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Review Article

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The Role of Adipose Tissue in Cardiovascular Pathophysiology

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. CVD is primarily driven by modifiable risk factors, including physical inactivity, smoking, high fat and high salt diets resulting in hypertension and obesity. Amongst these modifiable risk factors, obesity has taken a central role in CVD development. Adipose tissue acts not only as a reservoir of fat, but as an endocrine organ, releasing a number of biologically active "adipokines" that can regulate metabolic homeostasis. Given the intricate relationship between obesity and CVD, is imperative to understand the signals by which adipose tissue influences cardiovascular physiology and disease. Indeed, many adipose tissue-derived molecules have the potential to act as biomarkers for diagnosis, prognosis and even therapeutic targets in CVD. In this review, we discuss the impact of adipose-derived molecules in the pathogenesis of several CVD etiologies, including ischemic heart disease and heart failure.

Keywords: Adipose tissue; Heart; Cardiovascular disease; Obesity; Fibrosis

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death worldwide and is projected to continue rising over the next years.[1] Globally, CVD prevalence increased from 271 million (95% uncertainty interval [UI], 257–285 million) in 1990 to 523 million (95% UI, 497–550 million) in 2019. Similarly, the number of CVD deaths increased from 12.1 million (95% UI, 11.4–12.6 million) in 1990, to 18.6 million (95% UI, 17.1–19.7 million) in 2019.[2] Of the major risk factors driving CVD, obesity continues to increase in prevalence globally. Indeed, the frequency of obesity doubled between 1980 and 2015 in 73 countries.[3] Obesity has an outsized impact on CVD. Not only does obesity promote the development and worsening of known CVD risk factors, including dyslipidemia, type 2 diabetes, hypertension and sleep disorders, but it also contributes to CVD independently.[4]

CVD is a large umbrella of diverse cardiovascular entities, including ischemic heart disease (acute myocardial infarction [MI], chronic stable angina), ischemic stroke, non-rheumatic valvular heart disease, rheumatic heart disease, atrial fibrillation and flutter, ischemic and non-ischemic heart failure (HF) with reduced ejection fraction, HF with preserved ejection fraction, hypertrophic cardiomyopathy, peripheral arterial disease, myocarditis, aortic

aneurism and others.[2,5] Many adipose tissue derived signals, including cytokines, adipokines, lipids, peptides and extracellular vesicles, have been implicated in CVD.[6-9] Here, we focus on the role of the these adipose derived signals in ischemic heart disease and HF.

ISCHEMIC HEART DISEASE

Ischemic heart disease (IHD) is characterized by a mismatch between oxygen supply and demand in the myocardium. Clinically, multiple etiologies can lead to myocardial ischemia, including any of the following: coronary atherosclerosis disease (CAD), vasospasm in both atherosclerotic plaque and plaque free coronaries, spontaneous coronary artery dissection, coronary arteritis, coronary emboli, myocardial bridging, proximal aortic dissection, and congenital abnormality of the coronaries.[5] Similarly, once an arterial blockage is removed, ischemia-reperfusion (I/R) injury can result. Given the wide range of processes leading to IHD is not surprising to have many biological processes involved in the pathogenesis.[10]

Adiponectin

Adiponectin is an adipocyte derived peptide initially characterized in the context of systemic insulin sensitivity.[11] However, adiponectin has been shown to play a role in many normal physiological and pathological disease settings, including CVD.[12] In particular with regards to IHD, adiponectin has been extensively studied at the clinical and pre-clinical level. In animal models, adiponectin plays a crucial role in the pathogenesis of atherosclerosis. In mice, adiponectin deficiency leads to the accelerated development of atherosclerosis. This has been suggested to occur via T lymphocytes accumulation,[13] although in other settings, such involvement could not be confirmed.[14] Similarly, adiponectin treatment results in less atherosclerotic plaque and thrombus formation, this is believed to occur through the suppression of vascular cell adhesion molecule-1 and tissue factor expression in macrophages.[15,16] At the clinical level, adiponectin has proven to be a complex molecule with distinct associations with IHD. High plasma adiponectin concentrations are associated with lower risk of MI in men and low risk of IHD.[17,18] Another meta-analysis found that increased serum adiponectin levels are linked to ischemic stroke, but no clear evidence regarding a positive relationship between adiponectin and IHD risk emerged.[19] In fact, no causative association between adiponectin levels and IHD pathogenesis was found in a Mendelian randomized study.[20] Although, in that study they were not able to test for effect modification by sex, age, or previous disease.[20]

Leptin

Leptin is a protein hormone with pleiotropic functions, known to regulate energy expenditure, reproduction, food intake, blood pressure.[21] Although leptin is secreted by many tissues, including skeletal muscle, placenta, gastric mucosa and heart, adipose tissue is its main source.[9,22] A narrow range of circulating leptin levels appears to be critical for optimal physiology/weight.[23-26] This is suggested by the observation that hyperleptinemia can lead to obesity, and a similar obesity phenotype in mice lacking leptin.[23-26]

In rodents, leptin deficiency has been shown to slow down atherosclerosis in apolipoprotein E knockout models, but has the opposite effect in in low-density lipoprotein receptor knockout mice.[27,28] Furthermore, LEPR knock out mice undergoing MI, experienced greater mortality, due to metabolic inflexibility for glucose utilization.[29] At the clinical level, plasma leptin is acutely elevated in patients with MI.[30] Similarly, high plasma leptin levels have been shown to be an independent risk factor for death in patients with CAD.[31]

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Resistin

Resistin is a hormone primarily secreted by adipocytes and macrophages.[32-35] Resistin is a pro-inflammatory hormone, acting via cell adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1.[36,37] With regards to IHD, in both human and murine atherosclerotic lesions, resistin has been shown to be expressed at high levels.[38] Similarly, serum resistin levels have been positively associated with CAD and in patients presenting with unstable atherosclerotic plaque.[38-40] However, there is also evidence both at the clinical and preclinical level suggesting resistin is not a risk factor for CAD and may even provide cardioprotective effect.[41,42] The latter shown in mouse models of I/R and thought to occur via the activation of phosphatidylinositol 3-kinase (PI3K), Akt, protein kinase C (PKC) ATP-sensitive potassium channel K (ATP) pathways.[41,42] Altogether, the involvement of resistin in CAD and metabolic disease is still not clear, and the detailed mechanistic underpinnings of how resistin is exerting any of its postulated physiological roles remains poorly understood.

FGF21

FGF21, a protein primarily secreted by the liver, has been implicated in glucose homeostasis, insulin sensitivity and ketogenesis.[43] Under certain pathophysiological conditions, it has also been shown to be secreted by skeletal and cardiac muscle.[44-46] In particular, liver secreted fibroblast growth factor 21 (FGF21) ameliorates acute MI by inhibiting cardiomyocyte apoptosis.[44] Moreover, post MI cardiac remodeling is improved after skeletal FGF21 overexpression in mice.[46] Clinically, serum FGF21 have also been reported to be associated with CAD and elevated in patients with acute MI.[47,48] Adipocytes can express high levels of FGF21 as well, but the current view is that adipocytes-produced FGF21 does not enter circulation and only acts in an autocrine fashion. It remains to be seen whether this is true under all conditions and whether adipocyte-derived FGF21 exerts a direct or indirect effect on the cardiovascular system.

Galectins 3, 9, 12

Galectins are a family of glycan-binding proteins, known to participate in several pathophysiological processes, including inflammation, pro-fibrosis, apoptosis, adhesion, angiogenesis, cell migration, proliferation.[49] Although several organs express galectins, adipose tissue is a major source of galectins 3, 9 and 12.[50] Galectin 3 is found at higher levels in human and murine atherosclerotic plaques and promotes CAD by phenotypic transformation of vascular smooth muscle cells, and macrophage chemotaxis and activation.[51,52] With respect to MI, exogenous galectin-3 leads to increased infarct and fibrosis area in a rodent MI model.[53] Similarly, in humans with acute MI, serum galectin-3 are significantly higher when compared to the control group.[54]

Ceramides, palmitoleate

The fatty acid-derived lipids, ceramide and palmitoleate, are plasma molecules shown to play a role in IHD. Ceramides are a subtype and essential precursor of sphingolipids as well as key modulators of the cellular stress response.[55] Plasma ceramides are predominantly secreted by the liver and adipocytes.[56] Both ceramides and their precursors, dihydroceramides, have been implicated in CVD.[57] Specifically, elevated levels of ceramides and dihydroceramides have been shown to be present in atherosclerotic plaques.[58,59]

Palmitoleate is a monosaturated fatty acid that regulates lipid metabolism and glucose homeostasis.[60] In mouse and human macrophages, palmitoleate been shown to prevent endoplasmic reticulum stress, decrease systemic inflammation and leading to reduced atherosclerotic plaques.[61]

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Extracellular vesicles (EVs)

EVs and exosomes are membrane-bound vesicles released by many different cell types into the extracellular space, enabling distant communication with cells from other organs. EVs cargo includes DNA, RNA, proteins, submitochondrial particles, which can directly affect both physiological and pathological processes of distant tissues.[62] In humans, elevated levels of EVs (Cystatin C, Serpin F2, CD14) have been associated with an increased risk for MI and vascular events.[63] At the preclinical level, a crosstalk between the injured myocardium and adipose tissue has started to emerge. It has been shown that dysfunctional adipocyte-derived EVs lead to a burst of reactive oxygen species in cardiomyocytes along with a compensatory antioxidant response, creating a preconditioning effect.[64] This response results in cardiomyocyte protection after I/R damage. Similarly, in the acute setting, adipocyte-derived EVs carrying miR-130b-3p can exacerbate I/R injury via multiple anti-apoptotic/cardioprotective molecules, and exacerbate I/R injury.[65]

HF

HF is a clinical syndrome categorized based on left ventricular (LV) ejection fraction (EF) as reduced EF <0.50 (HFrEF), mid-range EF >0.40, <0.50 and preserved EF >0.50 (HFpEF).[5] Despite this classification, HF is an spectrum and many features are shared across all types, including impaired LV diastolic dysfunction, elevated LV diastolic pressure, abnormal LV filling dynamics, neurohormonal activation, impaired exercise tolerance, frequent hospitalizations and reduced survival.[5,66] One of the key elements of HF is LV remodeling. LV remodeling is a broad term encompassing a series of complex pathophysiological processes, including cardiomyocyte hypertrophy, fibrosis, vascular stiffness, endothelial dysfunction and inflammation.[67] LV remodeling occurs in response to several risk factors, including age, genetics, hypertension, diabetes, obstructive sleep apnea and obesity.[67,68]

Several adipose tissue signals have been described to be instrumental in the pathogenesis of LV remodeling/HF, including adiponectin, leptin, resistin, FGF21, galectins and palmitoleate.

Adiponectin

The role of adiponectin in HF is complex, especially in the setting of HF-related mortality, leading to what is known as the adiponectin-mortality paradox.[69] Adiponectin was initially recognized as a cardioprotective adipokine.[70] The paradox comes from the observation that high adiponectin levels were linked to high mortality incidence in patients with HF.[71] In humans, this paradox has been in part explained by adiponectin resistance and HF heterogeneity of patients included in clinical trials. In advanced HF, there are higher levels of adiponectin which can be mediated by brain and atrial natriuretic peptides, both of which are elevated in HF.[72] In addition, at advanced HF stages, the adiponectin receptors AdipoR1 and AdipoR2 are downregulated which could contribute to adiponectin resistance.[73] Similarly, studies looking at mortality in HF patients, often grouped both HFrEF and HFpEF as one entity.[74,75] However, the pathophysiology is significantly different amongst both HF groups, therefore future studies should aim at distinguishing HFrEF from HFpEF.

In mice, lack of adiponectin results in enhanced concentric cardiac hypertrophy after a pressure overload challenge; suggesting a protective role of adiponectin in hypertrophy mediated via AMP-activated protein kinase (AMPK) signaling.[76,77] Similarly, angiotensin II-induced cardiac fibrosis, is worse in adiponectin deficient mice, whereas adiponectin supplementation ameliorates fibrosis.[78]

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Leptin

As with it's impact on obesity, leptin appears to have a narrow range for optimal physiological effects in HF as well, as noted by its dichotomous and paradoxical effects at high and low plasma levels.[9] On the one hand, elevated levels of leptin are seen in HF and positively correlated with unfavorable CVD outcomes.[79,80] Similarly, Leptin levels have been positively correlated with myocardial wall thickness in humans, suggesting a role for leptin in cardiac hypertrophy pathogenesis.[81] Paradoxically, lack of leptin also seems to have a negative impact in CV physiology as noted in preclinical studies, where leptin deficiency leads to cardiomyocyte hypertrophy.[82] Furthermore, leptin receptor deficient mice show LV contractile dysfunction, as measured by load-independent parameters.[83] A direct role of leptin signaling in cardiac structure and function is further highlighted by the observation that acute cardiomyocyte-specific deletion of the leptin receptor via tamoxifen results in lethal HF.[84] Thus the role of leptin is complex and appears to have detrimental effects at the end of the spectrum.

Resistin

Resistin levels have been positively associated with a higher incidence of HF in several clinical studies.[85,86] More recent studies have further refined the association of resistin and HF, suggesting that resistin has better association with HFrEF incidence than HFpEF.[87] Furthermore, rodent studies have revealed that by lowering plasma resistin levels in a HF model, the overall cardiac function is improved, in part, mediated by miR148b-3p and DNA damage response.[88]

FGF21

Circulating FGF21 levels have been associated with HF. In patients with end-stage HFrEF, plasma levels of FGF21 were higher than in healthy controls. Moreover, cardiac FGF21 expression was minimal, suggesting extra-cardiac expression, consisting with a model of hepatic production.[89,90] Similarly, high levels of FGF21 in patients with HF are associated with worse outcomes, including death and HF readmission.[91] Interestingly, low levels of FGF21 also seem to result in abnormal LV remodeling, as suggested by studies in mice lacking FGF21.[45] In these FGF21 KO mice, enhanced cardiac hypertrophy and pro-inflammatory pathway activation is seen.[45] Together, these results argue for an optimal range of FGF21 levels, needed for adequate cardiac physiology.[92]

Galectins

Galectin-3, known to play a role in inflammation, is also an important mediator of cardiac fibrosis/remodeling via macrophage activation.[93] In rodents, exogenous galectin-3 expression leads to cardiac fibrosis, hypertrophy and eventually LV dysfunction.[94,95] Moreover, both genetic and pharmacological inhibition of galectin-3 halts cardiac remodeling and improves LV dysfunction seen in animal models of HF.[96]

Palmitoleate

The fatty acid palmitoleate is involved in cardiac hypertrophy. In Burmese pythons, palmitoleate was shown to mediate the physiological cardiac hypertrophy observed in the post-prandial period. Furthermore, LV hypertrophy is also observed in mice treated with a mixture of fatty acids, including palmitoleate.[97] Comparably, studies in human athletes reveal a positive correlation between palmitoleate and cardiac hypertrophy, in particular interventricular septum thickness.[98] However, elevated plasma palmitoleate levels have been positively associated with higher odds of developing HF in male physicians.[99] Suggesting that optimal levels are needed for cardiac remodeling as elevated concentrations lead to HF.

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Collagen peptides

Collagen derived peptides have also being implicated in HFpEF. In particular collagen type I and type III cleavage peptides have been positively associated with the development of HFpEF, however a causative role has not been established.[100] More recently, a new collagen type VI derived peptide, named endotrophin (ETP), has been linked to HFpEF.[101] In this study, using a series of biorepositories from 7 clinical trials and observational cohorts with HFpEF patients, authors looked at the association between baseline circulating ETP levels and HF outcomes. Statistical analysis showed that ETP associated with both death (hazard ratio [HR], 1.74; 95% confidence interval [CI], 1.36–2.24; p<0.001) and the composite of death and HF hospitalization (HR, 2.11; 95% CI, 1.67–2.67; p<0.001).[101] Thus, ETP is a strong biomarker in HFpEF outcomes, however, its role in HFpEF pathogenesis has not been determined yet.

In contrast to previous collagen markers, ETP shows potential as a peptide involved in the pathogenesis of HFpEF due to its role in other inflammatory diseases. ETP is elevated in both cancer and obesity. Furthermore, inhibition of ETP via blocking antibodies, leads to reduced tumor growth and improved hepatic steatosis seen in obesity.[102-104] These results highlight ETP's role in the pathogenesis of pro-inflammatory diseases. Thus, testing the role of ETP in the pre-clinical models of HFpEF is highly relevant and promising.

CONCLUSIONS

The increased prevalence of CVD and obesity has proven to be a deadly combination and major health care problem. The interplay between adipose tissue signals and CV physiology and disease is paramount to the development of new diagnostic markers, as it has been for some of the signals outlined above. In parallel, adipose tissue derived molecules are increasingly known to be directly involved in the pathogenesis of CVD, which broadens the target for therapeutic intervention (**Figure 1**, **Table 1**).

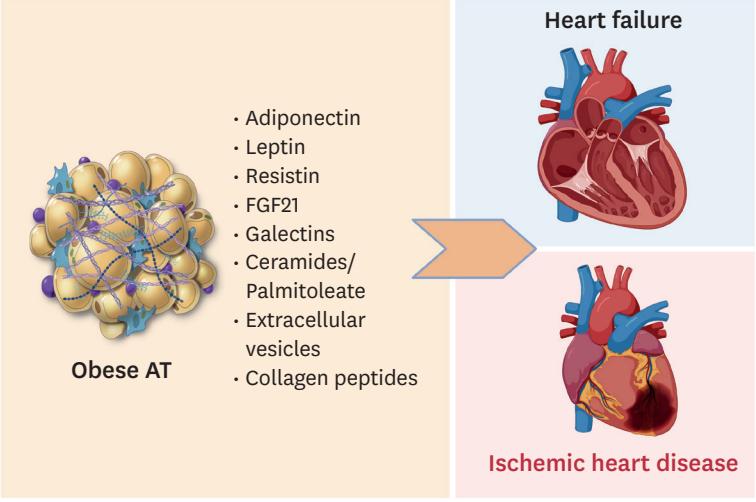

Figure 1. Adipose tissue signals in heart failure and ischemic heart disease. Obese adipose tissue, characterized in part by adipocyte expansion, hypertrophy, immune cell infiltration and increased extracellular matrix deposition, secretes multiple signals which have been implicated in heart failure and ischemic heart disease.

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Table 1. Reference table for adipose tissue signals implicated in heart failure and ischemic heart disease

AT signals	Ischemic heart disease	Heart failure
Adiponectin	[11-20] ([P][13-16] [C][17-20])	[69-78] ([P][76-78] [C][71-75])
Leptin	[9,21-31] ([P][23-29] [C][30,31])	[9,79-84] ([P][82-84] [C][79-81])
Resistin	[32-42] ([P][34,35,41,42] [C][38-40])	[85-88] ([P][88] [C][85-87])
FGF21	[43-48] ([P][44-46] [C][47,48])	[45,89-92] ([P][45] [C][89-91])
Galectins	[49-54] ([P][51-53] [C][54])	[93-96] ([P][93-96])
Ceramides/Palmitoleate	[55-61] ([P][51-61])	[97-99] ([P][97] [C][98,99])
Extracellular vesicles	[62-65] ([P][62-65] [C][63])	
Collagen peptides		[100-104] ([P][102-104] [C][101])

AT signals' publication references categorized by ischemic heart disease and heart failure. Preclinical studies (P) references are separated from references focusing on clinical studies (C).
AT = adipose tissue.

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