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Adipose Tissue Biology and Cardiomyopathy-Translational Implications

Aslan T. Turer[a,b], **Joseph A. Hill**[a,b], **Joel K. Elmquist**[a,c,e], and **Philipp E. Scherer**[a,d,f,*]

[a]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX

[b]Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX

[c]Division of Hypothalamic Research, University of Texas Southwestern Medical Center, Dallas, TX

[d]Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, TX

[e]Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX

[f]Department of Cell Biology, University of Texas Southwestern Medical Center, Dallas, TX

Abstract

It is epidemiologically established that obesity is frequently associated with the metabolic syndrome and poses an increased risk for the development of type 2 diabetes and cardiovascular disease. The molecular links that connect the phenomenon of obesity *per se* with insulin resistance and cardiovascular disease are still not fully elucidated. It is increasingly apparent that fully functional adipose tissue can be cardioprotective by reducing lipotoxic effects in other peripheral tissues and by maintaining a healthy balance of critical adipokines, thereby allowing the heart to maintain its full metabolic flexibility. The present review highlights both basic as well as clinical findings that emphasize the complex interplay of adipose tissue physiology, adipokine-mediated effects on the heart exerted by either direct effects on cardiac myocytes or indirect actions via central mechanisms through sympathetic outflow to the heart.

Keywords

obesity; diabetes mellitus; insulin-sensitivity; adipokines; adipose; heart failure

Introduction

The impact of the world-wide increase in obesity cannot be easily overstated. Current estimates suggest that ~70% of US adults are overweight or obese [1]. These numbers are rapidly mirrored across the rest of the globe. Perhaps most troubling are the statistics related to the prevalence of overweight/obesity in the pediatric population. Diseases previously observed only in adulthood, e.g. hypertension and type 2 diabetes mellitus (T2DM) are now

*Corresponding author: Philipp E. Scherer, Telephone: 214-648-8715, Fax: 214-648-8720, philipp.scherer@utsouthwestern.edu, 5323 Harry Hines Blvd, Dallas, TX 75390.

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increasingly diagnosed in children. This trend threatens to translate into a deluge of cardiovascular disease (CVD), presenting decades earlier than might otherwise have been expected based on the prevalence of obesity 30 years ago.

The complex biology between adipose tissue and the cardiovascular system, in many ways, lies at the center of the pathogenesis of CVD. Although much is known vis-à-vis the relationship between adiposity and traditional CVD risk factors, there is a growing appreciation of novel markers and mediators of disease that are adipose-derived [2]. Here, we summarize our current understanding of these interactions, with a particular emphasis on the association between adipose tissue biology and cardiomyopathy, as this has been an area of important recent advances in our understanding from a basic science and clinical perspective.

Constituents of Adipose Tissue

Over recent years, the notion of adipose tissue as a passive repository of lipid stored in adipocytes has been overturned. Adipose is now seen as a dynamic tissue, which is both responsive to and responsible for a wide variety of hormonal, inflammatory and metabolic interactions with other organs [3].

The prototypic cell of adipose tissue is the adipocyte, whose main, but certainly not only function is to store energy in the form of triglyceride (TG). Under the influence of insulin, the adipocyte takes up free fatty acids (FFAs) from the blood and then stores them in the form of intracellular lipid droplets. Conversely, during periods of fasting and in response to exogenous humoral signals, such as circulating catecholamines, TGs are hydrolyzed and liberated from the lipid droplet to be released into the bloodstream. FFAs can then be used at distant sites as metabolic substrates through transport into cells by interaction with fatty acid transport proteins or CD36. Alternatively, these lipids can potentially act as signals themselves. Adipocytes are also now recognized to secrete a number of more traditional hormones, referred to as adipokines, which report on the status of the adipose tissue itself. Adipokines exert effects on the central nervous system, peripheral metabolism and the immune system, as well as in a paracrine fashion on local cells in adipose tissue directly.

While adipocytes are important constituents of adipose tissue, making up the majority of tissue mass, they only account for about 50% of all cells. The remaining cells are frequently referred to as the stromal vascular fraction. Endothelial cells, pericytes and various types of immune cells make up the majority of the remaining cells. Amongst the immune cells, macrophages feature prominently in evolving and dysfunctional fat pads. These macrophages are either in a pro-inflammatory state polarized towards the M1 phenotype, or they have an alternative gene expression programs that leans more towards the M2 phenotype that is more prone to be involved in tissue remodeling. However, many additional immune cells play a vital role in maintaining adipose tissue homeostasis, including regulatory T cells, eosinophils and mast cells [4]. The relative number of each of these cell types varies with the changing metabolic state and functionality of the adipose tissue [5]. The macrophages play an important role in the disposal of adipocyte remnants that leave large lipid droplets behind. Lipid-phagocytosing macrophages that start to look like foam cells over time, surround lipid droplet remnants and form “crown-like structures” characteristic of dysfunctional adipose tissue [6, 7].

Adipose Tissue as an Endocrine Organ

Dysfunctional, inflamed adipose tissue in states of nutrient excess can promote systemic inflammation and insulin resistance. The ability to buffer excess nutrients is reduced, the secretion of inflammatory cytokines is increased and the secretion of the insulin-sensitizing

hormone adiponectin is lowered in obese adipose tissue. Furthermore, an enhanced capacity for lipid storage in adipocytes protects against metabolic disturbances, even in the context of massive nutrient excess [8]. An opposite phenotype can be observed in models of lipodystrophy, whereby the storage capacity of adipose tissue is limited [9]. Therefore, it is apparent, that adipocytes, through their function as nutrient storage cells, play a key role in the pathogenesis of the metabolic syndrome and have the capability to exert profound effects on whole body metabolism. Prolonged nutrient overload results in a state of chronic, low-grade inflammation in adipose tissue that is associated with the down-regulation of critical adipokines, such as adiponectin, and an upregulation of other factors, such as leptin, resistin and the recently identified endotrophin. Adipose tissue therefore serves as a potent endocrine organ, releasing a complex set of proteinaceous factors acting on many other metabolically active tissues [10].

Leptin—Leptin is the archetypical adipokine identified in 1994 [11]. With more than 20,000 papers focusing on leptin action or minimally using it as a biomarker, leptin has been widely studied for its established actions in the brain affecting food intake and energy expenditure [12]. Circulating levels of this hormone are directly correlated to fat mass, and as will be discussed in more detail below, it can affect metabolic processes in peripheral tissues either via direct action on the tissues or indirectly through neuronal innervation. Several splice variants of the leptin receptor are known [13], but its downstream intracellular effects are generally mediated by the JAK/STAT3 [14] and PI3K pathways [15, 16].

Adiponectin—This is another widely studied adipokine first described in 1995 with approximately 10,000 publications since that time [17]. Adiponectin is a member of a growing family of paralogues known as C1q/TNF-related proteins (“CTRPs”) based on its structural similarities to these proteins [18]. Its effects are widely considered to be beneficial, with potent insulin-sensitizing, anti-apoptotic and anti-inflammatory properties [19]. Adiponectin receptors are ubiquitously expressed leading to a host of effects on different target tissues [20]. Previous work had identified an adiponectin mechanism involving downstream AMPK [21, 22] or PPARα-mediated effects [23]. It has subsequently been shown that adiponectin has both an AMPK-dependent and -independent mechanism [24]. More recent work, however, has identified activation of intracellular ceramidase activity as critical to adiponectin’s actions in a number of different cell types, including the cardiomyocyte [25]. Hence, a potentially unifying mechanism for the diverse beneficial effects of adiponectin may be related its ability to alter cellular sphingolipid metabolism via activation of its receptors adipoR1 and adipoR2.

Resistin—Resistin has become regarded as another important adipokine [26], at least in rodents. It is generally upregulated in the obese state [27] and has been implicated as a causative factor in insulin-resistance. In distinction to rodents, resistin expression in humans is mainly limited to macrophages and circulating monocytes, which makes the relevance of animal models examining the role of this cytokine somewhat difficult to interpret. Nonetheless, as will be discussed later in this review, this cytokine has been correlated with clinical conditions in humans, namely, hypertension, atherosclerosis, and HF.

Collagen VIα3-C5/Endotrophin—Collagen VI is ubiquitously expressed, but its most abundant source is adipose tissue. It contains three chains, α1-α3, which associate further to form intracellular tetramers. Once secreted, the C5-domain of the α3 chain (also known as *endotrophin*) is cleaved off by a protease that has yet to be identified [28] and the tetramers subsequently aggregate into microfibrils. Local endotrophin levels within adipose tissue are high in obese mice and accumulate within areas of dysfunctional adipocytes and infiltrating macrophages (“crown-like structures”). Indeed, there is a correlation seen between total

collagen VIα3 levels and macrophage infiltration in adipose tissue of obese patients [29, 30]. Most recently, endotrophin has been shown to play a critical role in malignant mammary tumor progression, both in terms of primary tumor growth and distal metastasis (*Park and Scherer, 2012, J Clin Inv., in press*). This paracrine factor appears to be an important link in the connection between obesity and malignancy, but, more generally, ties metabolic dysregulation to a more fibrotic extracellular environment.

Other hormones—Many additional factors have been shown to be expressed in adipocytes, including many pro-inflammatory factors and acute phase reactants, omentin, chimerin and visfatin, which are merely enriched in adipocytes and found in other tissues as well [10].

Brown Adipose Tissue and Its Hormonal Control

The past several years have brought considerable excitement in the field regarding the progress made in the area of brown adipose tissue physiology. There is an increased appreciation for these cells in humans. They are not only relevant in the newborn state- as it was the general believe for many years- as they may be playing an important role in systemic metabolic homeostasis even in the adult. What makes the brown adipocytes somewhat harder to detect is that unlike in rodents, brown and white adipocytes are mixed together in the various depots. Strong indications regarding the presence of brown adipocytes came from ^{18}F-FDG (Fluorodeoxyglucos) PET/CT scans that suggested disproportionate uptake into certain fat depots, particularly in the subclavicular region [31]. The hope is that with an increased abundance of brown adipocytes in the system, an increase in overall energy expenditure can be solicited. Beyond the inducibility of brown adipocytes by exposure to cold, a number of additional mechanisms have recently been discovered that can increase the proportion of brown adipocytes, including actions by vascular endothelial growth factor (VEGF) on adipose tissue[32], a newly identified, muscle-derived molecule called irisin,[33] as well as the natriuretic peptides[34]. Future studies need to demonstrate whether the mere increased presence of brown adipocytes is sufficient to increase energy expenditure, or whether additional steps need to be taken to activate these newly acquired "brown", "brite" or "beige" adipocytes, as several different laboratories refer to them[35-37].

Distribution of Adiposity Influences Its Biological Effects

The ability of the fat mass to expand is key in maintaining the overall health of the tissue. Subcutaneous fat depots are relatively inert from an inflammatory/insulin-resistance standpoint and serve as an important energy storage depot before ectopic fat deposition. As the subcutaneous adipose tissue (SAT) mass continues to increase, fat becomes deposited in visceral adipose tissue [VAT, (e.g. intraperitoneal, retroperitoneal, and intrahepatic)]. VAT releases more inflammatory mediators (such as IL-6) than does SAT [38, 39]. Furthermore, the expression of β_3-adrenoreceptors is higher in VAT than SAT, [40] making this tissue more sensitive to catecholamine-induced lipolysis [41-43] and perhaps less sensitive to inhibitory α_2-effects [44]. VAT is also less sensitive to the anti-lipolytic effects of insulin [45, 46].

Even among those who are already obese, preferential fat expansion in SAT, rather than VAT, is associated with a generally more favorable cardiovascular risk factor profile (*Neeland IJ et al, Obesity, in press*; [47]). Site-specific location of fat also appears to be important. Higher degrees of lower extremity adiposity relative to central deposition of fat have been associated with improved insulin sensitivity, lipid parameters and cytokine profiles [48-51]. Conversely, increasing central fat deposition, even in the setting of normal BMI, is associated with worse cardiovascular risk profiles [52], insulin-sensitivity[52, 53] and diastolic function [53].

Taken to the extreme, the most dramatic examples of altered fat distribution, the congenital and acquired forms of generalized lipodystrophy, are associated with loss (or lack of development) of peripheral adipose and accumulation of adipose centrally. Insulin resistance, dyslipidemia, hepatic steatosis, hypoadiponectemia and hypertension are extremely common in this population, and patients are predisposed to developing atherosclerosis at a young age. [54,55]. Women are not only more easily identified from an anthropomorphic standpoint, but also are significantly more likely to develop metabolic complications than men [56]. Early-onset cardiac hypertrophy is common, likely reflecting the influences of comorbid conditions; left ventricular (LV) dilation is less frequent [57].

More recently, the specific role of intrapericardial fat as a form of visceral adipose tissue has garnered increasing attention. Although pericardial and epicardial fat are biologically distinct [58,59], their differentiation and measurement from static images may be difficult, and these terms appear to be often interchanged in the reported literature. Similar to intra-abdominal VAT, pericardial fat is associated with overall adiposity and tightly associated with the presence of adverse metabolic phenotypes, including insulin-resistance [60, 61]. Its accumulation has been associated with LV structure-function changes [62, 63]. Pericardial fat is also associated with not only prevalent coronary artery disease [64, 65], but progression of atherosclerosis [66], ischemia on stress testing [60], and future adverse clinical events [67]. The proximity of epicardial fat and the coronary arteries to one another may allow this tissue influence one another. Indeed, epicardial fat from patients with coronary atherosclerosis is associated with pro-inflammatory macrophage polarization [68] and higher levels of cytokine production [69].

Adipokine Action on the Heart Mediated by Central Mechanisms

Although traditionally thought of as acting through cognate receptors in peripheral target tissues, we now know that several key metabolic hormones have important central inputs, which in part mediate their peripheral effects. Insulin and leptin act in the hypothalamus to regulate glucose homeostasis independent of body weight. Central administration of insulin suppresses hepatic glucose production, and insulin-induced suppression of hepatic glucose production is attenuated in mice lacking insulin receptors in the brain. Likewise, leptin signaling in the hypothalamus is required for the control of glucose balance. It has been shown that central administration of leptin alters peripheral glucose uptake and hepatic glucose output [70]. Leptin also plays a central role in the regulation of the sympathetic nervous system [71], and leptin acts within the CNS to affect heart rate and blood pressure [72]. Notably, direct injections of leptin into the arcuate nucleus increased mean arterial pressure by increasing renal sympathetic nerve activity [73]. More recently, Hall and colleagues produced mice with selective deletion of LEPRs in POMC neurons. They found that POMC leptin receptor knockouts had normal mean arterial pressure despite obesity. Moreover, the deletion of leptin receptors in POMC neurons blunted the effects of leptin administration to increase blood pressure, increase energy expenditure and to exert anti-diabetic effects[74]. Collectively, work from multiple groups has highlighted that POMC neurons are a key targets for leptin to regulate the cardiovascular system.

These central effects are clearly best described for leptin, but it is likely that additional adipocyte-derived factors exert at least some of their effects on the cardiovascular system via central action, including adiponectin [75] as well as resistin [76, 77].

Mechanisms of Insulin Resistance in the Heart

Obesity and whole-body alterations in insulin sensitivity are well-recognized to go hand-in-hand, but insulin-resistance specifically at the level of the heart has important implications for cardiac metabolism and function. Obesity and systemic insulin-resistance are marked by

enhanced lipid synthesis in hepatocytes and increased lipolysis in adipocytes which together lead to increases in circulating FFA and TG. Also, elevated levels of insulin, which typify these disorders, will stimulate FFA transport into cardiomyocytes [78]. Thus, hyperlipidemia and hyperinsulinemia together increase FFA delivery to myocytes, which rapidly adapt by promoting fatty acid utilization. At baseline, the myocardium is a "metabolic omnivore" capable of switching between metabolic substrates, e.g. FFA and carbohydrates, in response to changes in substrate availability and physiological conditions [79]. However, if FFA delivery exceeds the oxidative capacity of the cell, these substrates accumulate, with resulting lipotoxicity as a result [80]. This promotes cardiac dysfunction via several mechanisms, including the generation of reactive oxygen species (ROS) [81], ceramide production [25, 82], further impairing insulin signaling [83], depressing contractility by influencing sarcoplasmic reticular Ca^{2+} stores [84], and promoting mitochondrial dysfunction[8586], all while increasing oxygen demand.

In the setting myocardial insulin-resistance, metabolic flexibility is diminished, and the heart's reliance on FFA for energy supply increases. Accumulation of FFAs leads to impaired insulin-mediated glucose uptake through inhibition of IRS and Akt. The serine protein kinases PKC-θ and IKK, which elicit serine phosphorylation of IRS1, are activated [87]. In turn, this reduces signaling through PI3K and Akt, all of which has major implications for insulin-responsiveness under these conditions [88].

Several lines of evidence point to phosphorylation-dependent negative regulation of IRS1, triggering its proteolytic degradation, as a critical event in the pathogenesis of insulin-resistance. Degradation of IRS1 elicits impaired insulin signaling in a number of cell types [89], and low levels of IRS1 correlate with development of T2DM [90]. This negative feedback occurs primarily through the post-translational modification of IRS1 by serine phosphorylation, an event that can both disrupt the function of this adaptor protein and target it for degradation by the ubiquitin proteasomal machinery.

Much less is known about the phosphatases that antagonize these inhibitory phosphorylation events, although protein phosphatase 2A (PP2A) has been implicated [91]. Prior work has demonstrated that FoxO1 can inhibit PP2A activity. [92] This may be a relevant mechanism behind serine phosphorylation of IRS1 in T2DM, a condition under which persistent FoxO1 activation has been observed [93]. Furthermore, cardiomyocytes transfected with a GFP-tagged FoxO1 show increased levels of IRS1 serine phosphorylation and decreased steady state levels of total IRS1 [93]. These data, along with *in vivo* data from *FoxO1* null mice suggest that regulation of IRS1 activity and stability by FoxO1 may contribute to cardiomyocyte insulin resistance and subsequent cardiac dysfunction.

Hence, increasing adiposity may set the stage for cardiac dysfunction by promoting excessive myocardial FA utilization and the development of lipotoxicity. However, obesity also promotes global insulin resistance, which eventually leads to chronic systemic hyperglycemia. Glucotoxicity also contributes to cardiac injury through multiple mechanisms, including direct and indirect effects of glucose on cardiomyocytes, cardiac fibroblasts, and endothelial cells. Hyperglycemia promotes the over-production of ROS [94-96], which can induce apoptosis and activate poly (ADP-ribose) polymerase-1 (PARP)[97]. By subsequent PARP-mediated ribosylation and inhibition of glyceraldehyde phosphate dehydrogenase (GAPDH), glucose is diverted from the glycolytic pathway toward alternative biochemical cascades that participate in hyperglycemia-induced cellular injury. These pathways include the creation of advanced glycation end products (AGEs) and the activation of the hexosamine pathway, the polyol pathway, and protein kinase C [98, 99]. Hyperglycemia-induced apoptosis is stimulated by these end-products, namely ROS, PARP, AGEs and aldose reductase. Hyperglycemia also contributes to altered cardiac structure and

function through post-translational modification of extra-cellular matrix proteins (e.g. collagens) and altered expression/function of intramyocellular calcium channels (e.g. the ryanodine receptor and sarcoplasmic reticulum Ca^{2+}-ATPase) which contribute to both systolic and diastolic dysfunction [99]. In these ways, both glucotoxicity and lipotoxicity, each manifestations of insulin-resistance, participate in the pathogenesis of the clinical entity known commonly as the diabetic cardiomyopathy.

Obesity and Heart Failure- a Clinical Perspective

Although there is a wealth of mechanistic data linking adipose tissue biology and insulin resistance with cardiomyopathy, it can be clinically difficult to differentiate heart failure (HF) symptoms arising from cardiac limitations from other etiologies in the obese patient. The Framingham Criteria set the gold standard for the diagnosis of HF, but these criteria have not been validated in the obese population. Nevertheless, there is a robust literature supporting obesity as an independent risk factor for the development of clinical HF [100-102]. This relationship persists even after controlling for the obvious confounders, such as T2DM, hypertension and coronary atherosclerosis. In a seminal study in the field, Kenchaiah *et al,* reporting on the Framingham cohort, estimated the 10-year age-adjusted risk of HF at ~7% in women and 10% in men with BMI≥30 [103]. The hazard ratio was even higher among patients with more severe degrees of obesity.

Despite the clinical data supporting the relationship between increasing adiposity and the development of HF, the structural and mechanistic underpinnings behind this association remain largely unresolved. In particular, while it is known that obesity is associated with HF events, it is unknown whether such patients have abnormal ventricular morphology [e.g. concentric left ventricular hypertrophy (LVH) or LV dilation] as an anatomic correlate at the time of their HF events are diagnosed. In general, however, cardiac hypertrophy and diastolic abnormalities are commonly seen in patients with obesity [104-107]. This begs the question as to why then some obese patients develop HF in the face of these structural changes and others do not. It may be that in some patients the observed LVH is compensatory (i.e. eccentric from increased stroke volume), while in others, it is pathologic (i.e. concentric thickening); careful morphologic studies in obese patients with and without HF are needed to determine which mechanism is at work in this context.

Whether isolated obesity (i.e. the “metabolically healthy obese individual”) [108] is associated with pathologic LVH independent of T2DM and hypertension is a matter of debate [104-107]. For instance, the potential association between obesity and *subclinical* hypertension, impaired glucose tolerance and sleep apnea, highlights the difficulties in using large databases in studying LVH in cohorts of otherwise healthy obese patients. Detailed studies to date have been relatively small in scope and cross-sectional in nature. This has limited our ability to unambiguously assign a causal role to obesity *per se* in promoting LVH. Indeed, many of these studies have reached contradictory conclusions.

A related question is whether it is total adiposity that is the driving force, or whether site-specific fat depots are related to HF and LV structural changes. Different depots are known to have distinct biological activities. In particular, VAT and SAT are thought to exert rather distinct physiological effects, and it is possible that the purported association between obesity and LV structure/functional is mediated primarily through the differential impact that these subtypes of fat pads exert. This hypothesis remains to be formally tested in the context of HF. We appreciate that VAT releases more inflammatory cytokines and less adiponectin than SAT, which is consistent with findings from cross-sectional studies concerning the relationship between adipokines and prevalent LVH.

Amongst all the adipokines, the association between circulating adiponectin and LVH is the best studied. Several groups have shown that lower adiponectin levels correlate with higher LV mass, even after controlling for insulin-sensitivity and BMI [109-111]. A report from the Jackson Heart Study suggested that adiponectin had a more complex relationship with LVH among African Americans, i.e. the directionality of its association depended on the presence or absence of hypertension and insulin-resistance [112]. Animal models are supportive of adiponectin's influence on LVH. In mice lacking adiponectin, an exaggerated cardiac hypertrophic response to pressure-overload is seen but can be blunted with adenoviral-mediated restoration of adiponectin levels [113]. This suggests that adiponectin is important in modulating cardiac hypertrophy, perhaps through an AMPK or ceramidase-mediated mechanism [25].

The relationship between both resistin [110] and leptin [114, 115] with LVH is less well explored. The existing studies, while they have methodological limitations, suggest that there is some association between elevated resistin and leptin levels with LVH. However, the mechanistic underpinnings behind these associations are still a matter of investigation. The biological effects of leptin on cardiac hypertrophy in animal models have been conflicting, with either pro- [116] or anti-hypertrophic [117] responses being observed. In the case of resistin, adenovirally-mediated cardiac-specific overexpression does result in LVH through several signaling pathways (e.g. mTOR) [118], but it is unclear how well these observations translate into the clinical setting.

To date, reports on the association between adipokines and LV structure have been cross-sectional in nature, but suggest that markers of adiposity (e.g. high leptin, low adiponectin) and inflammation (e.g. high resistin, low adiponectin) are related to the presence of hypertrophy. Since the levels of most adipokines tend to be reasonably well correlated with one another, either directly or inversely, it is not necessarily clear whether each adipokine is independently informative or simply reflective of confounding from another biomarker unadjusted for in the modeling. Potential mechanistic pathways to explain adipokines as primary drivers of LVH in animal models have been suggested. However, with prospective studies largely lacking in humans, it is perhaps still premature to assign causality between adipokines and LV structural changes. Such studies are also needed to understand whether long-term favorable changes in circulating adipokine profiles may be associated with actual regression of LV mass.

In terms of clinical HF, the role of adipokines has been explored in several large cohort studies. Although adiponectin has been associated with LVH, it has not been independently associated with the development of HF, *per se* [119]. Studies of leptin have led to conflicting results [120, 121], perhaps because leptin is so tightly correlated with adiposity and its statistical relationship with BMI difficult to separate. Longitudinal follow-up from the MESA study group reported that the effect of obesity on HF events could be explained by CRP and IL-6 levels, suggesting that inflammatory adipokines may be mediating this clinical association [122]. Similarly, resistin has been independently associated with incident HF events in the Framingham cohort [119]. The mechanisms by which these inflammatory mediators may be promoting HF is unclear, but these data are suggestive that accumulation of the pro-inflammatory VAT may a key driving force for the development of obesity-related HF and pathologic LVH.

Adiposity, insulin resistance and cardiac steatosis

Intramyocardial triglyceride (mTG) accumulation is a prominent feature of several models of cardiomyopathy generated from interruption of normal cardiac FFA metabolism. Examples include, transgenic overexpression of fatty acyl-CoA synthetase [123], lipoprotein lipase [124], acyl CoA:diacylglycerol acyltransferase (DGAT) [125], and PPAR-α [126] and –

γ [127]. In general, these models of lipotoxic cardiomyopathy involve increased FFA flux or delivery to the heart, and highlight the potential for adipose tissue, the source of most circulating FFAs derived from lipolysis, to impact cardiac metabolism from the distance by influencing serum concentrations of these substrates.

Adiposity also promotes myocardial steatosis by promoting insulin-resistance, which occurs on a whole-body, as well as cardiac-specific level. Murine models of diabetic cardiomyopathy accumulate significant amounts of mTG [126, 128, 129]. This can be reversed by cardiac-specific restoration of insulin sensitivity. Recent work has highlighted the critical role of FoxO transcription factors, specifically FoxO1, in a pathway linking insulin signaling to the development of cardiomyopathy [93]. Whereas high-fat diet induces a severe cardiomyopathic phenotype with prominent myocardial steatosis in mice, this can be completely abrogated with cardiac-specific *FoxO1* deletion. Without FoxO1, signaling downstream from the insulin receptor, which becomes disrupted after chronic high fat feeding, is once again restored and cardiac insulin-sensitivity is improved. This results in normalization of cardiac glucose uptake, metabolic enzyme profiles, and steatosis. These data highlight that mTG may accumulate as a consequence of local increases in FFA delivery to the heart or alterations in either global or cardiac-specific insulin-sensitivity.

In humans, mTG accumulation is also well documented and appears to occur in two major clinical contexts: (1) obesity/insulin resistance and (2) LV failure (*see below*). It should be recognized, however, that mTG changes observed in the diseased human heart are somewhat less dramatic than may be seen in transgenic animal models. Whereas a patient with T2DM may have 1-1.5% mTG (compared with 0-0.5% in controls), the long-chain acyl-CoA synthetase overexpressing mouse displays a dramatic 12-fold increase in mTG [123] and high-fat diet alone induces a 4-fold increase in mTG [93]. Furthermore, fat accumulation in the heart is approximately an order of magnitude lower than in the liver, which is also known to accumulate fat under similar metabolic challenges.

Given the practical limitations of acquiring cardiac tissue specimens in non-transplant settings, proton magnetic resonance spectroscopy (^{1}H-MRS) has emerged as a useful tool to non-invasively quantify the degree of myocardial steatosis. ^{1}H-MRS has been successfully employed, on a larger scale for measuring hepatic fat [130], and TG quantification for both the liver [131, 132] and heart [133] correlate well with that obtained from biopsy. Several studies have demonstrated that mTG levels are influenced by total adiposity. However, there is a clear further increase once insulin- resistance occurs [134]. Interestingly, there is no close correlation between the degree of cardiac and hepatic fat although visceral fat is an independent predictor of mTG after multivariate modeling [134]. Likewise, circulating FFA levels are linked to both hepatic and cardiac TG accumulation. Adiponectin levels also correlate with cardiac steatosis (though it is unclear whether this effect is independent of insulin-sensitivity) [135]. Taken together, these observations also suggest that, similar to the relationship between LVH and obesity, the accumulation of VAT may be the primary upstream culprit to accumulation of mTG by virtue of its ability to influence on circulating adipokines, lipolysis and global insulin-sensitivity.

The clinical effects of cardiac steatosis have not been well defined, particularly in the setting of normal LV function. This is largely because of the few patients studied to date, and lack of long-term follow-up. Rijewijk *et al* demonstrated the degree mTG to be an independent predictor of diastolic dysfunction among a cohort of patients with relatively well-controlled T2DM (HbA1c <8.5%) [136]. Similarly, another recent study, again in patients with well-controlled T2DM, demonstrated an inverse relationship between mean diastolic strain rate as assessed by MRI and mTG levels [137]. These observations could be clinically meaningful and may suggest a possible direct effect of mTG towards impaired diastolic function. However,

it could also reflect effects of confounding factors associated with co-morbities. Importantly, the largest study reported to date on patients with T2DM (enrolled across a wide range of varying glycemic control) failed to demonstrate any relationship between the degree of mTG and diastolic function [138]. Hence, the clinical implications of cardiac steatosis in the setting of insulin resistance, independent of other comorbid factors, remains ambiguous but certainly represents a relevant area for further study.

Adipose tissue function and the failing ventricle

Curiously, although obesity is an independent risk factor for the development of clinical HF, it consistently appears to be associated with improved prognosis in the setting of existing HF [139-142]. This is referred to as the "obesity paradox" of HF, and we completely lack a mechanistic basis for an explanation. This implies that adipose tissue either directly or indirectly promotes survival of cardiac myocytes. Alternatively, the lack of adipose tissue (i.e. the inability to maintain a stable BMI) is associated with a deficiency of a factor, lack of which leads to a worsened clinical outcome. It is clear though that this not simply due to protection from cardiac cachexia that is frequently seen at the opposite end of the BMI spectrum. To be sure, however, BMI itself may be an inadequate measure of nutritional status, and even HF patients with high BMI may manifest hypoalbuminemia [143].

HF is well known to result in neurohormonal activation. As such, circulating levels of catecholamines and natriuretic peptides are increased. These hormones act to drive TG hydrolysis from fat and raise systemic FFAs [144, 145]. Levels of FFAs are significantly elevated in HF patients [146, 147]. This is, at least in part, due to the altered neurohormonal environment, as well as a consequence to the associated increase in cytokines and the accompanying insulin resistance associated with HF. Such dramatic elevations in circulating FFAs have unquestionably important implications for myocardial metabolism, given the general affinity of the heart towards FFA uptake and the well-described impairments of substrate oxidation in the failing ventricle [148].

Beyond the changes in FFAs, adipokine levels are also significantly altered in HF patients. Adiponectin is perhaps the best-studied marker in this context. Levels of adiponectin increase in a step-wise fashion with worsening scores in the New York Heart Association (NYHA) functional classification system. Higher plasma adiponectin concentrations are associated with higher mortality [149-152]. This finding, that we refer to as the "adiponectin paradox" associated with HF, has been reproduced in several different populations. This observation seems to defy any easy explanations based on what we know about adiponectin action, particularly in light of the generally positive functions ascribed to adiponectin in terms of metabolism and cardioprotection. After left ventricular assist device (LVAD) support, elevated adiponectin levels have been reported to drop dramatically, in parallel with a lowering of systemic and adipose-specific markers of inflammation, as well as improvements in insulin sensitivity [153]. It is possible that adiponectin is increased in this setting due to a state of "adiponectin-resistance." Interestingly, however, LVAD support is also associated with a reduction in key mediators of lipolysis, such as natriuretic peptides [154-156]. This also correlates with increases in adipocyte size (i.e. cross-sectional area) [153]. While this suggests that systemic adiponectin levels may be passively coupled to the degree of TG hydrolysis and FFA release from adipose tissue, more recent data in rodent models argues against this explanation [157]. Additionally, adiponectin has well-described effects on metabolism of lipotoxic intermediates [25, 158], so the dramatic increases in circulating adiponectin concentrations may be an active response to HF-induced lipolysis. Supporting this paradigm is the close correlation between BNP levels and adiponectin [152], and the finding that natriuretic peptides can directly promote adiponectin expression/release from the adipocyte [159, 160]. Finally, although adipose is the major source of adiponectin, it has been reported that the heart may be a source of this cytokine, as well [143, 161, 162].

Although an attractive potential explanation for the elevations seen with HF, the available human data have not demonstrated any increased adiponectin production during LV failure [163, 153].

The levels of both leptin [164, 165] and resistin [165] are also increased in HF patients, but, in distinction to adiponectin, levels of these adipokines do not change following mechanical unloading with LVAD support [153]. The increase in serum leptin levels with HF appears to be independent of weight. Cardiac expression of leptin receptor mRNA and protein levels is upregulated in HF, and both levels drop with LVAD support [166]. In parallel, there is an observed decrease in both STAT3 and AMPK-activation following LVAD treatment. Although the exact role and relative importance of leptin signaling in the failing heart is largely unknown, these findings suggest that there is likely some further important biology to be discovered in this area.

As seen in the insulin-resistant state (which includes HF), the failing human heart also accumulates mTG. Although it is again unclear whether the lipid accumulation is "lipotoxic" *per se*, intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart [167]. This can be *partially* reversed following mechanical unloading. In particular, ceramides, which have well-described pro-apoptotic effects, but not total mTG or fatty acids, have been shown to significantly fall with LVAD [168]. Thus, myocardial lipid overload in the setting of HF appears to be derived from a surplus of FFAs delivered from adipose tissue hydrolysis and a superimposed inability of the failing heart to oxidize the substrate. Improvement in HF, e.g. following LVAD, likely improves lipid-overload by decreasing the lipolytic drive at the level of adipose, although this hypothesis remains to be directly tested.

The Obesity Paradox

Increasing adiposity is unquestionably associated with the aggregation of multiple risk factors for HF and vascular disease. However, obesity is associated with an improved survival following the diagnosis of these CVD conditions. Specifically, evidence of the "obesity paradox" has been observed in chronic [163, 169-171] and acute [172, 173] coronary heart disease, stroke [172, 174, 175], and peripheral vascular disease [176], in addition to HF noted above. This paradox is more generally referred to as an example of "reverse epidemiology," a somewhat misleading term referring to the apparent reversal of classic associations of risk factors with disease outcomes.

A variety of explanations have been offered for these observations. Some of these seek to explain the obesity paradox as an artifact- e.g. due to residual confounding at the statistical level [176], due to differences in treatments/management strategies by BMI grouping [177], survival bias, or the fact that obesity patients may become symptomatic earlier in their disease course and present earlier (e.g. lead time bias). Furthermore, it has been suggested, that at least for acute coronary syndromes, the absolute amount of additional prognostic information offered by BMI is small once statistically accounting for other more clinically relevant risk variables [178]. Lead time bias, as well as the potential for misclassification of HF symptoms in the obese due to ambiguity of the Framingham criteria in this clinical context (i.e. diagnostic bias) may certainly be potential contributors to the observation of the obesity paradox of HF. However, there is a strong evidence base that "reverse epidemiology" (i.e. the counterintuitive protection observed for obesity and high cholesterol and the corresponding association with greater survival) is a real biological phenomenon. The dramatic changes in circulating adipokine profiles, lipolytic signals, insulin-sensitivity, and FFAs highlight the interplay between adipose tissue and the failing heart. How the adipose may be protective under these circumstances remains ambiguous.

Clearly, it is difficult to reconcile how obesity may on one hand promote CVD and on the other be protective once it has been diagnosed. This paradox has rightly caused some consternation among physicians, as it has become unclear whether, once controlling risk factors for disease progression, weight loss should specifically be encouraged [178, 179]. Ultimately, clinical trials aimed specifically at such lifestyle interventions will be needed to address this critical question prospectively and definitively.

Outstanding Questions and Future Directions

Over the last several years, there has been an exponential increase in our understanding of adipose biology and its relevance to the CVD. Nonetheless, there are still many unanswered questions in this field. One of the most puzzling, mentioned previously, is that of the obesity paradox. How can adipose both increase the risk of CVD risk factors, and yet be protective once CVD develops? Is this phenomenon mediated through adipokines or differential SAT/VAT masses?

Much needs to be explored in the context of adipokine biology and the failing heart. Are adipokine- and insulin-resistances at the myocardial level occurring and are they a cause or consequence of HF? What is the etiology of the “adiponectin paradox” and what is the role of adiponectin in the context of HF, i.e. is it a bystander or an active counter-regulatory hormone designed to offset the insulin-resistance and lipotoxicity which accompany HF? Furthermore, we do not completely understand what the drivers of the significantly elevated adiponectin levels in HF are. PPAR-γ and C/EBPα are the two major drivers of adiponectin expression in adipose tissue but whether their activities are increased in adipose during HF is not clear. Similarly, there are additional secretagogues for adiponectin, in addition to the natriuretic peptides, e.g. FGF21; whether such circulating factors are important in driving adiponectin release from fat needs to be elucidated further.

Leptin has been extensively studied in many contexts, but our understanding of its influences on the heart is still incomplete. The direct actions of leptin in the hypothalamus can reverse hepatic insulin resistance [180], and it is fascinatingly possible that central influences of adipokines may have indirect effects on the cardiovascular system and the failing heart (i.e. mediated through actions in the brain).

Finally, much has been written about myocardial lipotoxicity, but the clinical effects of mTG accumulation in humans are not clear. Data from transgenic murine models make a strong case for the detrimental effects of local accumulation of lipotoxic intermediates. These models include the overexpression of DGAT[181], PPAR-γ overexpressing hearts in the background of PPAR-$\alpha^{-/-}$ [182], long-chain acyl-CoA synthetase overexpression [123] or the increased presence of lipoprotein lipase on cardiac myocytes [124]. No systematic analysis has been performed across all these mouse models to help us understand what specific species of lipid metabolites are toxic. Detailed analysis of intramyocardial fatty acids, ceramides, diacylglycerols and acylcarnitines from human samples will be informative here but may inevitably need to be coupled with metabolic fatty acid flux data to assure proper interpretation [183]. These unanswered questions are important since the accumulation of mTG alone is not sufficient[181,182] and may, in fact, be protective. In other word, it may not only be absolute levels of these lipotoxic species that drive local insulin resistance, inflammation and propensity to cell death, but rather the subcellular distribution of the lipids that matters the most. Finally, whether these phenomena related to cardiomyocyte dysfunction a cause or an effect of HF also remains to be seen with refined time course studies.

Conclusions

It is apparent that adipose tissue has a role beyond serving as a mere storage compartment of TGs. When dysfunctional, it exerts a negative impact on all other tissues by creating a much more lipotoxic environment in peripheral tissues, including the heart. Combined with ensuing insulin resistance and a dysregulation of key adipokines, it is at the core of systemic metabolic dysfunction, with the cardiovascular system representing the key organ system affected. This suggests that therapeutic interventions early in the progression to cardiovascular disease need to target specific metabolic and structural derangements, particularly at the level of adipose tissue. This will require an improved understanding of adipokine biology, hypothalamic control of organ homeostasis, potently influenced by adipokines, and direct effects of these adipokines on cardiovascular metabolism (Fig. 1).

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Non-standard Abbreviations

CVD	cardiovascular disease
FFA	free fatty acid
LVAD	left ventricular assist device
LVH	left ventricular hypertrophy
LV	left ventricle/ventricular
mTG	myocardial triglyceride
SAT	subcutaneous adipose tissue
T2DM	type 2 diabetes mellitus
TG	triglyceride
VAT	visceral adipose tissue

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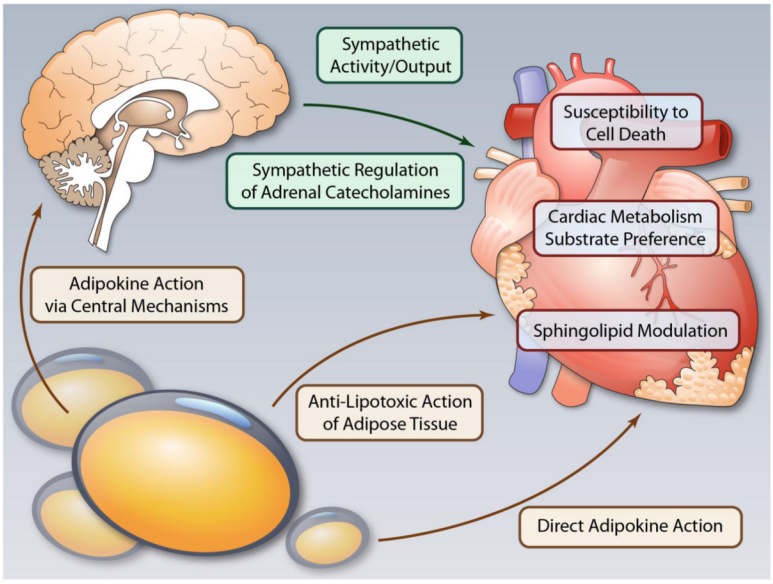

Fig.1.

The cardiovascular system is influenced by adipose tissue, not just through effects on systemic insulin-sensitivity but also through direct and indirect effects of adipokines. Adipokines have effects on the central nervous system, which in turn, influence sympathetic outflow, peripheral metabolism, and (at least in the liver) organ steatosis. Better understood are the direct effects of adipokines on the heart, which may influence substrate metabolism, detoxify lipid intermediates, and promote cell-survival. (Ilustration Credit: Ben Smith).