756,1757]

Intriguingly, the crosstalk between adipose tissue and the heart is bidirectional, with cardiac-specific stresses and interventions leading to effects on adipose biology,[129,141,142,247,796,821] potentially representing a signal from the heart to adipocytes to fine-tune the synthesis of adipokines, which can then respond (in an endocrine manner) to ameliorate or exacerbate conditions of cellular stress within the myocardium.[247]

INTERVENTIONS THAT SHRINK THE MASS AND IMPROVE THE BIOLOGY OF VISCERAL ADIPOSE TISSUE HAVE FAVORABLE EFFECTS ON THE ADIPOKINE SECRETION PROFILE AND IN HFpEF. In the clinical setting, the results with weight loss interventions provide the most persuasive support for the clinical relevance of the adipokine hypothesis of HFpEF. The weight loss that follows bariatric surgery not only produces an amelioration of adipose tissue hypertrophy and inflammation, but it also reverses most of the well-characterized abnormalities in adipokine signaling, with a remarkable restoration of Domain I adipokines along with normalization of Domain III adipokines. These responses are paralleled by exaggerated shrinkage of visceral fat depots (disproportionate to the decrease in body weight), suppression of systemic inflammation, amelioration of structural abnormalities in the left atrium and ventricle, favorable effects on symptoms, health status and exercise tolerance, and a reduction in the risk of worsening heart failure events.

The responses to bariatric surgery demonstrate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a cardioprotective profile. It is particularly noteworthy that the suppression of systemic inflammation following bariatric surgery in people with obesity is not related to an effect on circulating inflammatory cells, but instead, it is related to down-regulation of inflammation-related genes in adipose tissue.[1519]

Incretin receptor agonists as well as current FDA-approved drugs for HFpEF (MRAs, SGLT2 inhibitors, and angiotensin receptor neprilysin inhibitors) also cause a meaningful reduction in visceral adipose tissue mass that is disproportionately larger than the minimal change in body weight produced by these drugs. Furthermore, during treatment with these drugs, this shrinkage of visceral fat is accompanied by increases in Domain I adipokines and decreases in Domain III adipokines.

Interestingly, both bariatric surgery and current drugs for HFpEF lead to increases in several Domain II adipokines—FGF21, GDF-15, and ATGL; obesity may be accompanied by biological resistance to the effects of these proteins.[251-253,280] Drugs for HFpEF also increase circulating levels of several other Domain II adipokines (eg, irisin, apelin, HGF), whereas these adipokines are decreased by bariatric surgery. The

marked loss of weight with bariatric surgery may reduce the stimulus to the secretion of many Domain II adipokines. However, the action of currently prescribed drugs to up-regulate Domain II adipokines (simultaneous with suppression of Domain III adipokines) would be expected to produce unopposed favorable effects on adipose tissue and the heart.

The proposed framework identifies 2 generic drugs that might be usefully repurposed for HFpEF (ie, metformin and fenofibrate) as well as promising adipokine targets that can be exploited by existing novel pharmacological agents (ie, sotatercept and other activin antagonists, FGF21 analogs, leptin antagonists, and PDE9 inhibitors).

ARE CURRENT ASSUMPTIONS OF EXCEPTIONAL HFpEF HETEROGENEITY JUSTIFIED? The proposal of a single unifying hypothesis for HFpEF—based on adipose tissue dysfunction and its dissemination to the heart through secreted adipokines—may be viewed skeptically by those who have long believed that the pathogenesis of HFpEF is too complex to be described in a straight-forward manner that would be applicable to the vast majority of afflicted patients. Many investigators believe that HFpEF is an exceptionally heterogenous disorder and that evolution and progression of the disease is determined by distinct independent pathways, driven in different cohorts by numerous coexisting conditions, eg, sedentary aging, systemic and pulmonary hypertension, diabetes, coronary artery disease, aortic stiffness, cardiac hypertrophy and fibrosis, atrial fibrillation with atrial myopathy, microvascular abnormalities, systemic inflammation, natriuretic peptide deficiency, and chronic pulmonary or kidney disease.

However, the widespread belief that HFpEF is a heterogenous disorder lacks strong evidentiary support. The current impression of heterogeneity simply reflects the clinical appreciation that HFpEF is characterized by a large number of obvious comorbidities and pathophysiological abnormalities, whose presence and severity may vary from patient to patient. Yet, these same comorbidities and structural and functional derangements (along with their variability) are also seen in patients with HFrEF, in whom they are *not* believed to represent individual pathways, and instead, they are regarded as being consequences of neurohormonal activation. The comorbidities (or clusters of comorbidities) in HFpEF have not identified a particular group of responders in clinical trials. Furthermore, no evidence suggests that the treatment of hypertension, diabetes, coronary artery disease, elevated pulmonary artery pressures, cardiac hypertrophy, or chronic kidney disease has any influence on outcomes in HFpEF. No unifying mechanism has been identified by which these comorbidities might exert convergent effects to promote systemic inflammation, coronary arterial endothelial dysfunction or microvascular rarefaction,[19] and myocardial hypertrophy and fibrosis.

Therefore, instead of considering the comorbidities of HFpEF as representing separate pathways or distinct mechanisms, the "adipokine hypothesis of HFpEF" suggests that these coexisting disorders are the expected clinical manifestations of a single underlying mechanism, ie, a nutrient excess-induced overabundant and dysfunctional visceral fat mass that transmits its biological derangements to distant sites through adipokines acting as intermediaries. Accordingly, the comorbidities of HFpEF do not cause HFpEF, but instead, HFpEF, its comorbidities, and the systemic inflammatory state are all caused by the action of adipokines on the heart, vasculature, and kidneys.

A NEW CONCEPTUAL MODEL AS A LAUNCH POINT FOR RESEARCH AND DEBATE. The adipokine hypothesis is presented herein as an intentionally bold proposal that warmly welcomes feedback and criticism. The framework is proposed with the intent of inviting discourse and debate, so as to motivate new ways of thinking and ignite new directions in research. This paper represents an early first step, because it does not cover hundreds of other adipose-secretory products that are likely to transmit the biological stress of inflamed adipocytes to the heart.

More work is needed to explore the role of adipokines in explaining the pathophysiological and clinical differences in the evolution and progression of HFpEF in men and women as well as the influence of aging.[35] When compared with men, women with visceral adiposity (identified by dual-energy x-ray absorptiometry) are more likely to be misclassified as not having obesity (defined by body mass index). In a 10-year survey of >9,000 people, 48% of women were misclassified as being nonobese by body mass index, but were found to have obesity by measurements of percent body fat.[1816] A similar pattern of discordance was not seen in men, and the biological importance of visceral adiposity in women in this study was confirmed by their markedly elevated levels of leptin. Circulating levels of leptin are better correlated with cardiovascular stress and systemic inflammation in women than in men,[1817] and the influence of leptin in women is heightened as people age.[1818]

According to the adipokine hypothesis, new treatments for HFpEF should not seek to achieve

weight loss for its own sake, but instead, they should act to ameliorate the dysfunctional adipose tissue biology that drives the pathogenesis of HFpEF—without producing off-target effects. Historically, certain weight-loss drugs have had independent adverse cardiovascular and neuropsychiatric actions, eg, sibutramine and rimonabant.[1814,1815] Similarly, amylin agonists can potentiate the weight loss produced by other incretin-based drugs,[1812] but increased amylin signaling may cause proteotoxic effects, pathological cardiomyocyte remodeling, and diastolic dysfunction.[1813]

In conclusion, the adipokine hypothesis of HFpEF is presented as a testable and falsifiable model for the conceptual organization, synthesis, and reconciliation of available experimental and clinical evidence. It seeks to provide a new coherent lens through which HFpEF can be investigated, understood, and treated. Its ultimate value, if any, will be determined by its ability to galvanize new thinking, prompt decisive experiments, and improve the care of patients.

DISCLOSURES

Dr Packer has received consulting fees from Abbvie, Actavis, Alnylam, Altimmune, Ardelyx, Amgen, ARMGO, AstraZeneca, Attralus, Biopeutics, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Daiichi Sankyo, Eli Lilly and Company, Imara, Medtronic, Moderna, Novartis, Pharmacosmos, Regeneron, and Salamandra.

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APPENDIX For supplemental material, please see the online version of this paper.