

## Review Article

# Adipocyte dysfunction and hypertension

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**Abstract:** Obesity is increasingly a public health problem due to its high risk of developing insulin resistance, diabetes, atherosclerosis, hypertension, chronic kidney disease, and increased cardiovascular morbidity and mortality. In particular, the association of obesity and hypertension is well recognized; however, the underlying mechanisms are not fully understood. This article reviews recent advancements of cellular and molecular mechanisms by which adipocyte dysfunction and obesity contribute to hypertension through endocrine and paracrine effects of the adipose tissue-derived adipokines on the function of vascular endothelial cells, smooth muscle cells and macrophages.

**Keywords:** Obesity, adipocyte, adipokine, vascular function, hypertension

### Introduction

Obesity is increasingly a public health problem due to its high risk of developing insulin resistance, diabetes, atherosclerosis, hypertension, chronic kidney disease, and increased cardiovascular morbidity and mortality [1-4]. In particular, the relationship between obesity and hypertension is well recognized; some studies suggest that 65-75% of the risk for hypertension is attributed to excess body weight [5-7]. Blood pressure can be lowered when body weight control is effective by using caloric restriction, aerobic exercise, weight loss drugs, or bariatric surgery [8-10]. On the other hand, it has been shown that activation of sympathetic nervous system (SNS) and renin-angiotensin system (RAS) and impairments of pressure natriuresis play an important role in the development of obesity-associated hypertension [11-16]. Now it is clear that adipose tissue is an active endocrine and paracrine organ, which releases a variety of cytokines and hormones (adipokines) to influence not only energy homeostasis but also blood pressure regulation [17-19]. This review summarizes recent advancements that link adipocyte dysfunction and obesity to vascular deregulation and hypertension through endocrine and paracrine mechanisms of adipose tissue-secreted factors. We will specifically fo-

cus on the role of adipokines in the regulation of vascular endothelial and smooth muscle cell function and inflammation.

### Adipose tissue

Adipose tissue consists of white adipose tissue (WAT) and brown adipose tissue (BAT). WAT makes up to 20% to 25% of total body weight; it acts mainly as an energy store (in the form of triglycerides and free fatty acid [FFA]) however expands during obesity. WAT accumulation is responsible for many adverse outcomes of obesity such as hypertension, insulin resistance, atherosclerosis and chronic kidney disease [17-19]. The role of BAT is to maintain body temperature during the exposure to a cold environment, but not to maintain a normal body weight in the obesogenic environment [20]. The major cell type in an adipose tissue is adipocytes, which are mixed with endothelial cells, vascular smooth muscle cells (VSMCs), macrophages, and fibroblasts. Adipose tissue is predominantly located around internal organs (i.e., visceral adipose tissue), underneath the skin (i.e., subcutaneous adipose tissue), and around blood vessels (i.e., perivascular adipose tissue, PVAT).

In the last few years, a large amount of scientific knowledge about adipose tissue has been

learnt. Adipose tissue is no longer considered solely a fat deposit, but one of the largest endocrine organs, producing a variety of bioactive factors termed adipokines including cytokines (e.g., tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], interleukin-6 [IL-6], plasminogen activator inhibitor-1 [PAI-1], fibrinogen, Visfatin and Omentin) and hormones (e.g., leptin, angiotensinogen, agouti-related peptide, resistin and adiponectin). Adipokines act in either paracrine or endocrine manner to regulate energy homeostasis, glucose and lipid metabolism, and cardiovascular function. Bioactive factors secreted from the adipose tissue can easily enter the systemic circulation and exert their effects on other peripheral organs or central nervous system through the brain-blood barrier. In particular, PVAT has direct contact to the adventitia of vessels without an anatomical barrier; bioactive factors secreted by PVAT may readily gain access into the blood vessel wall and function in a paracrine fashion to transduce metabolic signals to blood vessels. The identification of adipokine receptors in vascular endothelia and smooth muscles suggests that adipose tissue derived bioactive factors might have direct vasoactive properties and participate in the regulation of vascular function and peripheral resistance [21].

### **Adipokines and vascular function**

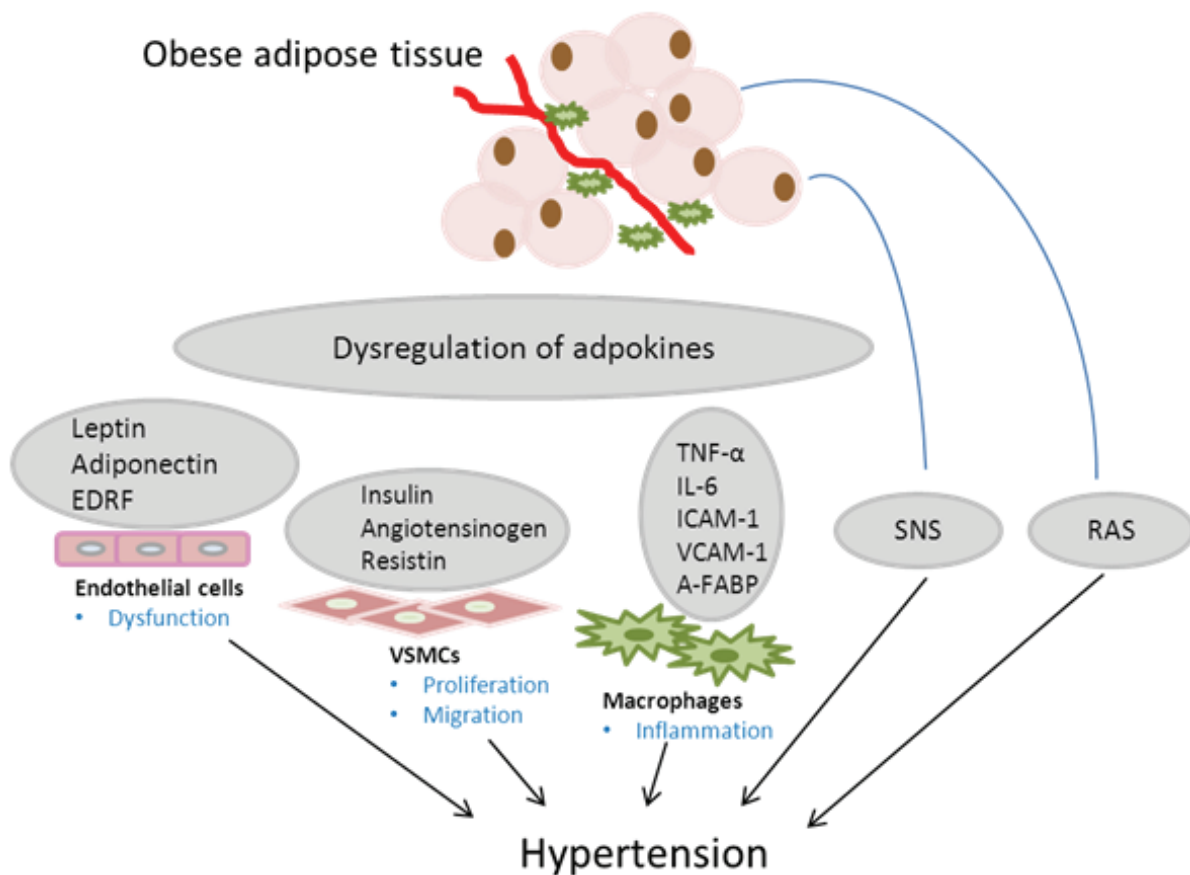
The cross-talk between adipose tissue and the vasculature appears to play an important role in maintaining vascular homeostasis [22, 23]. Both WAT and BAT, particularly PVAT, modulate vascular reactivity, inflammation and remodeling through the release of a variety of adipokines, which target adipocytes, endothelial cells, VSMCs and macrophages. Adipocyte dysfunction in obesity can lead to dysregulation of glucose and lipid metabolism, coagulation and inflammation [24, 25]. Obese adipose tissue is characterized by adipocyte hypertrophy and hyperplasia and excessive infiltration of macrophages and lymphocytes, leading to elevated production of pro-inflammatory adipokines and vasoactivators that result in endothelial dysfunction, VSMCs proliferation and migration, and vascular inflammation. Unlike most adipokines with detrimental effects on the vasculature, adiponectin exerts beneficial effects on vascular disorders through its vasodilator, anti-inflammatory and anti-oxidative activities in vascular cells [26, 27].

### *Adipokines and endothelial function*

Endothelial cells form the chief physical barrier between blood and vessel wall. For vascular homeostasis, endothelial cells play a critical role in the regulation of vasomotion, coagulation and inflammation by producing a variety of mediators such as prostacyclin, endothelium derived relaxing factor (EDRF)/nitric oxide (NO), angiotensin II, and endothelin-1 (ET-1) [23, 28]. Insulin induced vasodilation, an effect mediated by the NO release, is impaired in obese individuals who display insulin resistance [29]. Adiponectin directly exerts effects on endothelial function through eNOS-dependent and COX-2-dependent regulatory mechanisms, respectively [30-32] (**Figure 1**). Resistin promotes endothelial cell activation through the release of ET-1 and up-regulation of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) [33]; TNF- $\alpha$  inhibits eNOS, therefore causing a reduction in NO bioavailability [34].

### *Adipokines and smooth muscle cell function*

VSMCs form middle layers within the vessel wall and control blood flow by contraction and relaxation in response to external stimuli. VSMCs do not proliferate under normal physiological condition; however, after injury, aberrant proliferation and migration of VSMCs can lead to pathologic changes in the vessel wall. Adipose tissue at physiological state has been shown to preserve normal VSMC function. Removal of periadventitial fat enhances neointima formation after endovascular injury, which can be attenuated by transplantation of subcutaneous adipose tissue from mice fed on regular chow [35]. In patients with coronary artery bypass surgery, harvesting the saphenous vein with preserved surrounding tissue (mainly PVAT) provides better short- and long-term patency rates [36]. However, during obesity, accumulation of visceral adipose tissues promotes synthesis of proinflammatory adipokines which cause an increase in the level of reactive oxygen species (ROS) derived from NADPH oxidase. ROS are important signaling molecules or second messengers that regulate the proliferation, hypertrophy, and migration of VSMCs [37, 38]. The vascular-protective effects of adiponectin have been largely attributed to its anti-oxidant actions [26]. Adiponectin exerts an inhibitory effect on the proliferation and migration of VSMCs by interacting with various atherogenic growth fac-



**Figure 1.** Obesity-associated adipocyte dysfunction contributes to hypertension by endocrine and paracrine effects of adipokines on endothelial cells, vascular smooth muscle cells (VSMCs) and macrophages. EDRF, Endothelium derived relaxing factor; TNF- $\alpha$ , Tumor necrosis factor- $\alpha$ ; IL-6, Interleukin-6; VCAM-1, Vascular cell adhesion molecule-1; ICAM-1, Intercellular adhesion molecule-1; A-FABP, Adipocyte fatty acid binding protein; SNS, Sympathetic nervous system; RAS, Renin-angiotensin system.

tors, including heparin-binding epidermal growth factor-like growth factor, platelet-derived growth factor and basic fibroblast growth factor, thereby blocking the binding of these growth factors to their respective membrane receptors and subsequent ERK1/2 activation and AMPK phosphorylation [39]. Adiponectin-deficient mice display enhanced proliferation of VSMC and increased neointimal thickening after mechanical injury, and these changes are reversed by adenovirus-mediated expression of adiponectin [26]. In contrast, Resistin induces human aortic SMC proliferation by ERK1/2 and Akt signaling pathways [40]. In human VSMCs, insulin inactivates the small GTPase RhoA and its target, Rho kinase, thereby leading to decreased phosphorylation of myosin light chain and subsequent vasodilation [41] (**Figure 1**).

#### *Adipokines and macrophage function*

Recent evidence suggests that the infiltration of macrophages in adipose tissue play an important role in the chronic inflammatory state and metabolic dysfunction associated with obesity [42]. The activity of macrophages in adipose tissue perpetuates a vicious cycle of increased macrophage recruitment, production of inflammatory cytokines, and impaired adipocyte function. Adipokines play multiple roles in this inflammatory process. TNF- $\alpha$  increased expression of ICAM-1 and VCAM-1 in vascular tissue by the activation of the nuclear factor-kappa B (NF- $\kappa$ B) signaling pathway, thereby leading to the enhancement of monocyte adhesion to the vessel wall and up-regulation of inducible nitric oxide synthase (iNOS), interleukins, superoxide

dismutase, etc [43]. Leptin, especially in the presence of high glucose, stimulates macrophages to accumulate cholesterol [44]. Resistin has been shown to induce pentraxin 3, an inflammatory mediator in human endothelial cells [45]. Adipocyte fatty acid binding protein (A-FABP) potentiates toxic lipids-induced inflammation in macrophages by inducing endoplasmic reticulum stress, thereby leading to the activation of JNK and NF- $\kappa$ B signaling pathways [46]. Frizzled-related protein 5 (Sfrp5) secretion by adipocytes exerts salutary effects on metabolic dysfunction by controlling inflammatory cells within adipose tissue [47] (**Figure 1**).

### Adipocyte dysfunction and hypertension

Normal adipose tissue maintains a specifically balanced adipokine profile, which modulates vascular homeostasis via endocrine and paracrine pathways [22, 23]. Excessive accumulation of adipose tissue may alter the expression of the adipokine profile and consequently the physiological effects of adipokines on the vessels. Excessive weight gain contributes to increased blood pressure in most patients with essential hypertension [5]. Blood pressure is a function of cardiac output and peripheral resistance. Weight gain leads to increased cardiac output and blood volume, which might be related to activation of SNS and RAS, and to physical compression of the kidneys by fat accumulation within and around the kidneys and excessive visceral fat. SNS activation and physical compression of the kidneys both cause activation of the RAS, and pharmacological blockade of either the RAS or the SNS attenuates obesity induced hypertension by at least 50-60% [48]. Several mediators in the obesity-associated hypertension have been suggested, including hyperinsulinemia, angiotensin II, FFAs and leptin. Hyperinsulinemia could lead to a rise in blood pressure by enhancing sodium retention [49, 50]. Adipocytes secrete angiotensinogen, which can be converted to angiotensin I and then angiotensin II, a potent vasoconstrictor and promoter of sodium and water absorption [12, 14]. FFAs could promote hypertension by means of adrenergic stimulation, increase in oxidative stress, endothelial dysfunction, or stimulation of vascular cell growth [51, 52]. Leptin activates SNS by stimulating opiomelanocortin neurons, with subsequent activation of central nervous system melanocortin 4 receptors [53]. The physiological importance of leptin in blood pres-

sure regulation has been demonstrated in animal models [54]. Obese Ob/ob mice deficient in leptin have significantly decreased blood pressure [55]. Increased peripheral resistance due primarily to changes in vascular structure and function appear to be the fundamental abnormality in hypertension. Adipokines induce the functional and structural changes in the vessels by endothelial dysfunction, VSMC proliferation and migration and vascular inflammation, thereby regulating vascular responses to constrictor and dilator stimuli and contribute to the increased arterial pressure.

### Conclusion and future perspectives

Adipocyte dysfunction and obesity contributes to hypertension by the endocrine and paracrine effects of adipose tissues-derived adipokines on vascular endothelial cells, VSMCs, and inflammatory cells including macrophages. Thus, investigations of adipokines and their local and systemic effects on vascular function may aid identification of novel molecular targets for treatment of obesity and obesity-associated hypertension.

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## Adipocyte dysfunction and hypertension

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