

Obesity, Diabetes, and Cardiovascular Diseases Compendium

Circulation Research Compendium on Obesity, Diabetes, and Cardiovascular Diseases

Obesity, Diabetes, and Cardiovascular Diseases: A Compendium
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Philipp E. Scherer and Joseph A. Hill, Editors

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 proinflammatory 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. (*Circ Res.* 2016;118:1786-1807. DOI: 10.1161/CIRCRESAHA.115.306885.)

Key Words: adipokines ■ adipose tissue ■ atherosclerosis ■ myocardial infarction ■ obesity

The prevalence of obesity, defined as a body mass index (BMI) ≥ 30 kg/m², 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 caused by augmented risk of cardiovascular death.⁴ Moreover, the increasing prevalence of obesity is changing the cause 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 obesity-associated remodeling generates a systemic proinflammatory state, which is mediated by an imbalanced production of adipocyte-derived cytokines (adipokines) that directly and indirectly affect the cardiovascular system. In this review article, we summarize the pathophysiological

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Nonstandard Abbreviations and Acronyms

AdipoR1, AdipoR2	adiponectin receptor 1, 2
AMPK	AMP-activated protein kinase
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)
CMD	cardiometabolic disease
CTRP3 (CTRP3, CTRP9)	C1q/tumor necrosis factor-related proteins (3, 9)
CVD	cardiovascular disease
IL (IL-4, IL-6, IL-10, IL-13)	interleukin (4, 6, 10, 13)
IL6R	interleukin 6 receptor
Ldlr/LDLR	low-density lipoprotein-receptor
MI	myocardial infarction
PVAT	perivascular adipose tissue
Sfrp5	secreted frizzled-related protein 5
Th1, Th2, Th17	T helper (1, 2, 17)
TNF-α	tumor necrosis factor- α
VEGF-A	vascular endothelial growth factor A
WAT	white adipose tissue
Wnt (Wnt5a)	wingless-type MMTV integration site family (member 5A)

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 Cardiovascular Risk

Although adipose tissue quantity (volume) is undoubtedly linked to cardiovascular risk, recent human data indicate that differences in fat tissue quality, which can be examined directly by immunohistochemistry or noninvasively by computed tomographic 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 BMI. 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. Although 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 interindividual 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: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 the 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 $\approx 80\%$ of total body fat mass, whereas abdominal visceral adipose tissue accounts for 5% to 20%.³² Despite visceral fat not being the predominate white adipose tissue (WAT) depot, inflammatory markers including interleukin (IL)-6, C-reactive protein, and tumor necrosis factor (TNF)- α tend to circulate at higher concentrations in subjects with abdominal than peripheral obesity,^{33–36} and visceral fat has been shown to be a significant source of circulating free fatty acids and IL-6.^{37,38} Although arterial disease tends to worsen with increasing overall weight burden in adults and children,^{18,39} computed tomographic or magnetic resonance imaging studies of fat compartments identify visceral fat volume to be more highly associated with systemic endothelial dysfunction than 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 proinflammatory, oxidative stress-related, and antiangiogenic 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 with 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 as 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 because of its potentially high oxidative capacity.⁵¹ Compared with WAT, BAT contains abundant mitochondria that are uncoupled, because of the expression of uncoupling protein 1 (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 seems 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

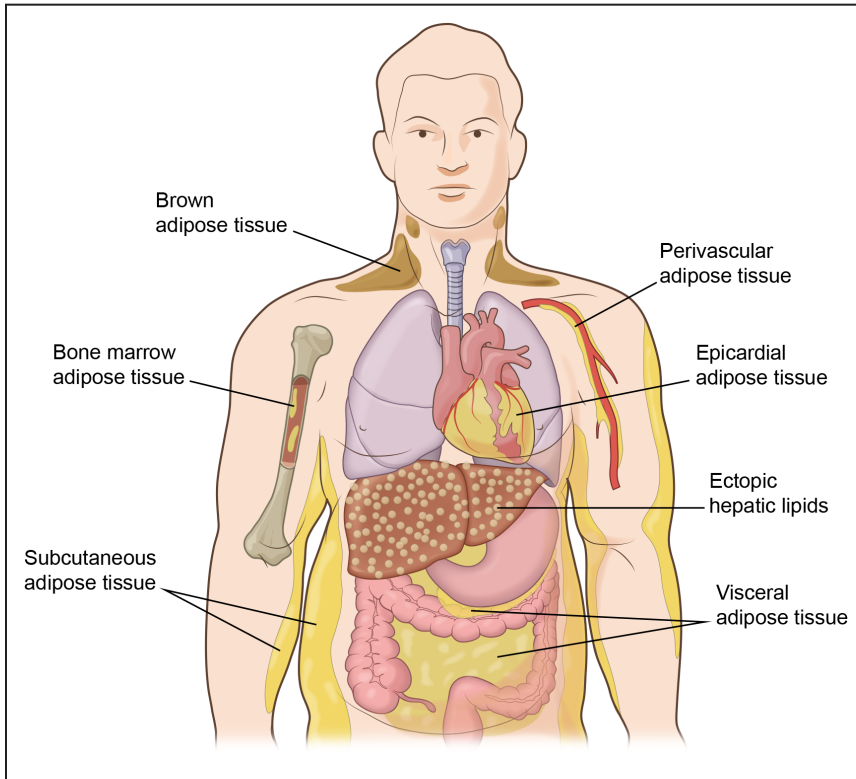


Figure 1. Adipose tissue depots occur throughout the body. Studies suggest that visceral adipose tissue accumulation is a major risk factor for cardiometabolic disease, whereas subcutaneous fat seems to be neutral or protective. Other adipose tissue depots of note include the epicardium, the perivascular 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 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.

secretion 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 an enlargement of adipocyte size (hypertrophy). It has been classically accepted that hyperplasia allows a healthy expansion of the adipose tissue because 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

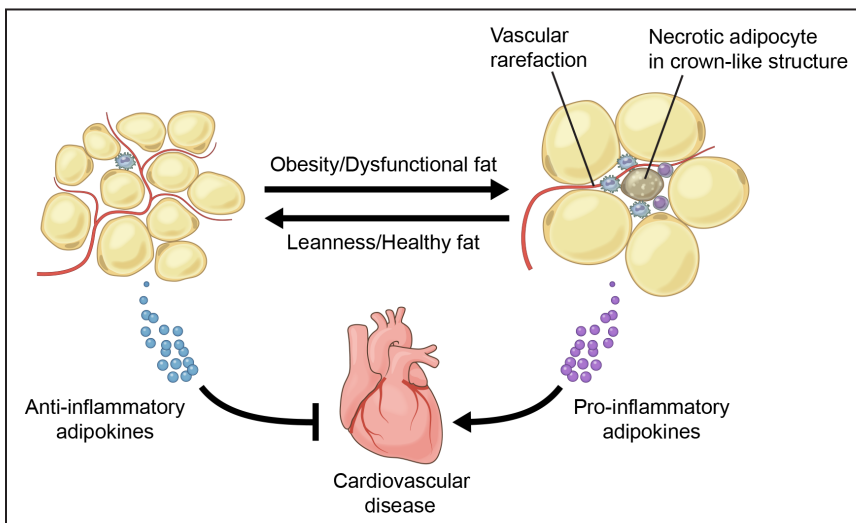


Figure 2. Functional adipose tissue (left), predominantly found in lean organisms, tends to express anti-inflammatory adipokines that protect against cardiovascular disease. In contrast, excess adipose tissue expansion promotes dysfunction (right), leading to the expression of proinflammatory adipokines 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.

limited expandability because of 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 cardiovascular 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 (ie, 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 high-fat diet exposure. Hence, at least in this depot, mouse models may mimic the conditions of human hypertrophic obesity. However, although 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, although 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 is 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 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 on 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 (eg, the mannose receptor cluster of differentiation [CD] 206), whereas ATMs in obese organisms typically express genes associated with a M1-like or classically activated phenotype (eg, 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 because of 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 Th1-type cytokines, including interferon- γ , induces an M1 phenotype in macrophages that leads to increased production of proinflammatory 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 contrary, stimulation with Th2-type cytokines (eg, 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 thought 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 thought 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 Th2-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} Proinflammatory cytokine production by effector T cells and Th1 cells is promoted by B cells recruited to the obese adipose tissue, which also contributes to M1 macrophage activation apparently through the production of pathogenic immunoglobulins.⁷⁴ Additional lymphocyte subsets such as Th17 or natural killer T cells may also play important roles in modulating macrophage phenotype and adipose tissue inflammation.⁷⁸

In addition to quantitative and phenotypic changes, obesity also changes the location of macrophages within the adipose tissue. Although ATMs are typically dispersed in lean individuals, in metabolically dysfunctional organisms, they tend to accumulate in crown-like structures, defined as clusters of lipid-scavenging macrophages that surround free lipid droplets of dead adipocytes both in animal models and

in obese patients^{79,80} (Figure 2). Importantly, this condition seems to contribute to adipose tissue dysfunction because the number of crown-like structure correlates with adipose tissue inflammation and insulin resistance in patients with metabolic syndrome.^{11,79} Consistently, obese subjects lacking crown-like structures exhibit better metabolic function, diminished inflammatory gene expression in adipose tissue, and reduced cardiovascular risk than body mass–matched individuals with crown-like structures.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 high-fat diet feeding,^{81–83} and they seem 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 when compared with 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 because of 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. Although 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 than 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 Proangiogenic angiopoietin-like 4 is downregulated in visceral fat and may play an important role.⁹⁶ In addition, an anti-angiogenic splice variant of VEGF, VEGF-A₁₆₅b, is expressed at higher levels in human visceral fat than in subcutaneous fat and is linked to impaired tissue angiogenesis.⁹⁸ Blood levels of VEGF-A₁₆₅b are elevated in obese compared with lean subjects and decrease after bariatric surgery weight loss. This observation has potential clinical implications as systemic upregulation of antiangiogenic 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-A₁₆₅b 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. Moreover, administration of anti–intercellular adhesion molecule-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 overexpressed in fat impair vasoregulatory and antiatherogenic properties leading to vasomotor dysfunction of the local microvasculature⁴¹ 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 with 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 endothelial nitrous oxide synthase phosphorylation at the activating site serine 1177 in vascular endothelial cells isolated from fat suggesting abnormalities in nitric oxide bioactivity as a significant contributing mechanism.⁴² Adipose microvascular dysfunction seems specific to the obese state as arterioles isolated from visceral tissue of lean subjects exhibit preserved vasomotor function,^{109,110} whereas 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 proinflammatory in visceral depots. Experimental studies in mice demonstrate that transplantation of inflamed visceral fat accelerates atherosclerosis in ApoE 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 toll-like receptor 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 after 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 nitric oxide-dependent vasodilation, mitochondrial hyperpolarization, and increased mitochondrial superoxide production in the adipose tissue of type 2 diabetic subjects.¹⁰⁸ Moreover, increased expression of cyclooxygenase-mediated vasoconstrictor prostanoids might also contribute to endothelial dysfunction, supporting a role of the eicosanoid/cyclooxygenase pathway in obesity-linked disease.⁴² Because the vasodilator responses and endothelial nitric oxide synthase phosphorylation status in the adipose microvasculature have been shown to correlate with cardiovascular 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 that provides mechanical support and participates in cell signaling. With the development of obesity, there is a general increase in the synthesis of several extracellular matrix 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, at least in part, because of hypoxia-induced up-regulation of hypoxia-inducible factor 1 α .^{117,118} Interestingly, hypoxia-inducible factor 1 α 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 hypoxia-inducible factor 1 α are not understood. Recent studies are uncovering additional mechanisms that modulate adipose tissue fibrosis in obesity. Endotrophin, a cleavage product of the $\alpha 3$ 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, platelet-derived growth factor receptor α polypeptide 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 cardiovascular 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 CVD

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 this term 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 cardiovascular functions. It is now widely accepted that dysfunctional adipose tissue remodeling leads to an unbalanced production of adipokines that contributes to the systemic proinflammatory state associated with obesity and has important adverse actions on the cardiovascular system,^{121,122} particularly in the obese state where adipose tissue mass can range from 30% to >50% of total body mass. In addition to their direct effects on pathophysiological processes in the cardiovascular system, adipokines can affect cardiovascular 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 cardiovascular risk. However, these indirect actions of adipokines will not be discussed in detail here.

Since the identification of adipisin in 1987,¹²³ the list of adipokines has expanded vastly. Notably, the majority of adipokines are proinflammatory. Examples include leptin,

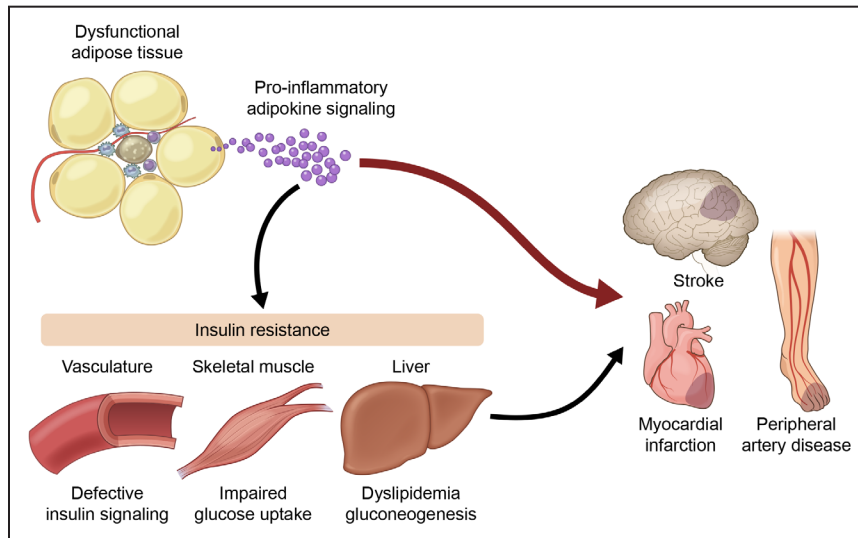


Figure 3. Obesity leads to adipose tissue dysfunction, triggering the release of proinflammatory adipokines that can directly act on cardiovascular tissues to promote disease. The adipokine imbalance can also affect the function of metabolically important tissues and the microvasculature, promoting insulin resistance and indirectly contributing to cardiovascular disease.

TNF α , IL-6, and resistin. In contrast, relatively few adipokines are anti-inflammatory. Examples include adiponectin, omentin-1, C1q/tumor necrosis factor-related protein 9 (CTRP9), and secreted frizzled-related protein 5 (Sfrp5). Most adipokines have been identified in visceral and 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 cardiovascular and metabolic diseases because 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 cardiovascular risk associated with an adipokine imbalance is because of a paracrine mechanism, ie, the local release of proinflammatory factors from epicardial adipose tissue and PVAT, or an endocrine mechanism secondary to changes in serum adipokines levels. Although both mechanisms probably contribute to obesity-associated CVD, mouse studies based on PVAT transplantation suggest that the anatomic location of PVAT is critical in some pathophysiological settings.¹²⁷ However, it remains to be established whether different PVAT depots, which display a varying degree of brown fat characteristics, exhibit distinct profiles of adipokine secretion. Furthermore, although 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 on 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 proinflammatory 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 proatherogenic actions. For example, leptin increases reactive oxygen species production in endothelial cells.^{147,148} In VSMCs, it promotes the expression of matrix metalloproteinase-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 on its role in atherosclerosis development. Low-density lipoprotein-receptor knockout (LDLR-KO) mice that are also leptin deficient develop more extensive atherosclerotic lesions than single LDLR-KO controls, likely because of 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 proatherogenic 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 because of the secondary metabolic defects that result from hyperphagia in mice deficient in leptin or the leptin receptor (eg, 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 nonobese mice. Supporting the proatherogenic role of leptin, 2 independent studies found that recombinant leptin administration aggravates atherosclerosis in apoE-KO mice without affecting blood lipids levels,^{155,157} and one study found that it strongly promotes plaque calcification.¹⁵⁸ Taleb et al¹⁵⁹ 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 anorexigenic and metabolic actions. 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, proinflammatory 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 calcification¹⁶⁰ 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 another study,¹⁶⁸ and one study found markedly different results, reporting that low plasma leptin predicted cardiovascular mortality in women.¹⁶⁹ This latter report is in line with many experimental studies suggesting a cardioprotective role of leptin after myocardial infarction (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 not only 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 metabolism 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 nonadipocyte cells, including

preadipocytes and macrophages.^{124,176,177} Importantly, expression and secretion of IL-6 are 2 to 3 times greater in visceral than in subcutaneous adipose tissue in humans,¹²⁴ and indexes of visceral adiposity associated with cardiovascular 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 on ligand binding forms a complex with the signaling receptor protein glycoprotein 130. Few cell types express membrane-bound IL6R, whereas essentially all cells exhibit glycoprotein 130 on the cell surface. Although the cells that only express glycoprotein 130 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, markedly expanding the spectrum of IL-6 actions and target cells.

IL-6 has been widely accepted to act as a proinflammatory cytokine since the discovery of its critical role in mediating the hepatic acute phase response.^{179–181} In addition, IL-6 has direct proinflammatory actions in a variety of immune and nonimmune 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 seems to play conflicting metabolic roles in different tissues, inducing insulin resistance in hepatocytes¹⁹⁰ and endothelial cells,¹⁹¹ but increasing insulin sensitivity in skeletal muscle under some conditions.^{191–193}

Similarly, the actions of IL-6 in the cardiovascular 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 caused by the 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 antiatherogenic activities by preventing cholesterol deposition in the vessel through increased cholesterol efflux in macrophages²⁰⁴ and high-density lipoprotein 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, a 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, postnatal inhibition of IL-6 trans-signaling (by treatment with a fusion protein of soluble glycoprotein 130 and immunoglobulin 1-Fc) has been shown to reduce atherosclerosis development and plaque inflammation in LDLR-KO mice.²⁰⁶

The role of IL-6 in pathological cardiac remodeling after ischemic injury is similarly complex. Although 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 remodeling, or mortality after permanent coronary ligation.²¹² In contrast, another study found that a single injection of an IL6R-blocking antibody after MI suppresses myocardial inflammation, resulting in the amelioration of left ventricular remodeling.²¹³ In addition, IL-6 may even exert some cardioprotective actions because treatment with a combination of recombinant IL-6 and the soluble form of IL6R inhibits cardiomyocyte apoptosis and reduces infarct size in a rat model of cardiac ischemia/reperfusion 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. Although 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 proinflammatory 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 interactions²³⁸ and proinflammatory activation of macrophages,^{239,240} which suggests an important role in the development of atherosclerosis. Consistently, periadventitial 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 important role for resistin in atherosclerotic disorders. Elevated circulating levels of resistin have been reported to be associated with coronary artery calcification²⁴⁶ and CAD²⁴⁷ 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 cardiovascular events in patients with CAD.^{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 because high circulating levels of resistin are present in patients with acute coronary syndrome.^{251,255,256} In addition, resistin expression and secretion by epicardial adipose tissue have been shown to be increased in these patients.²⁵⁷

Adiponectin

Adiponectin is a widely studied adipokine that is abundantly expressed in plasma (range, 3–30 $\mu\text{g/mL}$ in human).^{258,259} The adiponectin peptide contains a collagen-like domain followed by a globular domain that is similar to complement factor C1q. Adiponectin exists in blood stream as 3 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 proinflammatory 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.

Many clinical studies demonstrate that low plasma adiponectin levels are associated with systemic inflammation^{258,261} and obesity-linked cardiovascular disorders.^{262–266} Plasma adiponectin concentrations are lower in patients with CAD than in age- and body mass index-adjusted control subjects.^{263,264} Circulating adiponectin levels are also reduced in patients with acute coronary syndrome,²⁶⁵ and adiponectin levels rapidly decline after acute MI.²⁶⁶ High plasma adiponectin levels are associated with a decreased risk of MI in healthy men²⁶⁷ and diabetic men.²⁶⁸ Low adiponectin has been reported to be an independent risk factor of coronary heart disease in some studies²⁶⁹ but not in 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 many chronic inflammatory and autoimmune diseases.²⁷⁵ The upregulation of adiponectin in these severe diseases may represent a compensatory response because 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 adiponectin knockout and wild-type mice. In this model, adiponectin stimulates cyclooxygenase-2 expression and synthesis of prostaglandin E₂, a vascular-protective autocooid that inhibits inflammatory cytokine production in cardiac myocytes. Adiponectin-induced expression of cyclooxygenase-2 in myocytes is reduced by inhibition or deletion of sphingosine kinase-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 cyclooxygenase-2 expression, adiponectin protects the myocardium from ischemic injury through its ability to activate AMP-activated protein kinase (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 ischemia/reperfusion injury.²⁷⁶ Notably, a 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 antiatherogenic role. For example, adiponectin suppresses lipopolysaccharide-stimulated TNF- α production,^{292,293} inhibits Toll-like receptor-mediated nuclear factor- κ B activation,²⁹⁴ and enhances the production of the anti-inflammatory cytokine IL-10 in cultured macrophages.^{293,295} Consistently, adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype²⁹⁶ 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.²⁹⁸

Consistent with the above-mentioned *in vitro* findings, overproduction of circulating adiponectin inhibits the formation of atherosclerotic lesions and decreases mRNA levels of class A scavenger receptor, TNF- α and vascular cell adhesion molecule-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, a 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*.

CVD and Adiponectin Receptors

Although a large number of studies have shown that adiponectin acts as a cardiovascular-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 adiponectin receptor (AdipoR) 1 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 cardiovascular 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 antihypertrophic effects of adiponectin.³⁰⁸ Similarly, AdipoR1 has been shown to mediate the proangiogenic actions of adiponectin in cultured endothelial cells.²⁷⁷ Relatively few studies have analyzed the roles of AdipoRs in the cardiovascular 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.

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 glycosylphosphatidylinositol-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 after pressure overload in the heart³¹³ and on adiponectin-stimulated revascularization in a murine model of peripheral artery disease.³¹⁴ Thus, T-cadherin plays a key role in mediating the cardiovascular effects of adiponectin although it lacks a transmembrane signaling domain. Hypothetically, T-cadherin may function as a coreceptor 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.

C1q/Tumor Necrosis Factor-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 cardiovascular system. Systemic delivery of CTRP9 protein reduces myocardial infarct size and apoptosis after MI 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 after MI in an AdipoR1 and AMPK-dependent manner.³²³ Because circulating CTRP9 levels are reduced in mice after ischemia-reperfusion or MI,^{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 MI, 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 fibroblasts³²⁵ and promotes cardiac myocyte survival and VEGF-A expression through its ability to activate an Akt (Ak refers to the mouse strain and t to thymoma)/hypoxia-inducible factor 1 α -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 subjects³²⁹ and in patients with impaired glucose tolerance and type 2 diabetes mellitus.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 cardiovascular 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 cardiovascular system.^{337–340} Systemic administration of omentin-1 attenuates cardiac injury after ischemia-reperfusion in mice through Akt- and AMPK-dependent mechanisms.³⁴¹ In vitro, omentin-1 has been shown to suppress TNF α -induced inflammatory responses in vascular endothelial cells via an AMPK-endothelial nitric oxide synthase 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 cardiovascular dysfunction in obese individuals.

Secreted Frizzled-Related Protein 5

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 in WAT in lean mice, and it is downregulated in severely obese rodents, such as 20-week-old ob/ob mice. Mechanistically, Sfrp proteins are known to function as soluble modulators that sequester wingless-type (Wnt) proteins in the extracellular space and prevent their binding to receptors. In this context, Sfrp5 seems to function as an inhibitor of wingless-type MMTV integration site family member 5A (Wnt5a)-mediated noncanonical Wnt signaling, which contributes to proinflammatory cytokine production via c-Jun N-terminal kinase activation.^{44,344,345} Although some conflicting data have been reported on 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, a study found a positive association between increased serum Sfrp5 levels and high homeostatic model assessment-insulin resistance, 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 increased serum concentration of

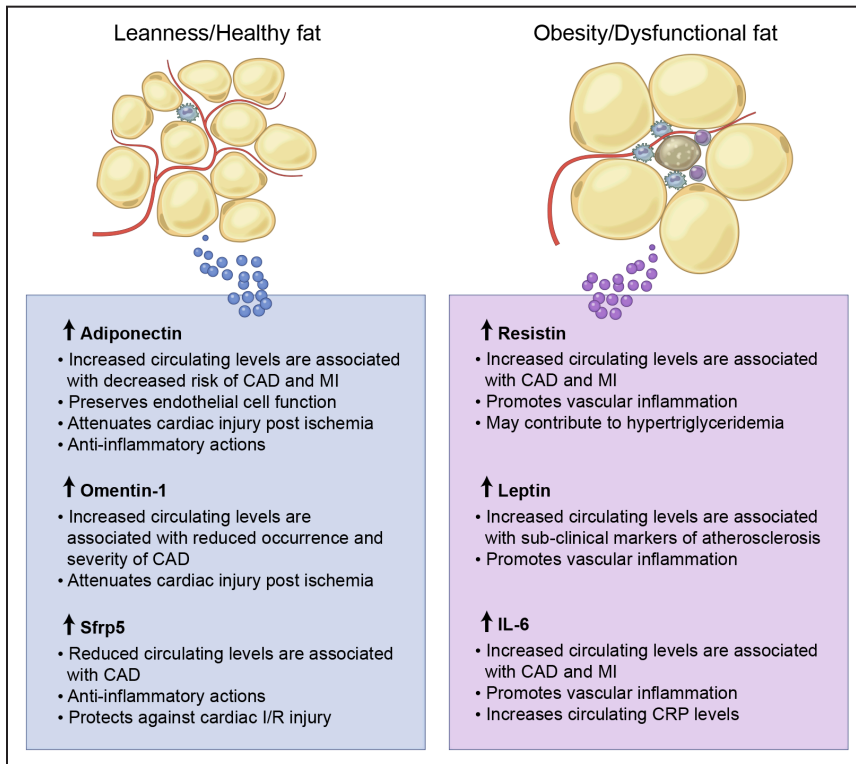


Figure 4. Selected anti- and proinflammatory adipokines with summaries of their regulation and actions in the cardiovascular system. CAD indicates coronary artery disease; I/R, ischemia/reperfusion; and MI, myocardial infarction.

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 ischemia/reperfusion 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 many 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 patients³⁵⁷ 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. 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 cardiovascular complications. Although 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 one 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 cardiovascular risk in obese individuals.

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