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Visceral adiposopathy: a vascular perspective

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Abstract

Obesity has emerged as one of the most critical health care problems globally that is associated with the development of insulin resistance, type 2 diabetes mellitus, metabolic dysfunction and cardiovascular disease. Central adiposity with intra-abdominal deposition of visceral fat, in particular, has been closely linked to cardiometabolic consequences of obesity. Increasing epidemiological, clinical and experimental data suggest that both adipose tissue quantity and perturbations in its quality termed “adiposopathy” contribute to mechanisms of cardiometabolic disease. The current review discusses regional differences in adipose tissue characteristics and highlights profound abnormalities in vascular endothelial function and angiogenesis that are manifest within the visceral adipose tissue milieu of obese individuals. Clinical data demonstrate up-regulation of pro-inflammatory and pro-atherosclerotic mediators in dysfunctional adipose tissue that may support pathological vascular changes not only locally in fat but also in multiple organ systems, including coronary and peripheral circulations, potentially contributing to mechanisms of obesity-related cardiovascular disease.

Keywords

adiposopathy; endothelium; obesity; vascular disease; visceral fat

Introduction

Obesity has emerged as one of the most critical health care problems worldwide as nearly 1.5 billion of the world’s population is either overweight or obese [1]. The cost of battling obesity is estimated to be nearly $2 trillion, ranking third after smoking and military conflicts among the social burdens that impact global gross domestic product. Alarmingly, adult and childhood obesity rates, particularly in categories of severe obesity, are continuing to rise globally with significant short- and long-term health, social and economic consequences [2, 3]. Obesity represents a disease state characterized by chronic systemic inflammation that appears to be derived largely from adipose tissue inflammation and overproduction of pro-inflammatory cytokines such as TNF-α, MCP-1, and IL-6 and activation of NFκB-dependent pathways that are strongly implicated in mechanisms of

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systemic insulin resistance [4]. Obesity is a strong predictor of all-cause mortality and is closely associated with a number of chronic diseases such as insulin resistance, type 2 diabetes mellitus, cancer and ischemic heart disease. Cardiovascular disease is currently the major cause of mortality in this population [5–8]. While cardiometabolic risk increases with rising body mass index (BMI), intra-abdominal deposition of ectopic visceral fat has been more closely associated with cardiovascular risk, metabolic syndrome and type 2 diabetes [9, 10]. In this brief review we will discuss qualitative and quantitative differences between fat depots focusing on ectopic visceral fat as a potential negative regulator of vascular function and whole-body cardio-metabolic disease.

Visceral adiposopathy

Adipose tissue is a complex highly secretory endocrine organ capable of physiological modulation of signals that regulate appetite, energy expenditure, insulin sensitivity, endocrine and reproductive functions, bone metabolism, inflammation and immunity [11–13]. Consisting mostly of adipocytes, fat contains several other cell types including pre-adipocytes, endothelial cells, fibroblasts, mesenchymal cells, macrophages and other leukocytes that reside in the stromal vascular fraction. Although there are complex genetic and environmental components to the development of obesity, the resulting expansion in fat mass appears to occur largely due to an imbalance of food intake and energy expenditure [14]. Clinical studies suggest that subcutaneous adipose tissue accumulation may in part represent a physiological buffer for nutrient surplus, acting as a potential metabolic sink for excess free fatty acids (FFA) and triglycerides. However, in the face of persistent obesogenic stress and limited capacity for regional adipocyte hypertrophy or hyperplasia, adipose tissue storage is forced into ectopic regions in and around specific organs or compartments of the body [15]. Ectopic fat is defined by excess adipose tissue accumulation in locations not classically associated with adipose storage. As such, subcutaneous fat is categorized as a non-ectopic depot and visceral fat as the classic ectopic depot [16]. Certainly, omentum and mesenteric visceral fat is present in normal weight individuals and play an important physiological role. However, the expansion of these depots which are not teleologically designed to accommodate significant adipose storage is associated with functional abnormalities referred to as adiposopathy, or “sick fat” [17]. While we have chosen to focus on ectopic visceral fat specifically for the purposes of this review, accumulation of fat in other ectopic regions such as muscle, kidney, heart and liver have also been linked to adverse cardiometabolic risk and reviewed thoroughly elsewhere [9, 15, 16, 18, 19].

Adiposopathy is classically described as pathogenic adipose tissue changes that occur due to the toxic combination of positive caloric energy balance, sedentary lifestyle and genetic predisposition that results in dysfunctional endocrine, metabolic and immune adaptations [20]. While this occurs in all fat depots to some extent, abnormalities tend to be more prominent in visceral fat. Visceral and subcutaneous adipose depots arise from different origins during development, which may in part explain the propensity for visceral fat to develop differing metabolic, inflammatory, angiogenic and lypolytic properties compared to subcutaneous fat in obesity [21–25]. Subcutaneous fat comprises approximately 80% of total body fat mass, with abdominal visceral adipose tissue accounting for 5%–20% [26]. Despite

not being the dominant adipose depot, clinical studies have demonstrated that FFA, interleukin (IL)-6, C-reactive protein (CRP) and tumor necrosis factor (TNF)-α circulate at higher concentrations in patients with greater deposition of visceral fat. These cytokines and mediators likely exert direct pro-inflammatory effects on target organs and play a role in hepatic insulin resistance [27–34]. Elevated circulating levels of CRP and IL-6 are also independent predictors for the development of type 2 diabetes and risk of myocardial infarction [35, 36]. Alarmingly, systemic inflammation is already evident in obese children [37–40] and associated with endothelial dysfunction and cardiovascular risk factors at early ages [38] recognized in toddlers as young as 3 years old. This is particularly concerning given the long-term disease exposure and potential impact on future metabolic and vascular health [41].

It has been well described in animal models and in some clinical studies that the source of pro-inflammatory cytokines originates largely from non-adipose cells that reside and/or infiltrate the stromal-vascular fraction of fat compartments in obesity [13, 27, 42–45]. The bulk of the immune response appears to be largely macrophage driven, primarily by pro-inflammatory M1 phenotype cells in animal models, although M2 macrophages have also been shown to be increased in clinical studies [46, 47]. The degree of adipose inflammation, however, tends to exhibit greater heterogeneity in clinical studies with lower degrees of adiposopathy being associated with healthier systemic cardiometabolic parameters in obese subjects [48–52]. Data from the Framingham Heart Study show that inflammatory markers correlate significantly with degree of fat burden in both subcutaneous and visceral compartments, but visceral reserves appear to have a stronger relation [53]. Transcriptomic studies of human tissue specimens from our group and others suggest a more atherogenic gene expression profile in visceral compared to subcutaneous fat, characterized by greater expression of pro-inflammatory, oxidative stress-related and anti-angiogenic genes [23, 46, 47, 54–62]. We have recently shown the pivotal role of non-canonical Wnt signaling in obesity-induced adipose inflammation and metabolic dysfunction [56]. Additionally, studies demonstrate that visceral fat releases increased amounts of IL-6, IL-8, vascular endothelial growth factor (VEGF), plasminogen activator inhibitor (PAI)-1, TNF-α and vasoconstrictor prostaglandins compared with subcutaneous adipose tissue, while anti-atherogenic factors such as adiponectin are reduced in obesity [27, 47, 55, 63]. A summary of mediators elaborated by adipose tissue that have been implicated in cardiovascular disease mechanisms is listed in Table 1.

Adiposopathy and vascular dysfunction

Pro-inflammatory mechanisms represent the key mechanistic underpinnings of cardiovascular disease progression from the early stages of endothelial dysfunction to atherothrombosis leading to adverse clinical events [64]. It is tempting to hypothesize that as a consequence of adiposopathy and altered biology of adipose tissue, increased synthesis and release of fat-derived pro-atherogenic mediators might promote the development of atherosclerosis in obesity. Although direct causal links have not yet been definitively established that would allow for therapeutic targets, clinical studies are presently investigating pathogenic adipose-vascular connections. The vascular endothelium plays a critical role in the regulation of arterial tone, blood flow, inflammation and thrombosis.

Endothelial phenotype serves as a barometer of overall vascular health and displays impairment in insulin-resistant states as an early sign of atherosclerosis [65–67]. Furthermore, the severity of dysfunction in coronary and peripheral vessels independently predicts future cardiovascular events [68–73]. Recent work from our laboratory demonstrated a significant association between histological adipose tissue inflammation and systemic vascular endothelial function assessed by brachial artery flow-mediated dilation (FMD) [48]. The findings built on prior data demonstrating a relation between adipose quantity and risk of arterial disease, as macrovascular function is significantly impaired with increasing weight burden in adults and children [74, 75]. Microvascular vasodilation to intra-arterial infusion of endothelium-dependent agonist acetylcholine is also blunted in obese subjects and tracks measures of insulin sensitivity and central adiposity independently of other cardiovascular risk factors [76]. Imaging computed tomography (CT) or magnetic resonance imaging studies of fat compartments identify visceral fat volume to be more highly associated with impaired flow-mediated vasodilation compared to subcutaneous [77, 78].

We have recently demonstrated that in BMI-matched obese individuals, reduced adipose tissue inflammation was associated with improved insulin sensitivity, decreased pro-atherogenic gene expression and preserved vascular function similar to lean subjects [50]. In multivariate analyses, both waist circumference and adipose inflammation were independent predictors of FMD, suggesting that in addition to obesity burden qualitative features of adipose tissue may be an important determinant of cardiovascular disease risk. This notion is supported by other clinical data demonstrating extensive adipose tissue inflammatory changes in insulin-resistant but not BMI-matched insulin-sensitive subjects [79]. Additionally, recent data from the Framingham Heart Study showed that lower CT radiodensity attenuation of adipose tissue, as measured by Hounsfield units (HU), was closely linked to adverse metabolic parameters such as insulin resistance beyond quantification of total fat volume [80]. Thus, CT imaging differentiation of tissue HU may provide a non-invasive and indirect measure of adipose tissue composition and quality. As such, adipose tissue with lower lipid content, smaller adipocytes, altered fibrosis and higher vascularity may exhibit less negative HU [80, 81]. Clinical studies continue to emerge supporting a relationship between adiposopathy and systemic disease, and it appears likely that collectively quality, quantity and location of adipose accumulation all relate to whole-body disease processes, but pathogenic mechanisms and their relative contributions remain poorly understood.

Vasomotor dysfunction in visceral fat

We recently considered that if adipose tissue is a regulator of vascular function with visceral milieu seemingly more pro-atherogenic, then differences in vasomotor function should be manifest in arterioles examined from different fat compartments within the body. Inflammatory cytokines over-expressed in visceral fat may impair vasoregulatory and anti-atherogenic properties owing in part to reduced endothelial nitric oxide synthase (eNOS) and loss of nitric oxide (NO) bioactivity, leading to vasomotor dysfunction. In this regard, our group [47, 55] and others [82–89] have started to examine these mechanistic interactions by directly studying physiological properties of microvessels within human fat by utilizing

videomicroscopy and culture myograph techniques. In recent experiments, we collected paired subcutaneous and visceral adipose tissue biopsy samples from obese subjects during planned bariatric surgery, isolated tiny microvessels (75–250 μm in diameter) from different fat compartments and assessed vasodilator function using videomicroscopy. Endothelium-dependent, acetylcholine-mediated vasodilation was severely impaired in visceral arterioles compared to the subcutaneous depot [47]. The degree of vasomotor impairment is profound and consistent across varying systemic phenotypes. Our most recent cumulative data from a cohort of 104 obese subjects are displayed in Figure 1. Treatment with N^{ω}-nitro-L-arginine methyl ester significantly reduced acetylcholine-mediated vasodilation by 40% in subcutaneous arterioles, whereas no significant effect was observed in visceral microvessels that already exhibited severe dysfunction, suggesting impairment in vascular NO bioavailability. Complementary to physiological studies, we observed significant impairment in acetylcholine-mediated activation of eNOS at the phosphorylation site serine 1177 in vascular endothelial cells isolated from visceral fat [55]. Responses to non-endothelium-dependent agonists papaverine and sodium nitroprusside were preserved in both depots, indicating intact smooth muscle responses and thus selective impairment in endothelial function. Similar findings have been confirmed by others who reported arteriolar dysfunction in visceral fat [82] and demonstrated that the impairment is specific to the state of obesity as arterioles isolated from visceral tissue of lean subjects exhibit preserved vasomotor function [83, 84].

There are likely multiple mechanisms that negatively regulate vascular responses in visceral obesity. Cytokinedriven inflammation likely plays a key role as we and others have demonstrated the adipose secretome and transcriptome to be markedly pro-inflammatory in visceral depots. Experimental studies in mice demonstrate that transplantation of inflamed visceral fat accelerates atherosclerosis in Apo-E knockout mice [90]. Adipose gene expression of inflammatory mediators correlate inversely with acetylcholine- mediated vasodilation of human microvessels [47, 55]. Endothelial cells isolated from visceral fat exhibit upregulated expression of pro-inflammatory mediators such as CCL-5, IL-6, TNF-α and toll-like receptor-4 [47]. More direct evidence that inflammatory mechanisms are involved is provided by experimental studies demonstrating histological vascular inflammation and reversal of vasomotor dysfunction following treatment with IL-6 and TNF-α antagonists [83, 88]. However, other pathogenic processes that involve oxidative stress, mitochondrial dysfunction and endoplasmic-reticulum stress are likely intertwined and may contribute to obesity-related vascular disease. For example, recent data demonstrated evidence of impaired NO-dependent vasodilation, mitochondrial hyperpolarization, reduced mitochondrial mass and increased mitochondrial superoxide production in the adipose tissue of type-2 diabetic subjects [87]. We recently identified increased expression of cyclooxygenase (COX)-mediated vasoconstrictor prostanoids in visceral fat that contribute to endothelial dysfunction. Treatment with indomethacin, a COX-specific inhibitor, significantly improved endothelium-dependent vasodilation by twofold. This improvement was associated with phosphorylation and stimulation of eNOS at serine 1177 in visceral endothelial cells, supporting a contribution of the eicosanoid/cyclooxgenase pathway to adipose microvascular dysfunction in obesity [55]. Vasodilator responses in the adipose microvasculature have been shown to correlate with cardiovascular risk factors and

brachial arterial responses; thus, investigation of the adipose microenvironment may provide novel translational information relevant to systemic vascular disease mechanisms [85, 89].

Vascular insulin resistance

Insulin resistance represents a highly prevalent metabolic disturbance in obesity. In particular, regional adiposity with central accumulation of visceral fat has been closely associated with insulin resistance, endothelial dysfunction and cardiovascular disease [12, 16]. Although insulin resistance generally implies diminished actions of insulin in mediating glucose uptake in target organs such as fat, liver and muscle, insulin also exerts important physiological actions upon the vasculature that regulate metabolism and blood flow via eNOS activation and endothelial NO production [91, 92]. In animals, endothelium-specific deletion of the insulin receptor impairs eNOS bioavailability, promotes atherogenesis and is associated with whole-body insulin resistance, hypertension and ischemia [93]. Recent work from our group also demonstrated impaired insulin-stimulated eNOS phosphorylation, inflammation and vasodilator dysfunction of endothelial cells isolated from the vascular wall of obese diabetics [94]. Under conditions of obesogenic stress, insulin signaling in the vasculature becomes impaired promoting vascular inflammation, vasoconstriction and progression of atherosclerotic plaques [91, 93]. Compelling evidence from animal and clinical studies support a close link between insulin resistance and development of vascular disease, as preservation of insulin signaling represents a fundamental homeostatic mechanism of blood vessels [95–98]. Currently, however, regulatory mechanisms that govern these pathogenic processes are incompletely understood.

In our videomicroscopy experiments, we observed significant impairment in insulin-mediated vasodilation of visceral compared to subcutaneous adipose arterioles harvested from obese subjects as shown in Figure 2. The response to insulin was severely blunted in visceral compared to subcutaneous microvessels indicating a profound collapse of vascular homeostasis. This is consistent with responses to other agonists discussed above, demonstrating impairment of visceral arterioles to a broad range of physiological and pharmacological stimuli that modulate normal vascular function. We found evidence of down-regulated components of the insulin signaling cascade and reduced insulin-mediated activation and phosporylation of Akt in visceral fat. Disruption of this pathway polarizes insulin’s actions toward mitogen-activated protein kinase and proliferative pathways that support atherogenesis [99]. Mediators involved in promoting vascular dysfunction in adipose tissue may also have systemic pathophysiological actions that contribute to cardiometabolic disease and atherosclerosis, although specific therapeutic targets remain unclear. There is growing interest in targeting insulin sensitivity to combat obesity-related cardiovascular disease, especially in light of recent clinical data linking improved long-term cardiovascular survival following bariatric weight loss primarily to parameters of insulin resistance [100]. In line with these findings, we have recently shown that improved endothelial function with weight loss was directly tied to recovery of insulin sensitivity [101].

Angiogenesis and visceral adiposity

Angiogenesis, the generation of new blood vessels, is critical for adequate fat expansion and adipose tissue remodeling. As adipose tissue expands and regresses with weight change, tightly controlled regulation of angiogenesis within adipose tissue is required to maintain metabolic and oxygen exchange that is critical for maintaining whole body homeostasis [102]. Experimental studies suggest that expanding adipose tissue may “outgrow” its blood supply in obesity possibly owing to deficient angiogenesis that triggers a vicious cycle of ischemia, hypoxia, necrosis and inflammation within the adipose milieu that promotes whole body metabolic dysfunction [103–106]. Capillary dropout and deficient vascularization occur in the adipose depots of animals and humans, particularly in visceral fat, and is associated with inflammation and metabolic dysfunction [57, 104–108]. Experimental studies demonstrate that adipose-specific deletion of VEGF-A induces adipose hypoxia, apoptosis, inflammation and metabolic abnormalities including insulin resistance and hyperlipidemia [109], while its over-expression promotes neovascularization and improves glucose metabolism [110]. These data prompt speculation that qualitative features of fat and altered tissue homeostasis as a function of impaired vascular support may play a role in shaping metabolic health.

We and others have recently shown that subcutaneous adipose tissue exhibits higher capillary density and angiogenic capacity compared to the visceral depot despite paradoxically higher expression of several proangiogenic factors including VEGF-A [47, 57, 111–113]. Affymetrix microarray analysis reported significant differences in gene transcripts associated with angiogenesis between visceral and subcutaneous fat in obese humans [57]. Among several mediators, pro-angiogenic ANGPTL-4 is down-regulated in visceral fat and may play an important role [108]. We recently described a splice variant isoform of VEGF-A, anti-angiogenic VEGF-A_{165}b, that is over-expressed in human visceral fat and associated with impaired adipose tissue angiogenesis [111]. Targeted VEGF-A_{165}b inhibition restored pro-angiogenic VEGF receptor activation and vascularization. Circulating VEGF-A_{165}b blood levels were elevated in obese compared to lean subjects and decreased significantly following bariatric weight loss. This latter finding has potential clinical implications as up-regulation of systemic VEGF-A_{165}b in the state of obesity raises the possibility that this anti-angiogenic isoform could contribute to vascular disease and ischemia beyond the adipose environment. In this regard, our group recently described the key role of anti-angiogenic VEGF-A_{165}b in mechanisms of peripheral arterial disease in animal models and humans [114]. 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 cardio-metabolic complications. However, whether modulation of adipose tissue angiogenesis may alter clinical consequences of human obesity remains an open question.

Weight loss and visceral adiposity

There is great interest in promoting weight loss for the reversal of many obesity-related complications. Several short-term studies have shown that weight reduction improves cardiovascular function [115–120]. Bariatric surgery currently represents the most effective

and durable weight loss intervention. It is also the sole weight reduction method shown to reduce long-term (> 10 year) cardiovascular mortality, largely owning to decreased myocardial infarction risk [100, 121, 122]. Specific mechanisms for this improvement in cardiovascular health remains largely unclear, though recent data from the Swedish Obesity Study identified plasma insulin levels as the primary predictor of risk reduction [100]. We have similarly shown that improvement in systemic vascular function following significant weight loss from bariatric surgery is specifically tied to insulin sensitivity [101]. Few studies have examined the effect of bariatric weight loss on ectopic fat and relation to overall cardiometabolic risk and reported greater reduction in visceral compared to other ectopic regions and subcutaneous fat depots [123, 124]. Weight loss in insulin-dependent, type-2 diabetic subjects incurred by calorie reduction also showed preferential loss in visceral compared to subcutaneous adiposity in parallel with improved cardiovascular risk factors [125]. Serial imaging studies by CT in the multi-ethnic study of atherosclerosis study show that only visceral fat volume and its longitudinal changes independent of BMI were strongly associated with metabolic phenotypes [126]. While the concept that visceral fat “quantity” links to cardiometabolic risk is well accepted, essentially nothing is known about weight loss-induced “qualitative” alterations in visceral fat in relation to systemic disease. The literature suggests that bariatric surgery favorably remodels adipose tissue by attenuating macrophage-mediated inflammation and cytokine production [127, 128], and improved microvascular function has also been reported in subcutaneous fat [129]. However, additional studies are needed to examine the relative contributions of visceral adiposity and adiposopathy to human disease. A summary concept schematic illustrating the role of obesity in cardiometabolic disease is provided in Figure 3.

Conclusions

Obesity will remain one of the most important heath care challenges worldwide, and improving our understanding of mechanisms of obesity-related vascular disease is critical. Clinical, epidemiological and experimental data suggest that visceral adiposity is more closely linked to obesity-related cardiovascular disease. We have provided evidence that the visceral adipose tissue microenvironment is associated with profound abnormalities in vascular homeostasis. With clinical data consistently linking visceral adiposity burden to cardiovascular risk, characterization of pathophysiological mechanisms learned from the adipose microenvironment may provide valuable translational clues to mechanisms of systemic disease in human obesity.

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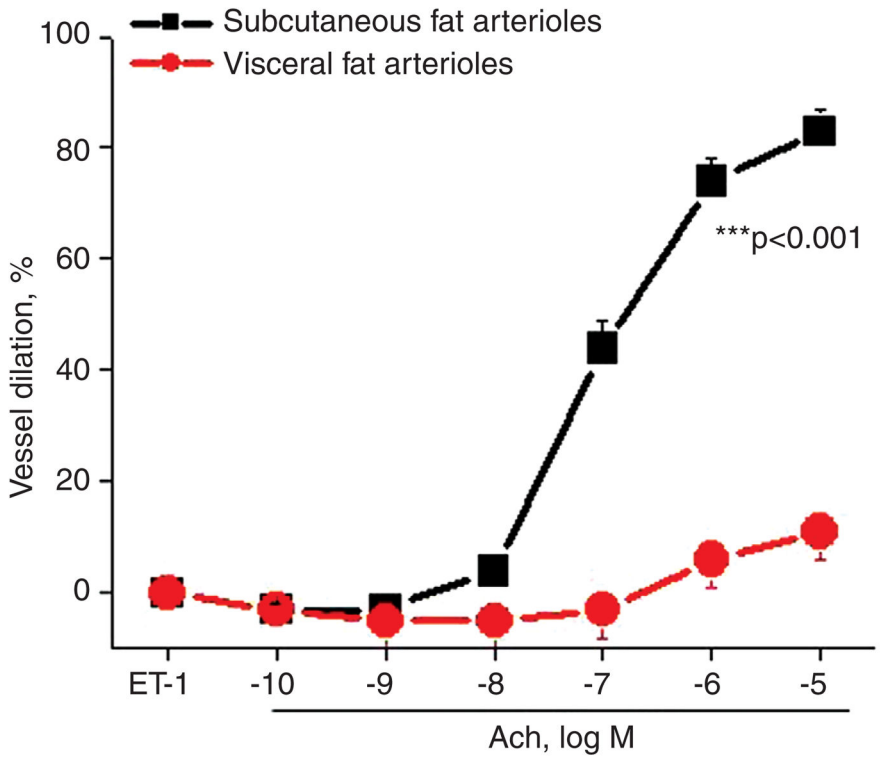

Figure 1.

Acetylcholine-mediated, endothelium-dependent vasodilation in blood vessels isolated from visceral fat is severely impaired compared to arterioles isolated from subcutaneous adipose tissue ($p < 0.001$, $n = 104$ obese subjects).

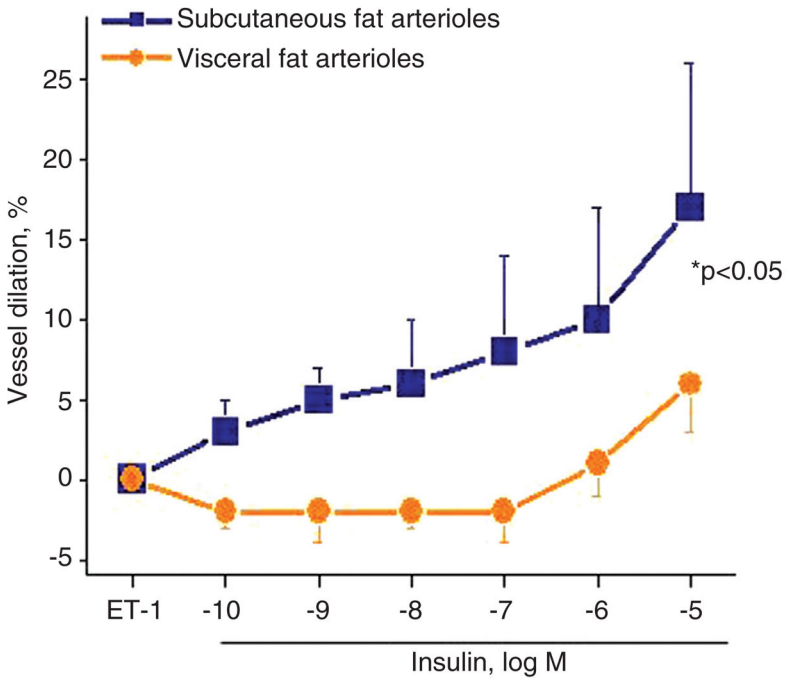

Figure 2.

Insulin-mediated, endothelium-dependent vasodilation is significantly impaired in arterioles from visceral fat compared to blood vessels isolated from subcutaneous adipose tissue ($p < 0.05$, $n = 23$ obese subjects).

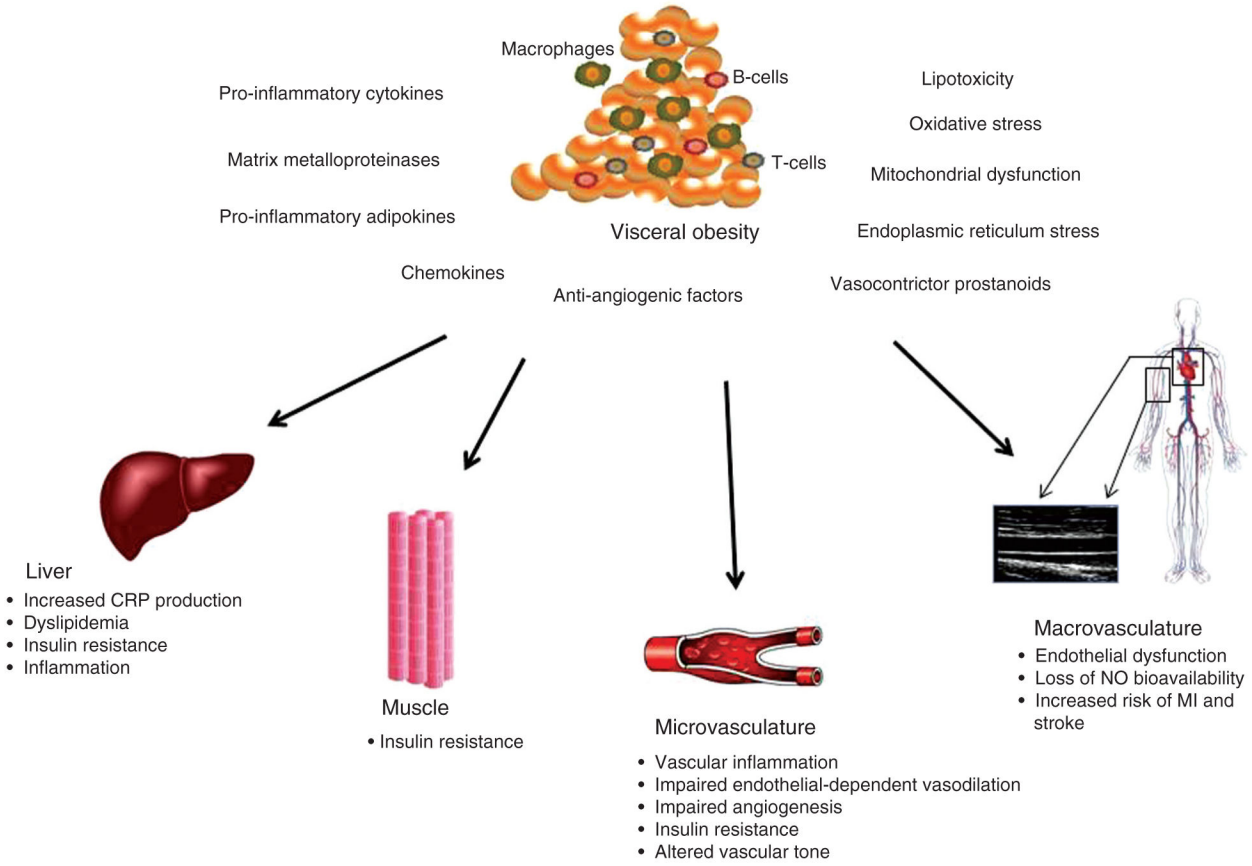

Figure 3.
Role of adiposopathy in cardiometabolic disease.

Table 1

Adipose-derived mediators implicated in cardiovascular disease mechanisms.

Adiponectin
Angiopoietin-like 2 (ANGPTL-2)
Angiopoietin-like 4 (ANGPTL-4)
Angiotensinogen
Apelin
C-reactive protein (CRP)
Chemokine (C-C motif) ligand-5 (CCL-5)
Free fatty acids (FFA)
Intercellular adhesion molecule-1 (ICAM-1)
Interleukin-18 (IL-18)
Interleukin-6 (IL-6)
Leptin
Matrix metalloproteinase
Monocyte chemotactic protein-1 (MCP-1)
Nuclear factor kappa B (NFκB)
Omentin
Plasminogen activator inhibitor-1 (PAI-1)
Prostaglandins
P-selectin
Rentionol binding protein 4 (RBP-4)
Resistin
Serum amyloid A (SAA)
Toll-like receptor-4 (TLR-4)
Tumor necrosis factor-alpha (TNF-α)
Vascular cell adhesion molecule-1 (VCAM-1)
Vascular endothelial growth factor-A (VEGF-A)
Vascular endothelial growth factor- A_{165}b (VEGF-A_{165}b)
Visfatin
Wnt5a