Advances in the Pathogenesis of Adipose Tissue and Obesity-Related Hypertension: Postprint

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Abstract

The prevalence of obesity-related hypertension has risen significantly worldwide, becoming a focal point of attention in the current medical community. Obesity increases the difficulty of hypertension control, promotes cardiovascular and cerebrovascular damage, and aggravates disease burden. Abnormal expansion and remodeling of adipose tissue are considered core manifestations of obesity, which are closely associated with hypertension pathogenic mechanisms including renin-angiotensin-aldosterone system activation, adipokine imbalance, inflammatory response, sympathetic activation, and insulin resistance. Given that the functional classification, somatic distribution, and endocrine effects of adipose tissue exhibit remarkable heterogeneity and complexity, this article systematically reviews the latest knowledge on adipose tissue, with emphasis on introducing different classifications, distributions, and pathological mechanisms of adipose tissue and their relationships with obesity-related hypertension, and provides an overview of current research evidence and future directions, offering new insights for basic and clinical research on obesity-related hypertension and inspiring investigation of emerging therapeutic targets.

Full Text

Adipose Tissue and the Pathogenesis of Obesity-Related Hypertension

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Abstract

The global prevalence of obesity-related hypertension is rising sharply, drawing significant attention in the medical field. Obesity complicates blood pressure management and exacerbates cardiovascular damage and disease burden. The abnormal expansion and remodeling of adipose tissue, central to obesity, are closely linked to hypertension pathogenesis through mechanisms including renin-angiotensin-aldosterone system (RAAS) activation, adipokine imbalance, inflammatory responses, sympathetic nervous system activation, and insulin resistance. Given the extreme heterogeneity and complexity of adipose tissue functional classification, somatic distribution, and endocrine effects, this review systematically examines current knowledge on adipose tissue, focusing on its classification, distribution, pathological mechanisms, and connections to obesity-related hypertension. We also summarize current research evidence and future directions, offering new insights for basic and clinical research on obesity-related hypertension and inspiring investigation of emerging therapeutic targets.

Keywords: Obesity; Hypertension; Obesity-related hypertension; Adipose tissue; Pathological mechanisms; Review

Obesity-related hypertension refers to hypertension that is closely associated with obesity, with effective blood pressure reduction through weight control being its key characteristic [1]. According to WHO surveys, as of 2016, the global number of obese individuals was approximately double that of 1975 [2]. In 2020, about 39 million children under five years old were overweight or obese [2]. By 2010, 31% of adults worldwide (1.39 billion people) had hypertension, and due to population aging and increasing lifestyle risk factors, global hypertension prevalence continues to rise [3]. Numerous studies have confirmed that overweight and obesity are major risk factors for hypertension and adverse cardiovascular events [4-6]. The Framingham Heart Study demonstrated that 65% of primary hypertension in women and 78% in men could be attributed to weight gain [7], with hypertension prevalence in overweight and obese patients reaching 61-77% [8]. In China, obesity-related hypertension and its associated cardiometabolic risks are also increasing. ZHANG et al. [9] analyzed data from the China Health and Retirement Longitudinal Study (CHARLS) and found that in 2015, among Chinese adults aged 45 and older, the prevalence of obesity-related hypertension was 22.7%, affecting approximately 120 million people and accounting for up

to 66% of all hypertension cases. SUN et al. [10] projected that by 2030, the prevalence of overweight/obesity and hypertension among Chinese adults would reach 71% and 35%, respectively.

Adipose tissue, the primary organ for energy storage, undergoes massive expansion and remodeling that is considered the core pathological manifestation of obesity [11]. In fact, adipose tissue is a dynamic organ distributed throughout the body, located in subcutaneous and visceral regions, and composed of adipocytes, preadipocytes, mesenchymal stem cells, fibroblasts, blood vessels, nerves, macrophages, and immune cells [12]. Human adipose tissue can be classified based on cellular composition and function into white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue. Its distribution also involves multiple body sites. Current research indicates that different fat depots have distinct pathological mechanisms and significance in cardiovascular diseases such as hypertension [13]. Obesity-induced hypertension involves multiple neuroendocrine mechanisms, including dysregulation of vasoactive and pro-inflammatory adipokines, hyperinsulinemia and insulin resistance, and kidney injury. As researchers have deepened their understanding of adipose tissue, it has become clear that dysfunction in any of its three major functions—lipid storage, endocrine function, and insulin responsiveness—can significantly impact cardiometabolic health [12]. Therefore, this review examines recent research on the role of adipose tissue classification, somatic distribution, and mechanisms in the pathogenesis of obesity-related hypertension, aiming to deepen understanding of this field and provide insights for preventing and treating obesity-related hypertension.

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1. Adipose Tissue Expansion and Functional Classification

Adipose tissue responds to energy excess through two dynamic mechanisms: hyperplasia and hypertrophy, with regulatory characteristics and metabolic impacts showing significant variation by age, sex, and fat depot distribution. Hyperplasia occurs primarily through proliferation and differentiation of preadipocytes into new adipocytes, a process notably active before adulthood, especially in abdominal subcutaneous adipose tissue [14]. Research confirms that subcutaneous fat depots form a protective expansion pattern by continuously generating metabolically flexible small adipocytes, effectively delaying insulin resistance and inflammation [15,16]. After adulthood, preadipocyte proliferation capacity declines significantly, activating only partially under specific stimuli such as long-term high-fat diet [17]. Hypertrophy, characterized by expansion of existing cells and adipose tissue remodeling, shows a marked predilection in visceral fat depots [18,19]. Compared with hyperplasia, pathological hypertrophy demonstrates stronger correlation with obesity-related metabolic risk: when lipid storage capacity is exceeded, hypertrophic adipocytes trigger ectopic lipid deposition through a "spillover" effect of free fatty acids, leading to lipotoxicity, insulin resistance, and type 2 diabetes in non-adipose

tissues [20].

1.1 White Adipose Tissue (WAT)

WAT is the predominant form of adipose tissue in humans [21]. It serves not only as an energy storage depot but also as a highly active endocrine organ that secretes nitric oxide, leptin, and other adipocytokines and mediators, exerting autocrine, paracrine, and endocrine effects on neighboring cells or distant organs. WAT accumulation, particularly visceral deposition, is a key determinant of increased relative risk for hypertension and cardiovascular disease. Additionally, as total fat increases, deposition of epicardial and perivascular WAT also rises [22-24], with their physiological functions discussed further in the section on adipose tissue distribution.

1.2 Brown Adipose Tissue (BAT)

BAT is a specialized adipose tissue that, unlike WAT, is relatively scarce in adults, comprising 4.3% of total fat mass. In adults, BAT is found in the cervical, supraclavicular, axillary, paraspinal, mediastinal, and abdominal regions [25], as well as in perivascular adipose tissue (PVAT) [26]. BAT consists of stromal tissue, white adipocytes, and thermogenic adipocytes containing uncoupling protein 1, functioning as a thermogenic organ. Recent studies demonstrate that BAT is negatively associated with individual risk of hypertension and coronary artery disease [27]. A retrospective study showed that individuals with detectable BAT had lower prevalence of cardiometabolic diseases and adverse cardiac events, with BAT' s beneficial effects being more pronounced in overweight or obese individuals [27]. An animal study that surgically removed interscapular BAT to create BAT-deficient mice revealed that these mice exhibited more significant blood pressure elevation and vascular injury compared with wild-type mice [28]. Furthermore, prospective studies suggest that BAT' s cardiovascular benefits may relate to cold-activated BAT increasing energy expenditure and enhancing glucose and free fatty acid handling [29,30]. BAT also secretes various molecules that alter BAT itself or remotely affect other organs through autocrine, paracrine, and endocrine mechanisms. For example, BAT-secreted fibroblast growth factor 21 (FGF21) helps counteract angiotensin II-induced blood pressure and vascular function changes and may activate peroxisome proliferator-activated receptor γ, ultimately stimulating adiponectin production to exert beneficial effects on the cardiovascular system and blood pressure regulation [31]. However, clinical studies have not yet demonstrated a direct effect of BAT on blood pressure control, requiring further investigation.

1.3 Beige Adipose Tissue

Researchers have identified a unique type of adipocyte in WAT upon cold exposure or β-adrenergic receptor activation, termed beige adipocytes, a phenomenon known as "WAT browning" [32,33]. Beige adipose tissue is primarily

distributed in the neck, supraclavicular, axillary, and paraspinal regions. Similar to brown adipocytes, beige adipocytes can acquire a thermogenic phenotype resembling BAT in response to various stimuli (such as cold, endocrine factors, or compounds). Animal experiments show that during cold exposure, beige adipose tissue exhibits high uncoupling protein 1 expression and high energy consumption similar to brown adipocytes [34]. Researchers have therefore hypothesized that inducing WAT browning into beige adipose tissue may reduce obesity-related complications. For example, activation of BAT and beige adipose tissue may be an effective strategy for treating obesity and type 2 diabetes. Regardless of sex or age, subjects with detectable cold-activated BAT had lower average BMI, body weight, and waist circumference [35]. In type 2 diabetic mice, β-adrenergic-induced BAT activation significantly reduced blood glucose levels, though similar results were not observed in the WAT browning group [36]. Additionally, PERSSON et al. [37] demonstrated that $ $3-adrenergic agonist-induced browning of perivascular WAT maintained PVAT' s anti-contractile effects, improved endothelial function, and reduced hypertension development. Currently, common strategies for inducing WAT browning include cold exposure, pharmacological agents, and exercise. However, research on whether beige adipose tissue improves obesity and its complications remains limited to animal studies, and several questions must be addressed to determine the clinical significance of WAT browning: whether enhancing thermogenesis alone is sufficient to reduce body mass, whether it will compensatorily increase energy intake, whether browning pathways are adipose tissue-specific, and what the overall effects of activation and blockade are [38].

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2. Adipose Tissue Distribution and Obesity-Related Hypertension

Based on anatomical location, adipose tissue can be divided into subcutaneous adipose tissue (SAT) and ectopic fat deposition (EFD). EFD can be further categorized into visceral adipose tissue (VAT) and PVAT [39]. Numerous studies suggest that fat distribution at specific sites shows stronger associations with cardiovascular risk than total fat volume [40]. Therefore, analyzing the relationship between body fat distribution and the pathology of obesity-related hypertension is of great significance.

2.1 SAT and VAT

SAT is primarily distributed beneath the skin, while VAT refers to fat surrounding internal organs [41], including abdominal and thoracic adipose tissue. Abdominal VAT is further subdivided into mesenteric, peritoneal, and retroperitoneal (perirenal) adipose tissue; thoracic VAT includes epicardial adipose tissue (EAT), pericardial fat, and non-pericardial thoracic adipose tissue (located anywhere in the thoracic cavity outside the pericardium) [42]. When energy

intake exceeds expenditure, excess free fatty acids and glycerol are stored as triglycerides in SAT [43,44]. However, SAT' s expansion capacity is limited and genetically determined. Once this capacity is exceeded, it promotes VAT accumulation or deposition in non-adipose tissues (such as liver and muscle), leading to hepatic steatosis and increased intramyocellular lipid content, thereby promoting cardiometabolic complications of obesity [45].

Extensive rodent and human studies demonstrate that visceral obesity is associated with metabolic syndrome [46], including arterial hypertension (nocturnal or persistent), metabolic syndrome, insulin resistance, impaired glucose metabolism, type 2 diabetes, dyslipidemia, and steatohepatitis [47]. VAT accumulation (intra-abdominal, mediastinal, epicardial, cervical regions) positively correlates with cardiometabolic disease risk, whereas SAT accumulation (gluteofemoral region) shows no correlation or even a negative correlation with cardiometabolic disease risk [48]. Therefore, identifying molecular mechanisms that control adipose tissue expansion and reversing adipose tissue remodeling during obesity may be key to improving obesity-related complications.

2.2 Perirenal Adipose Tissue (PRAT)

PRAT is a retroperitoneal fat pad surrounding the kidneys and adrenal glands, located between the renal capsule and renal fascia [49]. Multiple studies have linked perirenal fat to hypertension. Compared with normotensive individuals, hypertensive patients have greater PRAT thickness (13.6$\pm$4.8$mmvs$.1.6$\pm$$4.1 mm), and PRAT thickness positively correlates with elevated systolic blood pressure [50]. In another cross-sectional study of 42 overweight and obese patients, PRAT thickness independently correlated with 24-hour mean diastolic blood pressure [51]. INOKUCHI et al. [52] reported that increased PRAT thickness was more pronounced in patients with obesity-related complications (chronic kidney disease, cardiovascular disease, hypertension, and type 2 diabetes), suggesting PRAT may be involved in obesity pathogenesis.

Current understanding of PRAT' s blood pressure-regulating mechanisms involves three aspects: physical compression, paracrine effects, and neurohumoral regulation [53]. Excess intra-abdominal and retroperitoneal fat may compress the kidneys, increasing intrarenal pressure, altering renal hemodynamics, and inducing tissue hypoxia, subsequently leading to renal dysfunction and hypertension [54]. On the other hand, due to oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress, ectopic fat tissue around the kidneys may transmit lipotoxic immune and endocrine effects [55]. Adipokines released from adipose tissue may promote inflammation and enhance RAAS activity, increasing renal sodium and water reabsorption [56]. Additionally, PRAT afferent nerves in blood pressure regulation have recently attracted widespread attention [57]. Although only cross-sectional studies have demonstrated the close relationship between PRAT and elevated blood pressure, PRAT represents a potential target for hypertension management, and further clarification of causal relationships is necessary.

2.3 Epicardial Adipose Tissue (EAT)

EAT is a unique fat depot between the heart surface and visceral pericardium, with distinct structural and functional characteristics that significantly influence the development of cardiac diseases including coronary artery disease, atrial fibrillation, heart failure, and hypertension [58]. Research shows that epicardial fat accumulation leads to secretion of numerous pro-inflammatory cytokines and vasoactive peptides, such as tumor necrosis factor-α, interleukin-6, monocyte chemoattractant protein-1 (MCP-1), and angiotensin (Ang) II, which can activate RAAS and subsequently increase blood pressure [13]. Additionally, reduced adiponectin levels in EAT diminish endothelium-mediated vasodilation, potentially promoting hypertension development [59]. EAT also produces and releases large amounts of free fatty acids, promoting increased plasma catecholamine concentrations and activating cardiac autonomic nervous system, thereby elevating blood pressure [60]. A recent meta-analysis by GUAN et al. [61] on the association between EAT and hypertension and blood pressure circadian rhythm showed that hypertensive patients generally had higher EAT measurements (SMD=1.07, 95%CI=0.66~1.48; I^2=89.2%), and each 1 mm increase in EAT increased the risk of impaired blood pressure circadian rhythm by 2.55-fold. Similarly, two cross-sectional studies demonstrated that EAT volume closely correlated with hypertension in children and adolescents [62]. However, prospective studies revealing causal relationships between EAT and hypertension incidence are currently lacking and warrant further investigation.

2.4 Perivascular Adipose Tissue (PVAT)

PVAT is adipose tissue distributed around blood vessels, primarily surrounding arteries and veins with diameters >50 m [63]. PVAT not only fills and protects blood vessels but also performs various physiological functions, including regulating vascular tone, participating in local inflammatory responses, and modulating metabolic processes. Adipocytes surround nearly every blood vessel in the body, secreting numerous metabolically and vasoactively active adipokines [42]. In healthy states, PVAT exerts vasodilatory, antioxidant, and anti-inflammatory effects on the vasculature [64], mainly by secreting vasodilators such as adiponectin, apelin, leptin, and omentin, acting directly on vascular smooth muscle cells' relaxation and contraction properties [76].

In obesity, adipose tissue dysfunction leads to dysregulated adipokine secretion, diminishing PVAT' s protective effects.

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3. Pathological Mechanisms

3.1 Physical Mechanisms

Increased body fat in obesity may cause biomechanical and structural abnormalities at the physical level. For example, PRAT, enclosed by renal fascia, may

directly compress renal parenchyma when overgrown, elevating intrarenal pressure, altering renal hemodynamics, and inducing tissue hypoxia, subsequently leading to renal dysfunction and hypertension [69,70]. LI et al. [57] surgically removed PRAT in mice and found significantly increased renal cortical blood flow. Additionally, sustained renal compression stimulates RAAS activation. Historically, some researchers believed that excess visceral fat increased intra-abdominal pressure and correlated with systemic hypertension, but this view lacks recent research support [71].

3.2 Adipokines

Adipokines are bioactive substances secreted by adipose tissue. Based on current research, adipokines can be classified into pro-hypertensive and anti-hypertensive factors. In addition to classic pro-hypertensive adipokines like leptin and resistin, recent studies have identified factors such as chemerin, visfatin, and retinol-binding protein 4 that may be associated with hypertension development [72,73]. Anti-hypertensive adipokines include adiponectin and Omentin-1 [74,75]. Some studies also suggest that reactive oxygen species, leptin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and apelin possess both vasoconstrictive and vasodilatory properties [76].

In obesity, adipose tissue dysfunction leads to dysregulated adipokine secretion. Adipocyte hypertrophy causes local hypoxia, activating hypoxia-inducible factors and promoting release of inflammatory cytokines such as TNF-α and IL-6 while inhibiting adiponectin secretion, thereby weakening its anti-hypertensive effects [77]. Additionally, overactivation of RAAS in obese adipose tissue increases Ang II generation, further stimulating release of pro-hypertensive factors like leptin and resistin [72]. Consequently, the imbalance between pro-hypertensive and anti-hypertensive adipokines may promote obesity-related hypertension through key mechanisms including inflammation, vascular dysfunction, and sympathetic nervous system activation.

3.3 Renin-Angiotensin-Aldosterone System (RAAS)

RAAS comprises two pathways: a pro-inflammatory pathway involving the angiotensin-converting enzyme (ACE)/Ang II/angiotensin receptor 1 (AT1)/aldosterone/mineralocorticoid receptor (MR) axis, and an anti-inflammatory pathway involving the angiotensin receptor 2 (AT2)/ACE2/Ang1-7/Mas receptor axis [78,79]. Activation of the pro-inflammatory pathway may lead to excessive hypertension and cardiorenal risk in obese patients. Obesity is associated with mild-to-moderate increases in systemic and local adipose RAAS activity [69]. Angiotensinogen is produced not only by the liver but also by various adipose tissue depots, including subcutaneous and visceral fat as well as PVAT. In obesity, angiotensinogen secretion from these tissues increases. This substance can be converted to Ang II, which has potent vasoconstrictive effects that increase peripheral vascular resistance and elevate blood pressure. In obese individuals, adipocytes themselves may also produce aldosterone, and

their synergistic action further increases blood pressure. Multiple studies have demonstrated RAAS activity in both white and brown PVAT [80], though the role of adipose-derived Ang II in obesity-related hypertension remains unclear [69].

3.4 Hyperinsulinemia and Insulin Resistance

Hyperinsulinemia and insulin resistance also play important roles in obesity-related hypertension [81]. Several studies in experimental animals and humans have shown that hyperinsulinemia can increase sympathetic nervous system activity, activate RAAS, and promote sodium and water retention, which may increase blood pressure if persistent [82]. Insulin acts on nearly all nephron segments and is an agonist for sodium reabsorption. The sodium-proton exchanger type 3 on the luminal side of proximal tubules, the basolateral sodium bicarbonate cotransporter in proximal tubules, and epithelial sodium channels in distal nephron segments and connecting tubules are all regulated by insulin [83]. Insulin may also increase blood pressure by stimulating the sympathetic nervous system; studies have demonstrated that when obese patients reduce insulin through low-energy diets, both blood pressure and sympathetic nervous system activity decrease simultaneously [84]. Furthermore, when insulin resistance causes hyperglycemia and tissue oxidative stress, it accelerates glycation processes, and advanced glycation end products indirectly cause hypertension by increasing oxidative stress and RAAS activity [85].

This review systematically analyzes the complex roles of adipose tissue functional types, somatic distribution, and pathological mechanisms in obesity-related hypertension. Adipose tissue expansion, classification, and distribution are closely related to adipocyte function and play distinct roles in hypertension pathogenesis. Adipose tissue exhibits not only extreme heterogeneity but also interconnections among fat mass, distribution, and type, significantly increasing pathological mechanism complexity. Moreover, adipose tissue involvement in hypertension pathogenesis encompasses not only endocrine and paracrine effects but also physical compression impacts, which may relate to hemodynamics and mechanical stress. Abnormal accumulation of adipose tissue around the kidneys, heart, and vessels correlates with hypertension severity, indicating that ectopic fat tissue is a key pathogenic factor. The limited expansion capacity of subcutaneous adipose tissue determines the characteristics of visceral and intra-organ fat accumulation, suggesting that adipose tissue expansion mechanisms are critical for regulating obesity-related complications and may represent future intervention targets for hypertension.

However, current research on the direct relationship between adipose tissue classification/distribution and hypertension consists mainly of preclinical and cross-sectional studies, with few prospective studies and even fewer interventional trials. Therefore, future research should adopt precision medicine approaches

to deeply analyze different fat phenotype transitions and pathogenic mechanisms, providing new directions for obesity-related hypertension research and therapeutic strategies.

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