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Obesity-induced Changes in Adipose Tissue Microenvironment and Their Impact on Cardiovascular Disease

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Abstract

Obesity is causally linked with the development of cardiovascular disorders. Accumulating evidence indicates that cardiovascular disease is the “collateral damage” of obesity-driven adipose tissue dysfunction that promotes a chronic inflammatory state within the organism. Adipose tissues secrete bioactive substances, referred to as adipokines, which largely function as modulators of inflammation. The microenvironment of adipose tissue will affect the adipokine secretome, having actions on remote tissues. Obesity typically leads to the upregulation of pro-inflammatory adipokines and the downregulation of anti-inflammatory adipokines, thereby contributing to the pathogenesis of cardiovascular diseases. In this review, we focus on the microenvironment of adipose tissue and how it influences cardiovascular disorders, including atherosclerosis and ischemic heart diseases, through the systemic actions of adipokines.

Keywords

Obesity; Adipokine; Adipose Tissue; Atherosclerosis; Myocardial Infarction

INTRODUCTION

The prevalence of obesity, defined as a body mass index ≥ 30kg/m^2, is now recognized worldwide as a major health problem, reaching epidemic proportions probably as a consequence of changes in food composition and exacerbated by sedentary lifestyles in Western societies[1–3]. Large epidemiological studies have conclusively demonstrated that obesity is associated with increased mortality mostly due to augmented risk of cardiovascular (CV) death[4]. Moreover, the increasing prevalence of obesity is changing the etiology of cardiovascular diseases (CVD), which in many individuals can be viewed as the consequence of dysfunctional changes within the adipose tissues. Obesity induces a complex remodeling of adipose tissue, which expands to accommodate the excessive caloric intake and markedly changes its structure and cellular composition. It is widely accepted that this

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Conflict of Interest

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obesity-associated remodeling generates a systemic pro-inflammatory state, which is mediated by an imbalanced production of adipocyte-derived cytokines (adipokines) that directly and indirectly affect the CV system. In this Review article, we summarize the pathophysiological mechanisms underlying adipose tissue remodeling and dysfunction in obese individuals, and how this affects the production of adipokines and ultimately contributes to CVD.

Adiposopathy, regional adiposity and CV risk

While adipose tissue quantity (volume) is undoubtedly linked to CV risk, recent human data indicate that differences in fat tissue "quality", which can be examined directly by immunohistochemistry or non-invasively by computed tomography (CT) radiodensity attenuation imaging, are closely linked to insulin resistance, cardiometabolic risk and all-cause mortality, independent of total fat volume[5–8]. These data demonstrate that abnormalities at the adipose tissue level may be key factors that regulate systemic metabolism and drive cardiometabolic disease (CMD), independent of body mass index. These qualitative abnormalities in fat, which have been recently termed 'adiposopathy' or "sick fat"[9], are a growing area of research interest and may in part explain the clinical observation of metabolically healthy obesity. While animal models of obesity tend to generate fairly uniform phenotypes, the degree of adipose tissue dysfunction in obese humans exhibits significant heterogeneity with lower degrees of adiposopathy being associated with more favorable systemic metabolic profiles and vascular function[8, 10–13]. This inter-individual variability in adipose tissue 'quality' may be related, in part, to differences in lifestyle, as physical activity has effects on adipose tissue physiology and CMD risk[14, 15].

Differences in adipose tissue 'quality' are also closely linked with the observation that distinct fat depots have different impacts on the propensity to develop CMD. Numerous clinical studies using adiposity measures such as waist circumference and waist-to-hip ratio as markers of central obesity as well as cross-sectional abdominal imaging, have established clear links between overall fat burden and systemic CMD, with generally stronger associations for visceral adiposity[7, 8, 16–26]. It is now recognized that expansion of visceral fat is strongly associated with increased cardiometabolic risk[8, 16, 17, 26–29], whereas expansion of subcutaneous fat has a minor contribution or, in some cases, even decreases the risk of metabolic dysfunction[16, 17, 30, 31]. Thus, it has been hypothesized that visceral fat exhibits lower 'quality" than subcutaneous depots, exhibiting specific properties that are linked to a higher cardiometabolic risk. Subcutaneous fat comprises approximately 80% of total body fat mass, while abdominal visceral adipose tissue accounts for 5–20%[32]. Despite visceral fat not being the predominate white adipose tissue (WAT) depot, inflammatory markers including IL-6, CRP, and TNF-α tend to circulate at higher concentrations in subjects with abdominal compared with peripheral obesity[33–36], and visceral fat has been shown to be a significant source of circulating FFA and IL-6 levels[37, 38]. Although arterial disease tends to worsen with increasing overall weight burden in adults and children[18, 39], CT or MRI studies of fat compartments identify visceral fat volume to be more highly associated with systemic endothelial dysfunction compared to subcutaneous fat[20, 21]. In addition, gene expression analyses of human specimens suggest a more atherogenic gene

expression profile in visceral fat, characterized by greater expression of pro-inflammatory, oxidative stress-related and anti-angiogenic genes[40–46]. Visceral and subcutaneous adipose depots arise from different origins during development[47, 48], and this may in part explain the propensity for visceral fat to develop differing metabolic, inflammatory, angiogenic, and lipolytic properties that contribute to CMD compared to subcutaneous.

In addition to the subcutaneous and visceral fat depots, adipocytes are associated with many organs and tissues including heart, kidney and bone marrow and the degree of adiposity can vary with obesity and aging (Figure 1). Recently, the possibility of functionally significant brown adipose tissue (BAT) depots in adults has become of interest. BAT is primarily located beneath the clavicle, and it has a thermogenic function and it oxidizes rather than stores fat. Historically, BAT received little attention because it was thought to exist only in human infants, rodents, etc. to maintain body temperature. However, it is now recognized that some adults contain appreciable levels of BAT, and that its oxidative function declines with obesity and advanced age[49, 50]. Intriguingly, rodent studies have suggested that BAT may contribute significantly to overall systemic metabolic control due to its potentially high oxidative capacity[51]. Compared to WAT, BAT contains abundant mitochondria that are uncoupled, due to the expression of UCP1, and highly vascularized to accommodate the greater demand for oxygen. Interestingly, the phenotype of perivascular adipose tissue (PVAT), that surrounds the major blood vessels, appears to be intermediate between that of WAT and BAT, and its degree of “browning” varies in different vascular beds[52–55]. These morphological differences between PVAT depots suggest that it may contribute to the phenotypic variability between distinct vascular regions and their different susceptibility to atherosclerosis and other vascular disorders. In this regard, it is conceivable that differences in adipokine section by these various adipose tissue depots can selectively affect organ function via paracrine mechanisms.

CHANGES IN THE MICROENVIRONMENT OF THE ADIPOSE TISSUE ASSOCIATED WITH OBESITY

Adiposopathy in obese individuals is ultimately the consequence of a dysfunctional remodeling of the adipose tissue. Therefore, understanding both quantitative and qualitative aspects of this adipose tissue remodeling is of utmost importance to comprehend how obesity contributes to CVD.

Adipose tissue expansion

The mechanisms by which adipose depots expand in response to an excessive caloric intake represent a crucial determinant of the risk of metabolic dysfunction and CVD. This expansion is mediated by an increase in adipocyte numbers (hyperplasia) and/or an enlargement of adipocyte size (hypertrophy). It has been classically accepted that hyperplasia allows a “healthy” expansion of the adipose tissue, since it is mediated by the formation of functional adipocytes from progenitor cells (adipogenesis). In contrast, adipocyte hypertrophy typically leads to lipid-laden, dysfunctional adipocytes that undergo cell death and contribute to adipose tissue inflammation, dysfunction and associated pathologies. As discussed above, different adipose tissue depots contribute differentially to

disease processes, and this may be connected to a dysfunctional expansion of the different fat depots. It has been proposed that subcutaneous fat in many human individuals exhibits limited expandability due to a deficient adipogenic capacity, which leads to subcutaneous adipocyte enlargement (hypertrophic obesity) and ultimately promotes the storage of fat in visceral and other ectopic depots[56]. In this regard, it is noteworthy that several genetic modifications have been shown to improve insulin sensitivity in obese mice by inducing subcutaneous adipose tissue expansion without increasing adipocyte size[57, 58], highlighting the therapeutic potential of strategies aimed at promoting adipogenic/hyperplastic growth of subcutaneous fat as a mean of preventing the metabolic and CV complications of obesity.

Recent studies with a mouse strain that allows adipocyte tracing *in vivo* (AdipoChaser mice) have provided detailed insight into the mechanism and dynamics of adipose tissue expansion in obese mice[59]. These studies showed that visceral adipose tissue expansion in diet-induced obese mice is initially mediated by adipocyte hypertrophy, which is followed by a massive increase in adipogenesis after prolonged high-fat diet (i.e., 2 months). In contrast, subcutaneous adipose tissue expansion was shown to be mostly mediated by adipocyte hypertrophy, with minimal *de novo* adipogenesis regardless of the time of HFD exposure. Hence, at least in this depot, mouse models may mimic the conditions of human hypertrophic obesity. However, while these studies represent excellent examples of the application of mouse genetics to cardiometabolic research, they must be interpreted with caution given the many differences between the different mouse and human adipose tissue depots. For example, while in humans the prototypical visceral depot is omental fat, this depot is essentially absent in mice. Conversely, perigonadal fat is the most typical visceral depot in mice, but it does not have a truly equivalent depot in humans, and does not drain blood into the portal circulation, in contrast to human visceral depots. Thus, the extent to which the dynamics of fat depot expansion in mice mimics the processes involved in human obesity are unclear.

Immune cell infiltration

Regardless of the mechanisms of adipose tissue expansion, in most cases chronic excessive caloric intake eventually leads to adipocyte dysfunction, and this is paralleled by quantitative and qualitative changes in the cellular composition of adipose tissue. Immune cells are of particular relevance in this regard. Chronic, low-grade inflammation is a major hallmark of the obese adipose tissue, and it is now known that, at least in mice, almost every immune cell type can be found in the adipose tissue under one experimental condition or another. Total numbers of T cells, B cells, macrophages, neutrophils, and mast cells are increased in visceral adipose tissue of obese individuals and/or dietary obese mice. In contrast, the number of eosinophils and specific subsets of T cells – T helper type 2 (Th2) cells, regulatory T (Treg) cells – remain static or are decreased in the obese adipose tissue[60].

Macrophages are the most abundant immune cell in the adipose tissue of obese individuals, and their recruitment and proliferation upon high calorie feeding is generally associated with adipose tissue inflammation and insulin resistance[61–63]. In addition, the phenotype of adipose tissue macrophages (ATMs) is markedly different in obese and lean mice. Macrophages resident in the adipose tissue of lean organisms tend to express genes

associated with a M2-like or “alternatively activated” phenotype (e.g. the mannose receptor CD206), whereas ATMs in obese organisms typically express genes associated with a M1-like or “classically activated” phenotype (e.g. CD11c)[64]. The M1/M2 concept is an artificial binary classification of the inflammatory status of macrophage, and it should be noted that *in vivo* macrophages exist along the M1/M2 spectrum and frequently have mixed phenotypes. This is particularly evident in ATMs, which frequently exhibit a complex phenotype due to the simultaneous exposure to a variety of stimuli[65–67]. In spite of this, the M1/M2-like dichotomy is a useful starting point to understand the biology of ATMs. Stimulation with T helper 1 (Th1)-type cytokines, including interferon-γ induces an M1 phenotype in macrophages, that leads to increased production of pro-inflammatory cytokines, such as TNF-α, and higher levels of reactive oxygen and nitrogen intermediates. This class of macrophages is typically associated with inflammation and tissue destruction. On the other hand, stimulation with Th2-type cytokines (e.g. IL-4, IL-13) leads to M2 macrophages, which preferentially express anti-inflammatory cytokines, such as IL-10, and are typically associated with wound healing, angiogenesis and the resolution of inflammation. It is believed that M1-like macrophages promote insulin resistance, whereas M2-like macrophages protect against obesity-induced adipose tissue inflammation and insulin resistance[68]. Supporting this notion, ablation of CD11c-positive, M1-like cells normalizes insulin sensitivity in obese mice[69]. Consistently, an increased content of CD11c-positive macrophages has been associated with insulin resistance in obese human individuals[70]. The mechanisms accountable for ATM phenotypic shifting in obesity are still unclear, but are probably linked to changes in both immune cells in the adipose tissue[71–74] and myeloid progenitors in the bone marrow[75, 76]. The M2 phenotype of resident macrophages within the lean adipose tissue is believed to be maintained by the local production of Th2-type cytokines by eosinophils[71], and other immune cells abundant in the lean adipose tissue, such as $CD4^+$ $Foxp3^+$ Treg cells and T_H2-polarized T cells, that preserve adipose tissue function and insulin sensitivity[73, 77]. Under conditions of obesity, the accumulation of $CD8^+$ effector T cells and $CD4^+$ Th1 cells in the adipose tissue leads to a predominance of Th1 signals that promote the recruitment and M1-like activation of macrophages, contributing to adipose tissue inflammation[72, 73]. Pro-inflammatory cytokine production by effector T cells and Th1 cells is promoted by B cells recruited to the obese adipose tissue, which also contribute to M1 macrophage activation apparently through the production of pathogenic immunoglobulins[74]. Additional lymphocyte subsets such as Th17 or NKT cells may also play important roles in modulating macrophage phenotype and adipose tissue inflammation (reviewed in [78]).

In addition to quantitative and phenotypic changes, obesity also changes the location of macrophages within the adipose tissue. While ATMs are typically dispersed in lean individuals, in metabolically dysfunctional organisms they tend to accumulate in “crown-like” structures (CLS), defined as clusters of lipid-scavenging macrophages that surround free lipid droplets of dead adipocytes both in animal models and obese patients[79, 80] (Figure 2). Importantly, this condition appears to contribute to adipose tissue dysfunction, since the number of CLS correlates with adipose tissue inflammation and insulin resistance in metabolic syndrome patients[11, 79]. Consistently, obese subjects lacking CLS exhibit better

metabolic function, diminished inflammatory gene expression in adipose tissue, and reduced CV risk than body mass-matched individuals with CLS[11].

In addition to macrophages, other myeloid cells, such as neutrophils and mast cells, contribute to adipose tissue dysfunction in obesity. Neutrophils accumulate rapidly in the adipose tissue after HFD feeding[81–83], and they appear to promote macrophage recruitment and adipose tissue inflammation via neutrophil elastase secretion[82, 83]. Similarly, mast cells have been reported to accumulate in obese adipose tissue, and studies in mast-cell deficient mice suggest a role for this cell-type in obesity-associated metabolic dysfunction[84].

Impaired vascular structure and function

Several studies in humans and animal models have shown that obesity induces capillary rarefaction in adipose tissue, and this has been associated with metabolic dysfunction[40, 85–88]. Thus, it is widely accepted that obesity leads to reduced adipose tissue capillarization, which may limit nutrient delivery and contribute to adipocyte dysfunction and insulin resistance. Recent studies with genetically-engineered mice have provided evidence of a causal role of adipose tissue vascularization in obesity-associated metabolic dysfunction. Experiments with mice overexpressing vascular endothelial growth factor A (VEGF-A) in adipocytes show that increased VEGF-mediated angiogenesis in adipose tissue can attenuate some of the metabolic effects of diet-induced obesity, such as insulin resistance and hepatic steatosis[89–91]. Conversely, adipocyte-restricted deletion of VEGF-A results in diminished adipose tissue vascularization, which leads to increased adipose tissue inflammation and systemic metabolic dysfunction[51, 91], further supporting the noxious effects of reduced adipose tissue vascularity in obesity.

However, a major limitation of the above mentioned studies is that the current mouse genetic reagents generally do not permit depot-specific ablation or overexpression of candidate angiogenic regulators in adipose tissue. In this regard, a recent study compared the consequences of VEGF ablation (and obesity) on capillarization and hypoxia in WAT and BAT[51]. Whereas, VEGF-deficiency led to similar declines in capillarization in WAT and BAT, the effects on WAT dysfunction, assessed by measures of hypoxia, inflammation and mitochondrial status were marginal compared to the impact of VEGF ablation on these parameters in BAT. In contrast, VEGF deficiency in BAT led to robust mitochondrial dysfunction and loss, leading the tissue to take on a “whitened” phenotype due to the accumulation of lipid droplets. Notably, adenovirus-mediated delivery of VEGF to BAT could reverse the systemic metabolic effects of VEGF ablation. VEGF-mediated rescue of the vascular deficit in BAT can also improve metabolic parameters in models of diet-induced obesity[51, 92]. The differential effect of reduced capillarization in white versus BAT is consistent with the greater respiratory capacity of BAT, thereby increasing its tendency to undergo hypoxic stress in response to obesity or genetic VEGF ablation. While these data highlight the importance of angiogenesis in BAT with consequences on systemic metabolic function in the murine system, the question of whether the status of BAT can affect CVD processes should be evaluated by future studies. Furthermore, whereas it is well established that BAT activity contributes significantly to overall systemic metabolism in rodents[93], it is

not clear whether brown fat can serve a similar function in adult humans or whether it is a vestigial tissue.

Clinical studies have focused mainly on WAT and suggest that expanding fat may “outgrow” its blood supply possibly owing to deficient angiogenesis that triggers a cycle of ischemia, hypoxia, necrosis and inflammation within the adipose milieu[86, 87, 94, 95]. Capillary dropout and deficient vascularization develop in obese humans, particularly in visceral fat, and are associated with inflammation and whole body metabolic dysfunction[40, 86, 87, 95–97]. In contrast, subcutaneous fat exhibits higher capillary density and angiogenic capacity compared to the visceral depot[40, 90, 98–100]. Microarrays studies show significant differences in gene transcripts associated with angiogenesis between visceral and subcutaneous fat in obese humans[40]. Pro-angiogenic ANGPTL-4 is down-regulated in visceral fat and may play an important role[96]. Additionally, an anti-angiogenic splice variant of VEGF, VEGF-A_{165}b, is expressed at higher levels in human visceral fat compared to subcutaneous fat and is linked to impaired tissue angiogenesis[98]. Blood levels of VEGF-A_{165}b are elevated in obese compared to lean subjects and decrease after bariatric surgery weight loss. This observation has potential clinical implications as systemic upregulation of anti-angiogenic agents and other mediators in obesity raises the possibility of their contribution to vascular disease and ischemia beyond the adipose environment. In this regard, a possible role of VEGF-A_{165}b in mechanisms of peripheral arterial disease in animal models and humans was recently described[101]. It is thus becoming increasingly clear that qualitative features of adipose tissue, including its vascularity, could play an important role in the pathogenesis of obesity-induced cardiometabolic complications. However, whether modulation of adipose tissue angiogenesis in either white or brown fat could alter clinical consequences of human obesity remains an open question.

In addition to capillary rarefaction, obesity also leads to endothelial cell activation in the adipose tissue, which further contributes to the recruitment of immune cells. Endothelial cells within the adipose tissue of obese mice express higher levels of adhesion molecules such as P-selectin, E-selectin, and intercellular adhesion molecule 1 (ICAM-1). Moreover, administration of anti-ICAM-1 antibody to obese mice prevents macrophage infiltration into adipose tissue[102]. Collectively, these data illustrate the importance of a pathological interplay that can exist between adipose and vascular tissues. In fact, there is evidence from human studies that inflammatory cytokines over-expressed in fat impair vasoregulatory and anti-atherogenic properties leading to vasomotor dysfunction of the local microvasculature[41] as well as systemic vessels[11, 12, 41]. Clinical studies utilizing videomicroscopy and culture myograph techniques to study physiological properties of microvessels within human fat have demonstrated profound abnormalities in endothelial vasomotor dysfunction of obese individuals, particularly in visceral fat[41, 42, 103–110]. In experiments that examined paired subcutaneous and visceral adipose tissue biopsy samples from obese subjects during planned bariatric surgery, endothelium-dependent, acetylcholine-mediated vasodilation was severely impaired in visceral compared to subcutaneous arterioles[41]. The degree of vasomotor impairment is profound and consistent across varying systemic metabolic phenotypes and endothelial agonists such as bradykinin, shear stress and insulin[107]. Vessels from obese fat even exhibit paradoxical vasoconstriction, consistent with severe endothelial dysfunction[107]. In these vessels, responses to sodium nitroprusside and papaverine (endothelial-independent

vasodilators) are generally preserved, indicating functional impairment specifically at the level of the vascular endothelium early in the disease state. Complementary studies demonstrate impairment in eNOS phosphorylation at the activating site serine 1177 in vascular endothelial cells isolated from fat suggesting abnormalities in NO bioactivity as a significant contributing mechanism[42]. Adipose microvascular dysfunction appears specific to the obese state as arterioles isolated from visceral tissue of lean subjects exhibit preserved vasomotor function[109, 110] while extreme microenvironmental perturbations are observed in visceral obesity.

There are likely multiple mechanisms that negatively regulate vascular function in visceral fat. Cytokine-driven inflammation likely plays a key role, as the adipose secretome and transcriptome is markedly pro-inflammatory in visceral depots. Experimental studies in mice demonstrate that transplantation of inflamed visceral fat accelerates atherosclerosis in Apo-E knockout mice[111]. Adipose expression of inflammatory mediators correlates inversely with acetylcholine-mediated vasodilation of human microvessels[41, 42]. Endothelial cells isolated from visceral fat display enhanced expression of inflammatory mediators such as CCL-5, IL-6, TNF-α and TLR-4[41]. More direct evidence that inflammatory mechanisms are involved is provided by clinical studies that demonstrate vascular inflammation by histology and the reversal of microvascular dysfunction following treatment with IL-6 and TNF-α antagonists[106, 110]. However, other pathogenic processes that involve oxidative stress, mitochondrial dysfunction and endoplasmic-reticulum stress are likely to contribute to vascular diathesis. Recent data demonstrate evidence of impaired NO-dependent vasodilation, mitochondrial hyperpolarization, and increased mitochondrial superoxide production in the adipose tissue of type-2 diabetic subjects[108]. Moreover, increased expression of cyclooxygenase (COX)-mediated vasoconstrictor prostanoids might also contribute to endothelial dysfunction, supporting a role of the eicosanoid/cyclooxygenase pathway in obesity-linked disease[42]. Since the vasodilator responses and eNOS phosphorylation status in the adipose microvasculature have been shown to correlate with CV risk factors and systemic brachial arterial responses, further investigation into the vascular microenvironment of adipose tissue will likely provide translational clues relevant to systemic vascular disease mechanisms[103, 105, 112].

Adipose tissue fibrosis

Within the adipose tissue of lean organisms, adipocytes are surrounded by extracellular matrix (ECM) that provides mechanical support and participates in cell signaling. With the development of obesity, there is a general increase in the synthesis of several ECM components, in particular collagen VI, which leads to adipose tissue fibrosis and is associated with impaired metabolic function in mice[113]. In obese human individuals adipose tissue fibrosis is increased in both subcutaneous and visceral depots[114–116]. Obesity-induced adipose tissue fibrosis is due, at least in part, to hypoxia-induced upregulation of hypoxia-inducible factor 1α (HIF1α)[117, 118]. Interestingly, HIF1α activation does not contribute to an angiogenic response in this context, but instead promotes adipose tissue fibrosis. Mechanistically, the features that lead to these divergent tissue-specific actions of HIF1α are not understood. Recent studies are uncovering additional mechanisms that modulate adipose tissue fibrosis in obesity. Endotrophin, a cleavage product of the α3 subunit of collagen VI

that is secreted by adipocytes, has been shown to promote adipose tissue fibrosis and systemic metabolic dysfunction in obese mice[119]. In addition, PDGFRα signaling has been reported to oppose adipogenic differentiation of adipose tissue progenitors and to favor the generation of profibrotic cells that contribute to WAT fibrosis[120]. Whether profibrotic changes in adipose tissue contribute to the increased CV risk associated with obesity remains to be established. Thus, uncovering the causes and consequences of adipose tissue fibrosis is an area that deserves further attention.

ADIPOKINES AND CARDIOVASCULAR DISEASE

In addition to energy storage, adipose tissue is now recognized as an important factor in the regulation of many systemic, pathological processes through the secretion of multiple bioactive proteins referred to as adipokines. Although from a strict point of view these terms should be restricted to adipocyte-derived secreted proteins with immunomodulating actions, they are now widely used with a broader meaning to include any protein secreted by the adipose tissue – either by adipocyte or non-adipocyte cells- that is able to act as a modulator of immune, metabolic and/or CV functions. It is now widely accepted that dysfunctional adipose tissue remodeling leads to an unbalanced production of adipokines that contributes to the systemic pro-inflammatory state associated with obesity and has important adverse actions on the CV system[121, 122], particularly in the obese state where adipose tissue mass can range from 30% to more than 50% of total body mass. In addition to their direct effects on pathophysiological processes in the CV system, adipokines can affect CV risk indirectly by modulating metabolism in liver, skeletal muscle and heart (Figure 3). Adipokines can also promote insulin resistance in microvessels within the adipose tissue and in other vessels, contributing to endothelial dysfunction and thereby increasing CV risk. However, these indirect actions of adipokines will not be discussed in detail here.

Since the identification of adipsin in 1987[123], the list of adipokines has expanded vastly. Notably, the majority of adipokines are proinflammatory. Examples include leptin, TNFα, IL-6 and resistin. In contrast, relatively few adipokines are anti-inflammatory. Examples include adiponectin, omentin-1, CTRP9, and Sfrp5. Most adipokines have been identified in visceral and/or subcutaneous adipose tissue, which seem to produce different profiles of secreted proteins[46, 124–126], which may play a role in the above-discussed different contribution of these fat depots to cardiometabolic risk. However, in addition to these depots, the body exhibits other smaller fat depots in association with multiple organs, including heart, kidneys, bone marrow, lungs and blood vessels (Figure 1). In addition to conventional fat depots, ectopic lipid deposition in liver, skeletal muscle and heart occurs in metabolically dysfunctional organisms. Although the production of adipokines by spatially distinct fat depots has been less investigated in general, it must be noted that it could have important implications in CV and metabolic diseases since adipokines secreted by these depots may act in a localized manner to stimulate neighboring organs. Indeed, a mounting body of evidence coming from human and animal studies suggests that obesity modulates the phenotype of PVAT[52, 53] and that these changes directly influence vascular function and the development of vascular pathologies[127–134]. These studies open the question of whether increased CV risk associated with an adipokine imbalance is due to a paracrine mechanism, i.e. the local release of pro-inflammatory factors from epicardial adipose tissue and PVAT, or

an endocrine mechanism secondary to changes in serum adipokines levels. While both mechanisms probably contribute to obesity-associated CVD, mouse studies based on PVAT transplantation suggest that the anatomical location of PVAT is critical in some pathophysiological settings[127]. However, it remains to be established whether different PVAT depots, that display a varying degree of brown fat characteristics, exhibit distinct profiles of adipokine secretion. Furthermore, while the known adipokines are secreted by WAT depots, the role of BAT as a secretory organ remains largely unexplored.

CARDIOVASCULAR ACTIONS OF SELECT ADIPOKINES

Leptin

The adipokine leptin is an adipose tissue-specific secreted hormone encoded by the *ob* gene, which was identified in genetically obese ob/ob mice through positional cloning[135]. Leptin is highly expressed by adipocytes, and circulating leptin levels increase in parallel to adipose tissue mass[135]. Other tissues, such as the heart, have also been reported to express and secrete leptin to some extent[136]. Leptin exerts important metabolic actions by suppressing appetite and increasing energy expenditure[135]. Accordingly, leptin-deficient mice exhibit increased appetite and associated obesity and insulin resistance, which are reversed upon leptin administration[137, 138]. However, obese humans and rodents have elevated levels of leptin (hyperleptinemia) without the expected anorexic responses[137], suggesting that leptin resistance commonly occurs in obesity. Many lines of evidence suggest that hyperleptinemia contributes to CVD. Leptin has pro-inflammatory actions in many immune cell types including monocytes/macrophages[139–142], neutrophils[143], NK cells[144], and T cells[145, 146]. In addition, it exhibits several pro-atherogenic actions. For example, leptin increases ROS production in endothelial cells[147, 148]. In VSMCs it promotes the expression of MMP-2, a metalloproteinase linked to atherosclerotic plaque vulnerability[149]. In addition, leptin facilitates cholesterol accumulation in macrophages[150, 151].

Despite this body of evidence suggesting a pathogenic role for leptin in CVD, animal studies have given rise to inconsistent results regarding its role in atherosclerosis development. LDL-receptor knockout (LDLR-KO) mice that are also leptin-deficient develop more extensive atherosclerotic lesions than single LDLR-KO controls, likely due to the confounding effects of exacerbated insulin resistance and the general worsening of the circulating lipids profile caused by leptin deficiency-associated obesity and hyperphagia[152, 153]. Studies in apoE-KO mice, an atherosclerosis model that is less prone to obesity and insulin resistance[154], have also generated conflicting results. In one study, leptin deficiency was found to suppress atherosclerosis development in apoE-KO mice fed an atherogenic diet, supporting the pro-atherogenic role of leptin[155]. In contrast, apoE-KO mice lacking the long isoform of the leptin receptor have been reported to exhibit hastened atherosclerosis regardless of the type of dietary regime[156]. When considering these conflicting results, it must be noted that the interpretation of these studies is difficult due to the secondary metabolic defects that result from hyperphagia in mice deficient in leptin or the leptin receptor (e.g. hyperglycemia, hyperinsulinemia, and insulin resistance). To overcome this limitation and explore the consequences of hyperleptinemia in organisms with intact leptin signaling, some studies have investigated the effects of exogenous leptin

delivery on atherosclerosis development in non-obese mice. Supporting the pro-atherogenic role of leptin, two independent studies found that recombinant leptin administration aggravates atherosclerosis in apo-E-KO mice without affecting blood lipids levels[155, 157] and one study found that it strongly promotes plaque calcification[158]. Taleb et al. investigated atherosclerosis development in leptin-deficient, LDLR-KO mice and LDLR-KO controls matched according to circulating cholesterol levels to evaluate the actions of leptin independently of its anorexic and metabolic actions[159]. In this experimental setting, leptin-deficient mice exhibited markedly reduced atherosclerosis, coinciding with an attenuated Th1 immune response and improved Treg cell function. Overall, these results support the notion that leptin plays a major pathogenic, pro-inflammatory role in atherosclerosis. Importantly, many human studies support this hypothesis. Some studies have shown a significant correlation between circulating leptin levels and markers of subclinical atherosclerosis such as coronary artery calcification[160] and intima-media thickness of the common carotid artery[161, 162]. Similarly, several independent reports have shown that circulating leptin levels are a potent predictor of the risk of cardiac ischemic events[163_167]. However, this has not been replicated in other studies[168], and one study found markedly different results, reporting that low plasma leptin predicted CV mortality in women[169]. This latter report is in line with a number of experimental studies suggesting a cardioprotective role of leptin after MI, at least in part, through prevention of cardiomyocyte apoptosis[170_174]. Overall, most of the evidence from animal and human studies generally suggests a scenario where hyperleptinemia in obese individuals promotes atherosclerosis and thereby increases the risk of cardiac ischemic events, but also exerts some local protective actions in the cardiac tissue by attenuating tissue damage post-ischemia. Whether any of these protective actions are subjected to leptin resistance in obese individuals remains unanswered.

Interleukin 6

Interleukin 6 (IL-6) is a pleiotropic cytokine with complex roles in metabolic and CVD. IL-6 is known to be secreted by several tissues and can act in a local fashion. However, adipose tissue is a major source of this protein, capable of producing high levels of this protein in the blood. Therefore, IL-6 can be considered an adipokine with endocrine actions. It has been estimated that as much as one third of total circulating IL-6 originates from adipose tissue[175], where it can be secreted by both adipocytes and non-adipocyte cells, including pre-adipocytes and macrophages[124, 176, 177]. Importantly, expression and secretion of IL-6 are 2 to 3 times greater in visceral compared to subcutaneous adipose tissue in humans[124] and indexes of visceral adiposity associated with CV risk correlate with increased circulating levels of IL-6[33, 178].

IL-6-induced cell signaling is typically classified as either classic or trans-signaling, and it can lead to different cell responses. In classic signaling, IL-6 stimulates target cells via a membrane bound IL-6 receptor (IL6R), which upon ligand binding forms a complex with the signaling receptor protein gp130. Few cell types express membrane bound IL6R, whereas essentially all cells exhibit gp130 on the cell surface. While the cells that only express gp130 are not responsive to IL-6 alone, they can be stimulated, via trans-signaling,

by a complex of IL-6 bound to a naturally occurring soluble form of IL6R (sIL6R), markedly expanding the spectrum of IL-6 actions and target cells.

IL-6 has been widely accepted to act as a pro-inflammatory cytokine since the discovery of its critical role in mediating the hepatic acute phase response[179_181]. In addition, IL-6 has direct pro-inflammatory actions in a variety of immune and non-immune cell types, promoting the expression of adhesion molecules in endothelial cells and lymphocytes[182, 183], monocyte-to-macrophage differentiation[184], antibody production by B cells[185] and recruitment of T-cells to sites of injury[186]. In contrast, IL-6 has also been reported to exert regenerative and anti-inflammatory actions in some settings[187_189]. IL-6 also appears to play conflicting metabolic roles in different tissues, inducing insulin resistance in hepatocytes[190] and endothelial cells[191], but increasing insulin sensitivity in skeletal muscle under some conditions[191_193].

Similarly, the actions of IL-6 in the CV system are complex and incompletely understood. Human studies have provided compelling evidence supporting the notion that high circulating levels of IL-6 are associated with increased risk of coronary artery disease (CAD) and MI[194_197]. In addition, Mendelian randomization studies suggest that IL6R signaling contributes to the development of CAD[198, 199]. However, mouse studies cast some doubts onto the causative role of IL-6 in CVD, although these must be interpreted with caution given that mouse and human IL-6 proteins exhibit only 41% sequence identity. Early reports showed that chronic administration of supraphysiological doses of recombinant mouse IL-6 exacerbate atherosclerosis in apoE-KO mice[200]. However, systemic inactivation of IL-6 also results in larger atherosclerotic lesions in the apoE-KO model[201, 202] and does not seem to affect atherosclerotic plaque size in LDLR-KO mice[203]. These conflicting results could be due to compensatory activation of other IL-6 family proteins in IL-6-deficient mice. Alternatively, they may reflect the complex and multifaceted actions of this cytokine. In addition to its immunomodulatory actions, IL-6 may have some anti-atherogenic activities by preventing cholesterol deposition in the vessel through increased cholesterol efflux in macrophages[204] and HDL translocation through the endothelium[205]. Therefore, it is possible that IL-6 plays dual roles in atherogenesis, preventing early plaque formation via removal of cholesterol from the vessel wall, but promoting plaque development at later stages by contributing to the perpetuation of vascular inflammation. Supporting this notion, one study found that IL-6 deficiency results in larger plaques, but markedly reduces plaque inflammation[201]. Regardless of the mechanisms underlying the phenotype of IL-6 deficient mice, recent studies have begun to evaluate the therapeutic potential of pharmacological inhibition of IL-6 signaling in the setting of atherosclerosis. In this regard, post-natal inhibition of IL-6 trans-signaling (by treatment with a fusion protein of soluble gp130 and IgG1-Fc) has been shown to reduce atherosclerosis development and plaque inflammation in LDLR-KO mice[206].

The role of IL-6 in pathologic cardiac remodeling after ischemic injury is similarly complex. While human studies have shown a strong association between circulating IL-6 levels and the severity or prognosis of chronic heart failure[207_211], causality is uncertain given that mouse studies have generated conflicting data. One study found no effect of genetic IL-6 deficiency or recombinant IL-6 delivery on MI size, left ventricular (LV) remodeling, or

mortality after permanent coronary ligation[212]. In contrast, another study found that a single injection of an IL6-R-blocking antibody after MI suppresses myocardial inflammation, resulting in the amelioration of LV remodeling[213]. In addition, IL-6 may even exert some cardioprotective actions, since treatment with a combination of recombinant IL-6 and sIL6R inhibits cardiomyocyte apoptosis and reduces infarct size in a rat model of cardiac ischemia/reperfusion (I/R) injury[214].

Resistin

Resistin is a secreted protein that is highly expressed by mature adipocytes in rodents and was initially suggested to be a major link between obesity and insulin resistance[215]. Circulating resistin levels are increased in obese and diabetic mice[216], and several loss- and gain-of-function studies in mice have suggested an important role of resistin in obesity-associated metabolic dysfunction through pleiotropic effects on glucose metabolism and insulin sensitivity[215, 217–219]. However, human studies have yielded conflicting results on the role of resistin in insulin resistance[220–226], and have revealed striking differences in resistin expression patterns in rodents and humans. While in rodents resistin is mostly expressed by adipocytes[215, 227], the main sources of this protein in humans are monocytes and macrophages[228, 229]. Regardless of these differences between species, several studies suggest a tight connection between resistin and inflammatory disorders. Human resistin expression in monocytes/macrophages is increased in response to various pro-inflammatory stimuli[230–232] and serum resistin levels show a positive correlation with various circulating markers of inflammation, such as C-reactive protein, TNF-α, or IL-6 in different pathophysiological settings[233–237]. In addition, resistin has been reported to promote monocyte/endothelium interactions[238] and pro-inflammatory activation of macrophages[239, 240], which suggests an important role in the development of atherosclerosis. Consistently, peri-adventitial resistin gene transfer accelerates plaque development in rabbit models of atherosclerosis[241]. In addition, a recent study suggested that overexpression of mouse resistin can promote atherosclerosis by an alternative mechanism mediated by central leptin resistance and reduced BAT activity leading to hypertriglyceridemia[242]. Despite some conflicting studies[243–245], human studies also support an import role for resistin in atherosclerotic disorders. Elevated circulating levels of resistin have been reported to be associated with coronary artery calcification[246] and CAD[247], and to predict the occurrence and severity of CAD in several clinical studies[248–252]. Furthermore, resistin has been proposed to be an independent risk factor for major CV events in CAD patients[253, 254]. Although the role of resistin in cardiac ischemic events has not been investigated in animal models, some human studies suggest that it might also play a role in this setting, since high circulating levels of resistin are present in patients with acute coronary syndrome (ACS)[251, 255, 256]. In addition, resistin expression and secretion by epicardial adipose tissue has been shown to be increased in these patients[257].

Adiponectin

Adiponectin is a widely studied adipokine that is very abundantly expressed in plasma (range: 3–30 μg/ml in human)[258, 259]. The adiponectin peptide contains collagen-like domain followed by a globular domain that is similar to complement factor C1q. Adiponectin exists in blood stream as three major oligomeric complexes: trimers, hexamers

and high-molecular weight form[258, 259]. Plasma adiponectin levels are decreased in obese subjects relative to lean control subjects[259], and adiponectin levels negatively correlate with visceral fat accumulation[260]. Dysfunctional adipocytes produce lower levels of adiponectin but higher levels of pro-inflammatory cytokines, which further inhibit the production of adiponectin in adipocytes. Adiponectin expression by adipocytes is also inhibited by endoplasmic reticulum and oxidant stresses, which are features of adipose tissue dysfunction in obesity.

A number of clinical studies demonstrate that low plasma adiponectin levels are associated with systemic inflammation[258, 261] and obesity-linked CV disorders[262–266]. Plasma adiponectin concentrations are lower in patients with CAD than in age- and BMI-adjusted control subjects[263, 264]. Circulating adiponectin levels are also reduced in patients with ACS[265], and adiponectin levels rapidly decline following acute myocardial infarction[266]. High plasma adiponectin levels are associated with a decreased risk of MI in healthy men[267] and diabetic men[268]. Low adiponectin has been reported to be an independent risk factor of coronary heart disease in some studies[269] but not others[270–272]. On the contrary, hyperadiponectinemia is associated with mortality in patients with diseases that are associated with cachexia such as heart or respiratory failure[273, 274]. Adiponectin levels are also elevated in a number of chronic inflammatory and autoimmune diseases[275]. The upregulation of adiponectin in these severe diseases may represent a compensatory response since animal studies that model these diseases show that adiponectin is protective under these conditions.

Experimental studies have shown that adiponectin exerts anti-inflammatory and vasculoprotective actions in different settings[276–287]. In mice, lack of adiponectin results in an enhancement of myocardial ischemia-reperfusion injury, which is associated with increased myocardial cell apoptosis and TNF-α production[276]. Conversely, systemic adenovirus-mediated delivery of adiponectin diminishes infarct size in both APN-KO and wild-type mice. In this model, adiponectin stimulates COX-2 expression and synthesis of prostaglandin E_2 (PGE_2), a vascular- protective autocoid that inhibits inflammatory cytokine production in cardiac myocytes. Adiponectin-induced expression of COX-2 in myocytes is reduced by inhibition or deletion of sphingosine kinase-1 (SphK-1), or blockade of a sphingosine-1-phosphate (S1P) receptor[288], and it has been shown that adiponectin stimulates ceramidase activity in cardiac myocytes and other cell types to promote survival[289]. In addition to its effects on COX-2 expression, adiponectin protects the myocardium from ischemic injury through its ability to activate AMPK signaling[278, 279, 287]. Adiponectin also protects from ischemia-reperfusion injury through inhibition of peroxynitrite-induced oxidative and nitrosative stresses[290]. In extension of these genetic models, delivery of recombinant adiponectin protein can protect the heart in murine models of I/R injury[276]. Notably, one study showed that intracoronary injection of adiponectin protein improved cardiac function after ischemia-reperfusion in a pig model using similar instrumentation and standard of care as in patients[291].

Whereas experimental studies examining the effects of adiponectin on ischemic heart disease have been consistent in documenting a protective effect, adiponectin's role in atherogenesis is less clear. A series of studies show that adiponectin modulates macrophage

function promoting an anti-inflammatory phenotype that would be consistent with an anti-atherogenic role. For example, adiponectin suppresses lipopolysaccharide-stimulated TNF-α production[292, 293], inhibits Toll-like receptor-mediated NF-κB activation[294], and enhances the production of the anti-inflammatory cytokine IL-10 in cultured macrophages[293, 295]. Consistently, adiponectin promotes macrophage polarization towards an anti-inflammatory phenotype[296], and facilitates the rapid removal of apoptotic debris from the body which is critical in preventing pathological inflammation and immune system dysfunction[297]. Adiponectin also inhibits macrophage-to-foam cell transformation and reduces intracellular cholesteryl ester content in human macrophages by suppressing expression of class A scavenger receptor (SR-A)[298].

Consistent with the above-mentioned in vitro findings, overproduction of circulating adiponectin inhibits the formation of atherosclerotic lesions and decreases mRNA levels of SR-A, TNF-α and VCAM-1 in the vascular wall in apoE-knockout mice, suggesting that adiponectin attenuates atherogenesis through anti-inflammatory actions on macrophages and vascular endothelial cells[299, 300]. Adenovirus-mediated overexpression of adiponectin also attenuates angiotensin II-accelerated atherosclerosis[301]. Conversely, one study showed that adiponectin deficiency in ApoE-knockout mice exacerbates atherogenesis and accelerates T lymphocyte accumulation in atheromata[302]. In contrast, an extensive study reported that neither adiponectin overexpression nor deficiency has any effects on atherosclerotic lesion formation in either ApoE-KO or LDLR-KO mice when fed either a normal chow or a high cholesterol diet[303]. Thus, additional studies are required to determine whether adiponectin has a significant atheroprotective role in vivo.

Cardiovascular disease and adiponectin receptors

While a large number of studies have shown that adiponectin acts as a CV-protective adipokine in many systems, the receptor-mediated signaling systems that confer these protective actions are understudied. Early, it was reported that the beneficial actions of adiponectin on metabolic function and AMPK signaling pathway is mediated through combined signaling through its cell surface receptors AdipoR1 and AdipoR2[304]. However, subsequent studies suggest that AdipoR1 and AdipoR2 have opposing actions: AdipoR1-deficiency in mice leads to metabolic dysfunction, whereas AdipoR2-deficiency actually promotes resistance to obesity and insulin resistance[305–307]. The roles of AdipoR1 and AdipoR2 in CV tissues have mostly been deduced from cell culture studies. For example, in vitro studies in cardiac myocytes have shown that both AdipoR1 and AdipoR2 mediate the anti-hypertrophic effects of adiponectin[308]. Similarly, AdipoR1 has been shown to mediate the pro-angiogenic actions of adiponectin in cultured endothelial cells[277]. Relatively few studies have analyzed the roles of adiponectin receptors in the CV system using in vivo models. Functional evidence for receptor involvement in vivo would involve documentation that receptor-deficiency has a similar phenotype as adiponectin-deficiency and that the receptor-deficient mice would be impaired in their response to exogenously-administered adiponectin. In this regard, it was recently shown in a murine model of peripheral artery disease that AdipoR2-deficiency impairs the revascularization process (as does adiponectin-deficiency), and eliminates the enhanced revascularization response to exogenous adiponectin[305]. In contrast, AdipoR1-deficiency led to a dysfunctional metabolic phenotype,

suggesting that the in vivo vascular and metabolic effects of adiponectin diverge at the level of the AdipoR1/2 receptors.

When considering receptors it is important to reconcile the unusual properties of adiponectin as a ligand. For example, adiponectin levels are 1000-fold greater than most growth factors and cytokines[259], raising questions about receptor affinity and occupancy. Adiponectin also has an unusual structure that comprises a globular head and collagenous tail that is similar to the collectin family of proteins, including C1q, mannose binding lectin and lung surfactant proteins, that contribute to innate immune system regulation by functioning as "pattern recognition receptors" via low affinity interactions with various macromolecules[309]. Like other collectin family proteins, adiponectin preferentially forms higher order multimers, including dodecamers with a molecular mass in excess of 400 kDa, presumably to allow multivalent associations with low affinity targets. Studies have shown that adiponectin exhibits collectin-like properties, including the ability to opsonize apoptotic cells and facilitate their clearance[297, 310], and it has been shown that adiponectin can bind to C1q in serum[311]. Thus, one would not expect a simple binary, ligand/receptor-occupancy model to account for the interaction between adiponectin and the AdipoRs or other candidate receptor molecules. In light of these considerations, studies have documented that adiponectin is highly localized to the heart and the vascular endothelium through an interaction with T-cadherin, a GPI-anchored cell surface glycoprotein[312_314]. Data from mouse studies have shown that T-cadherin-deficiency leads to marked elevations in the level of circulating adiponectin, ostensibly because of its release from tissue depots. T-cadherin-deficiency in mice also blocks the salutary actions of exogenously administered adiponectin on ischemia-reperfusion injury and remodeling following pressure-overload in the heart[313], and on adiponectin-stimulated revascularization in a murine model of peripheral artery disease[314]. Thus, T-cadherin plays a key role in mediating the CV effects of adiponectin although it lacks a transmembrane signaling domain. Hypothetically, T-cadherin may function as a co-receptor molecule involved in the localization and presentation of adiponectin, or a particular configuration of adiponectin, to AdipoR1/2, potentially explaining how adiponectin can function to activate receptor-mediated signaling pathways in addition to its low affinity, pattern recognition activities.

CTRPs

C1q/TNF-related proteins (CTRPs) are conserved paralogs of adiponectin that contain collagen tail domain and a globular C1q-like domain at the C-terminus[315]. Recent studies demonstrate that, like adiponectin, some CTRPs act as adipokines that exert cardioprotective effects. Examples include CTRP3 and CTRP9, which are primarily expressed in adipose tissue and whose expression is downregulated in obese states[316_319].

CTRP9, which has the highest amino acid sequence similarity to adiponectin (45%)[320], has been shown to have protective actions in the CV system. Systemic delivery of CTRP9 protein reduces myocardial infarct size and apoptosis following myocardial infarction or ischemia-reperfusion injury in mice[317, 321]. *In vitro,* treatment of cardiac myocytes with CTRP9 protein attenuates hypoxia-reoxygenation-induced apoptosis via an AMPK-dependent pathway involving AdipoR1[317]. CTRP9 is also effective in reducing myocardial

infarct size, apoptosis and oxidative stress in diabetic mice after ischemia-reperfusion[322]. Consistently, recent studies with CTRP9-deficient mice have shown that CTRP9 promotes cardiac function and myocyte survival and diminishes fibrosis following myocardial infarction in an AdipoR1 and AMPK-dependent manner[323]. Because circulating CTRP9 levels are reduced in mice after ischemia-reperfusion or myocardial infarction[317, 321], replenishment of CTRP9 could be beneficial in the context of ischemic heart.

CTRP3 has a 28% amino acid identity with adiponectin[320], and supplementation of this adipokine has been reported to improve cardiac function and reduce fibrosis in mice after myocardial infarction, which is accompanied by increased capillary density and decreased apoptosis in ischemic areas of the heart[324, 325]. *In vitro*, CTRP3 inhibits TGF-β-induced profibrotic gene expression in cardiac fibroblasts[325] and promotes cardiac myocyte survival and VEGF-A expression through its ability to activate an Akt/HIF-1α-dependent pathway. In humans, circulating CTRP3 levels are negatively correlated with several markers of systemic inflammation and cardiometabolic risk[326].

Omentin

Omentin-1, also referred to as intelectin-1, was identified as a soluble lectin that recognizes galactofuranose in carbohydrate chains of bacterial cell wall[327]. Human omentin-1 is abundantly expressed in human visceral adipose tissue[328]. Omentin-1 is detectable in human blood, and circulating omentin levels are reduced in obese subjects[329] and in patients with impaired glucose tolerance and type 2 diabetes[330]. Furthermore, circulating omentin-1 levels negatively correlate with multiple cardiometabolic risk factors such as increased waist circumferences, dyslipidemia, elevated blood pressure, and glucose intolerance[331]. Recent clinical studies also suggest the relationship between omentin-1 and CV disorders. Circulating omentin levels are markedly lower in patients with CAD than in age-matched control subjects[332_334].. Another study demonstrated the inverse correlation between serum omentin-1 levels and the presence and severity of CAD in patients with metabolic syndrome[335]. In healthy men, omentin-1 levels negatively correlate with carotid intima/media thickness[336], which is a marker for subclinical atherosclerosis.

Experimental studies also support the notion that omentin-1 exerts protective actions on the CV system[337_340]. Systemic administration of omentin-1 attenuates cardiac injury following ischemia-reperfusion in mice through Akt- and AMPK-dependent mechanisms[341]. In vitro, omentin-1 has been shown to suppress TNFα-induced inflammatory responses in vascular endothelial cells via an AMPK-eNOS pathway[342]. More recently, omentin overexpression has been reported to attenuate atherosclerosis in hyperlipidemic mice[343]. Overall, it is plausible that low levels of omentin-1 can contribute to the development of CV dysfunction in obese individuals.

Sfrp5

Secreted frizzled-related protein 5 (Sfrp5) was identified as an adipokine that exerts salutary effects on metabolic function with anti-inflammatory properties[344]. Sfrp5 is expressed abundantly in WAT in lean mice, and it is down-regulated in severely obese rodents, such as 20-week-old ob/ob mice. Mechanistically, Sfrp proteins are known to function as soluble

modulators that sequester Wnt proteins in the extracellular space and prevent their binding to receptors. In this context, Sfrp5 appears to function as an inhibitor of Wnt5a-mediated non-canonical Wnt signaling, which contributes to pro-inflammatory cytokine production via JNK activation[44, 344, 345]. Although some conflicting data have been reported regarding the magnitude of Sfrp5 secretion by human WAT[346, 347], an increasing body of evidence suggests that Sfrp5 is dynamically regulated in humans. Several studies have shown that circulating levels of Sfrp5 are reduced in obese individuals, particularly in those exhibiting clear evidence of metabolic dysfunction, such as impaired glucose tolerance and insulin resistance[346, 348–350]. Consistently, human Sfrp5 transcript levels in visceral adipose tissue decrease with obesity[351]. In marked contrast, one study found a positive association between increased serum Sfrp5 levels and high HOMA-IR, an index of insulin resistance, in humans[352]. An additional study failed to replicate Sfrp5 downregulation in human obesity, but strikingly it showed that caloric restriction-induced weight loss increases serum concentration of Sfrp5[353]. Taken together, these studies suggest that Sfrp5 is downregulated in obesity-associated metabolic dysfunction in humans, although further investigations are still required to corroborate this notion.

Sfrp5 may also affect the development of obesity-linked CVD. A recent study demonstrated that genetic Sfrp5 ablation exacerbates cardiac I/R injury in mice, coinciding with increased inflammation and cardiomyocyte death[345]. In addition, in a murine model of peripheral artery disease, Sfrp5-deficiency promoted the influx of Wnt5a-positive cells into the ischemic limb and impaired revascularization[101]. The role of Sfrp5 in atherosclerosis remains unknown at this time, but a number of studies suggest a potential atheroprotective action of this adipokine. A recent clinical study demonstrated that low levels of serum Sfrp5 are associated with CAD[354]. Furthermore, Sfrp5 may affect atherosclerosis development by inhibiting Wnt5a, which is expressed in murine and human atherosclerotic lesions[355, 356]. It has been suggested that Wnt5a contributes to endothelial dysfunction in diabetic patients[357] and promotes inflammatory reactions in macrophages and endothelial cells[44, 355, 358]. Thus, it is plausible that Sfrp5 attenuates inflammatory response to Wnt5a in the vasculature, but additional studies will be required to clarify the role of Sfrp5 in the regulation of atherosclerosis development.

CONCLUSION

An increasing body of evidence supports the evolving concept that quantity, location and quality of adipose tissue are critical factors in shaping cardiometabolic phenotypes in obese humans but specific pathogenic mechanisms and their relative contributions remain incompletely understood. adipose tissue communicate with remote organs, including heart and vasculature, through the release of various adipokines. In mouse models and many human individuals' obesity leads to adipose tissue dysfunction or adiposopathy, particularly in visceral fat depots, which is mediated by dysfunctional tissue remodeling that involves adipocyte hypertrophy, exacerbated inflammation, increased fibrosis and impaired vascular function and structure. This ultimately creates an imbalance in adipokine levels (Figure 4), which contributes to a chronic, low grade systemic inflammatory reaction that is central to the initiation and progression of metabolic and CV complications. While some adipokines have been highly studied and have shown to be causally linked to various disease processes,

new adipokine candidates continue to be discovered and elucidated. In light of the fact that a third of the world's population is currently overweight or obese, and this proportion is expected to increase in the coming decades, studies of adipokine biology should provide a better understanding of the pathogenesis of CVD. As our understanding of adipokine biology and obesity-induced adiposopathy increases, the major challenge will reside in translating this information into new prognostic and therapeutic approaches to limit CV risk in obese individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

AdipoR1, AdipoR2	adiponectin receptor 1, 2
AdipoRs	adiponectin receptors
Akt	Also known as Protein kinase B. Ak refers to the mouse strain and t to thymoma.
AMPK	adenosine monophosphate-activated protein kinase
ANGPTL-4	angiopoietin-like 4
APN-KO	adiponectin knockout
Apo-E, apoE	apolipoprotein E
ATMs	adipose tissue macrophages
BAT	brown adipose tissue
BMI	body mass index
CAD	coronary artery disease
CD (CD4, CD8, CD11)	cluster of differentiation (4, 8, 11)
CLS	"crown-like" structures
CMD	cardiometabolic disease
COX	cyclooxygenase
CRP	C-reactive protein
CT	computed tomography

CTRPs (CTRP3, CTRP9)	C1q/tumor necrosis factor-related proteins (3, 9)
CV	cardiovascular
CVD	cardiovascular disease
ECM	extracellular matrix
eNOS	endothelial nitrous oxide synthase
FFA	free fatty acids
gp130	glycoprotein 130
GPI	glycosylphosphatidylinositol
HDL	high-density lipoprotein
HFD	high fat diet
HIF1α	hypoxia-inducible factor 1 alpha
HOMA-IR	homeostatic model assessment-insulin resistance
ICAM-1	intercellular adhesion molecule 1
IgG1-Fc	immunoglobulin 1-fragment, crystallizable
IL (IL-4, IL-6, IL-10, IL-13)	interleukin (4, 6, 10, 13)
IL6R	interleukin 6 receptor
JNK	c-Jun N-terminal kinase
Ldlr/LDLR	low-density lipoprotein-receptor
LV	left ventricular
MI	myocardial infarction
MMP-2	matrix metallopeptidase 2
MRI	magnetic resonance imaging
NF-κB	nuclear factor-kappa B
NK cells	natural killer cells
NKT	natural killer T cells
NO	nitric oxide
PDGFRα	platelet-derived growth factor receptor, alpha polypeptide
PVAT	perivascular adipose tissue
ROS	reactive oxygen species
Sfrp5	secreted frizzled-related protein 5
sIL6R	soluble form of interleukin 6 receptor

SphK-1	sphingosine kinase-1
Th1, Th2, Th17	T helper (1, 2, 17)
TLR-4	toll-like receptor 4
TNF-α	tumor necrosis factor alpha
VEGF-A	vascular endothelial growth factor A
WAT	white adipose tissue
Wnt (Wnt5a)	Wingless-Type MMTV Integration Site Family (Member 5A)

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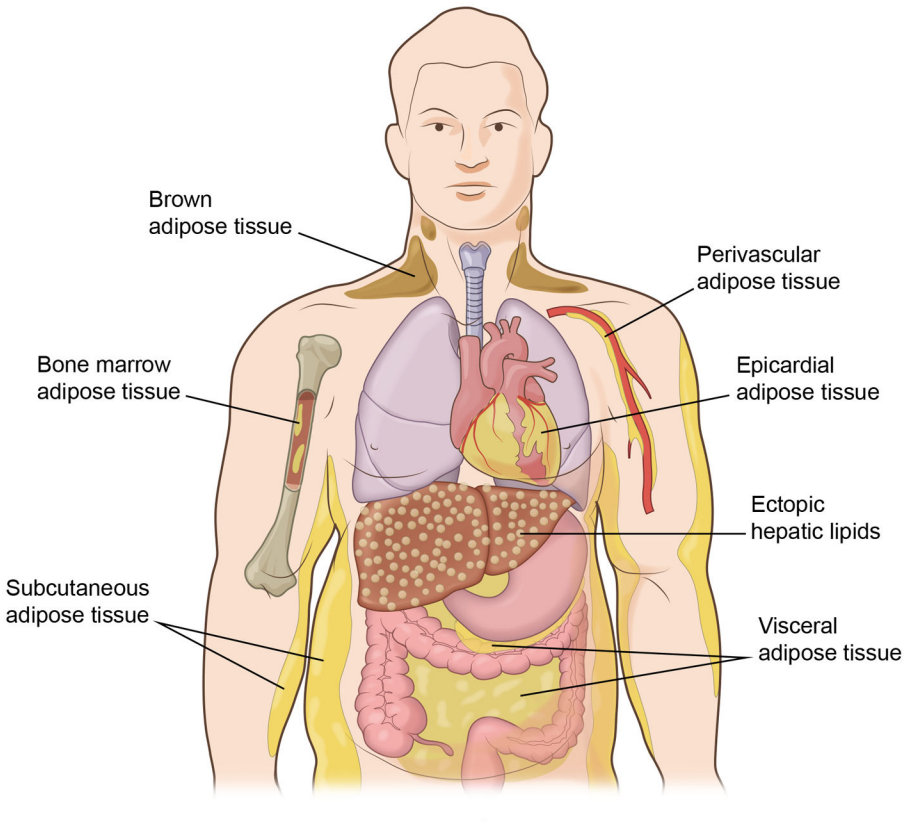

Figure 1.

Adipose tissue depots occur throughout the body. Studies suggest that visceral adipose tissue accumulation is a major risk factor for cardio-metabolic disease, whereas subcutaneous fat appears to be neutral or protective. Other adipose tissue depots of note include the epicardium, the perivascular space, and bone marrow, but the functional significance of these tissues is largely unknown. Brown adipose tissue occurs in the supraclavicular and paraspinal regions. In contrast to white adipose tissue, brown adipose tissue is very metabolically active and it functions to utilize fuel to produce heat. In addition, ectopic lipid can accumulate in tissues, such as liver, in metabolically dysfunctional organisms.

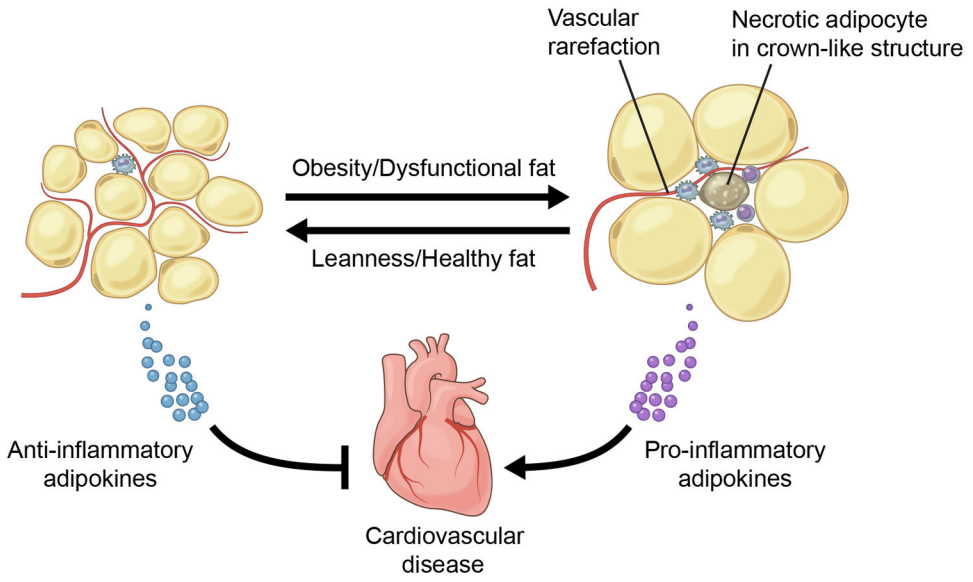

Figure 2.

Functional adipose tissue (left), predominantly found in lean organisms, tends to express anti-inflammatory adipokines that protect against cardiovascular disease. In contrast, excess adipose tissue expansion promotes dysfunction (right), leading to the expression of pro-inflammatory adipokines that promote cardiovascular disease. Dysfunctional adipose tissue is characterized by enlarged adipocytes, vascular rarefaction, increased inflammatory cell infiltrate and the appearance of crown-like structures.

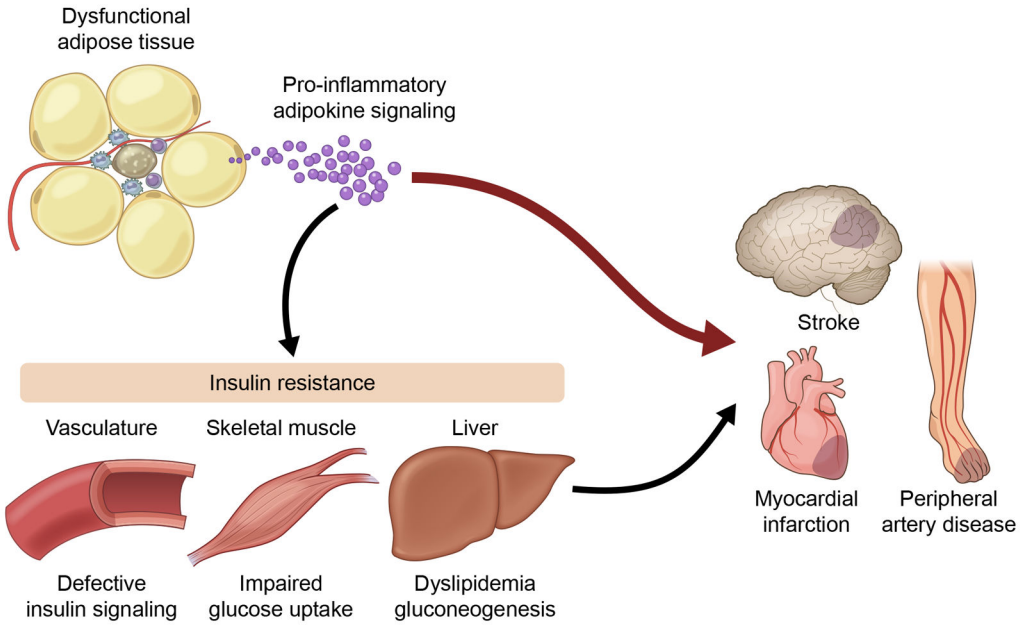

Figure 3.

Obesity leads to adipose tissue dysfunction, triggering the release of pro-inflammatory adipokines which can directly act on cardiovascular tissues to promote disease. The adipokine imbalance can also affect the function of metabolically important tissues and the microvasculature, promoting insulin resistance and indirectly contributing to CVD.

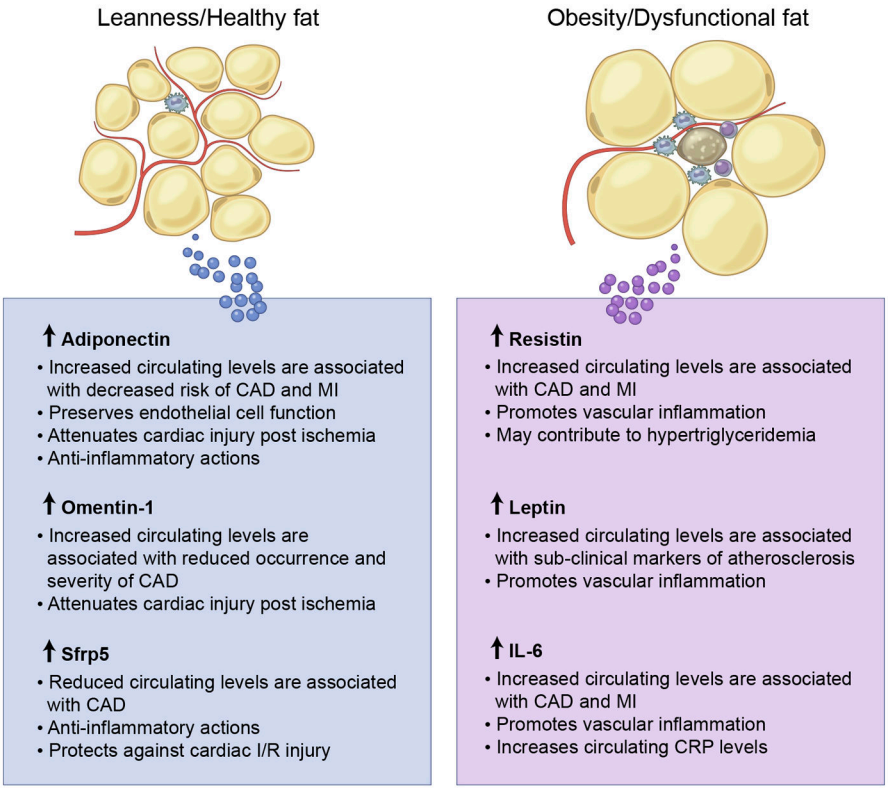

Figure 4.

Selected anti- and pro-inflammatory adipokines with summaries of their regulation and actions in the cardiovascular system.