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Progress on Adipose Tissue Dysfunction in the Pathogenesis of Obesity-Related Hypertension

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Abstract

Obesity has become one of the most prominent public health challenges of the new century, and its close association with hypertension constitutes a major global disease burden. Once considered a passive energy reservoir, adipose tissue is now redefined as a metabolically active endocrine and paracrine organ. In obesity, abnormal expansion and dysfunction of adipose tissue drive the elevation of blood pressure through multiple complex and intertwined mechanisms. This review aims to explore in depth the central role of adipose tissue dysfunction in the pathogenesis of obesity-related hypertension, with a particular focus on the latest advances regarding key pathways such as physical compression, imbalance in adipokine secretion, local activation of the renin-angiotensin-aldosterone system (RAAS), chronic low-grade inflammation, and insulin resistance. Understanding these mechanisms is crucial for developing novel strategies for the prevention and treatment of obesity-related hypertension.

Keywords

Obesity-related hypertension, Adipose tissue dysfunction, Pathogenesis.

Introduction

Globally, the prevalence of obesity and hypertension is rising in parallel at an alarming rate. Substantial evidence indicates that this is not coincidental but reflects profound pathophysiological links. According to the World Health Organization, the number of obese individuals worldwide has doubled since 1975, while hypertension affects 1.39 billion people, with a considerable proportion attributable to overweight and obesity. For instance, the renowned Framingham study reported that up to 78% of hypertension cases in men and 65% in women could be attributed to weight gain. In China, the situation is equally concerning. A study based on CHARLS data revealed that among individuals aged 45 and older, the prevalence of obesity-related hypertension reached 22.7%, accounting for 66% of all hypertension cases (Zhang et al.). Projections suggest that by 2030, the overweight/obesity rate among Chinese adults will reach 71% (Sun et al.). This compels us to ask: how does excessive fat accumulation leverage the regulation of blood pressure? The key lies in the dysfunction of adipose tissue itself.

1. Heterogeneity of Adipose Tissue: Function and Distribution as Determinants

Adipose tissue is not a homogeneous entity; its type and distribution dictate whether it acts as a “guardian” or a “culprit” in energy metabolism and blood pressure regulation.

1.1 White Adipose Tissue (WAT): The Primary Endocrine “Offender”

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White adipose tissue is the most abundant type of fat in the human body and serves mainly as an energy store. Under healthy conditions, it secretes beneficial adipokines, such as adiponectin, which exert anti-inflammatory, insulin-sensitizing, and vasodilatory effects. However, in obesity, WAT—particularly visceral WAT—undergoes pathological hypertrophy (enlargement of cell size rather than number). Hypertrophic adipocytes suffer from hypoxia, endoplasmic reticulum stress, and mitochondrial dysfunction, transforming into a source of chronic inflammation. They overproduce pro-inflammatory adipokines (e.g., leptin, resistin, TNF-α, IL-6) while reducing the secretion of protective ones (e.g., adiponectin). This imbalance directly disrupts vascular homeostasis, paving the way for the onset of hypertension.

1.2 Brown/Beige Adipose Tissue (BAT): A Potential "Protector"

In contrast to WAT, brown adipose tissue is rich in mitochondria and uncoupling protein-1 (UCP1), with its primary role being thermogenesis and energy expenditure, thereby counteracting obesity. Studies have shown that active BAT is associated with lower cardiometabolic risk (Becher et al.). Animal experiments provide more direct evidence: surgical removal of interscapular BAT in mice led to more pronounced hypertension and vascular injury (Yoneshiro et al.). Furthermore, under certain stimuli (e.g., cold exposure, exercise), some white adipocytes can undergo "browning," transforming into thermogenic beige adipocytes. Activating BAT and inducing WAT browning are regarded as potential therapeutic strategies. For example, β 3-adrenergic agonists have been shown to promote perivascular fat browning, maintaining its anti-contractile function and slowing the progression of hypertension (Persson et al.). Nevertheless, most of these findings derive from animal models, and their clinical translational value requires validation through large-scale human studies (Kurylowicz et al.).

2. Ectopic Fat Deposition: Location Determines Risk

Where fat accumulates is more important than how much fat accumulates. Once the storage capacity of subcutaneous adipose tissue (SAT) is exceeded, excess lipids are redirected to the viscera and organs, forming so-called "ectopic fat." Fat in these depots exhibits greater pathogenic potential.

2.1 Visceral Adipose Tissue (VAT)

VAT is primarily distributed within the abdominal cavity, surrounding organs such as the intestines and liver. Numerous studies have confirmed that VAT accumulation is closely associated with metabolic syndrome, insulin resistance, and hypertension. Compared with SAT, VAT exhibits higher metabolic activity, richer blood supply and innervation, and a stronger capacity for producing pro-inflammatory adipokines. The harmful substances secreted by VAT enter the liver directly via the portal vein, thereby impacting systemic metabolism.

2.2 Perirenal Adipose Tissue (PRAT)

PRAT refers to the fat pad surrounding the kidneys. Its expansion may physically compress the kidneys, increase intrarenal pressure and impairing sodium excretion, while also releasing adipokines via paracrine signaling and activating the local RAAS, directly interfering with renal blood pressure regulation. Multiple cross-sectional clinical studies have consistently shown that PRAT thickness is significantly greater in hypertensive patients compared to normotensive individuals, and that PRAT thickness correlates positively with systolic blood pressure (Ricci et al.; De Pergola et al.). More recently, a breakthrough animal study demonstrated that afferent neural signaling within PRAT is critical for maintaining pathological hypertension, and that severing these nerves effectively lowers blood pressure (Li et al.), providing a novel potential target for interventional therapy.

2.3 Epicardial Adipose Tissue (EAT)

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EAT is located between the myocardium and the visceral pericardium. It lies in direct contact with the myocardium and coronary arteries, without fascial separation. In obese individuals, EAT enlarges and becomes dysfunctional, secreting large amounts of pro-inflammatory cytokines and free fatty acids. These substances not only activate the local RAAS but can also directly infiltrate the myocardium, impair the coronary arteries, trigger arrhythmias, and elevate blood pressure by stimulating the cardiac autonomic nervous system. A meta-analysis integrating multiple studies clearly showed that EAT measurements are significantly higher in hypertensive patients (Guan et al.).

2.4 Perivascular Adipose Tissue (PVAT)

In healthy states, PVAT secretes a variety of vasoactive substances (e.g., adiponectin, nitric oxide), serving as an "extra-vascular protective layer" with anti-contractile, antioxidant, and anti-inflammatory effects. However, under obesity, PVAT becomes dysfunctional, losing its protective phenotype and instead secreting large amounts of vasoconstrictive substances and pro-inflammatory cytokines (e.g., angiotensin II, TNF-α), while attracting inflammatory cell infiltration. This leads to enhanced vasoconstriction, endothelial dysfunction, and aggravated oxidative stress, ultimately promoting vascular remodeling and hypertension. A recent meta-analysis also confirmed a significant positive correlation between PVAT and the prevalence of hypertension (Bragina et al.)

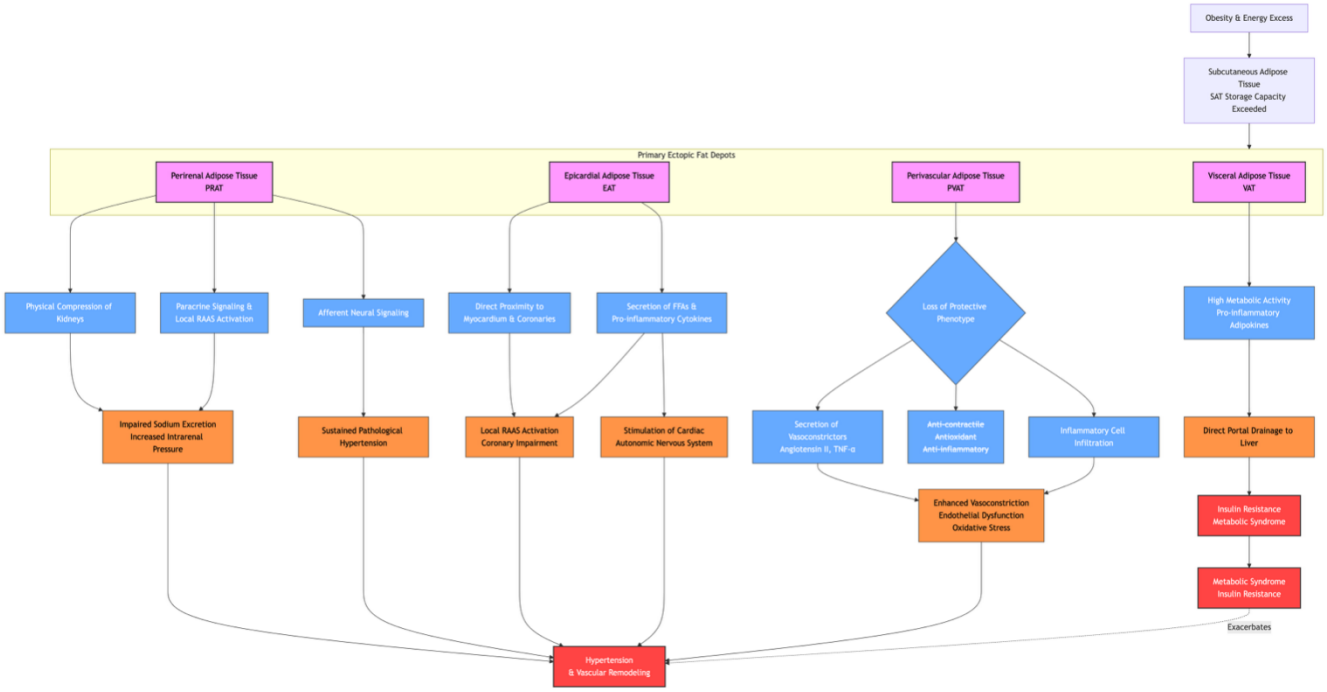

Figure1. Ectopic Fat Deposition: Location-Specific Mechanisms Leading to Cardiometabolic Disease

3. From Dysfunction to Elevated Blood Pressure: Core Mechanisms

The figure above illustrates four core mechanisms through which adipose tissue dysfunction leads to hypertension. These mechanisms are interwoven, forming a complex network.

3.1 Mechanical Compression Mechanism

This is mainly associated with excessive deposition of perirenal adipose tissue (PRAT). Since the kidneys are encased in a relatively fixed anatomical space, PRAT expansion mechanically compresses the renal parenchyma and blood vessels. This compression increases intrarenal pressure, alters renal hemodynamics, and may even induce tissue hypoxia. The direct

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consequence is impaired sodium excretion, leading to sodium retention, blood volume expansion, and a rise in blood pressure. Meanwhile, renal compression also activates the intrarenal RAAS, creating a vicious cycle.

3.2 Imbalance in Adipokine Secretion

Adipokines are bioactive substances secreted by adipose tissue. In healthy adipose tissue, pro-hypertensive factors (e.g., leptin, resistin) and anti-hypertensive factors (e.g., adiponectin, omentin) remain in balance. Obesity disrupts this balance. On one hand, hypertrophic adipocytes secrete less adiponectin, weakening its vasodilatory, anti-inflammatory, and insulin-sensitizing effects. On the other hand, they oversecrete leptin. Although leptin is supposed to suppress appetite, obesity induces "leptin resistance," while its sympathetic nervous system–stimulating effects become exaggerated, leading to increased heart rate, elevated cardiac output, and enhanced vascular resistance. Moreover, the rise in resistin, TNF-α, and IL-6 further exacerbates vascular inflammation and endothelial dysfunction.

3.3 Local Activation of the RAAS

The RAAS is a key system for regulating blood pressure and fluid-electrolyte balance. Traditionally, it was thought to operate mainly in the kidneys and liver. However, adipose tissue itself is now recognized as an important RAAS-active site. In obesity, adipocytes—particularly in visceral and perivascular depots—produce and secrete large amounts of angiotensinogen, which is locally converted into angiotensin II (Ang II), a potent vasoconstrictor. Adipose-derived Ang II not only acts in a paracrine manner to constrict nearby vessels but also stimulates aldosterone release, promoting sodium and water reabsorption. Thus, local RAAS activation in adipose tissue serves as an independent driver of obesity-related hypertension beyond systemic RAAS.

3.4 Chronic Inflammation and Insulin Resistance

In obesity, especially visceral fat, adipose tissue becomes a site of persistent low-grade inflammation. Immune cells (e.g., macrophages) infiltrate adipose tissue and, together with adipocytes, release large quantities of inflammatory cytokines (e.g., TNF-α, IL-6). This systemic inflammatory state disrupts insulin signaling in target organs (e.g., liver, muscle), resulting in insulin resistance. As compensation, the pancreas secretes more insulin, leading to hyperinsulinemia. Elevated insulin itself promotes renal sodium reabsorption and blood volume expansion. At the same time, insulin resistance and inflammation impair nitric oxide–mediated vasodilation and enhance sympathetic activity, together driving hypertension.

4. Summary

Adipose tissue has long surpassed its simplistic image as an energy reservoir. In the pathogenesis of obesity-related hypertension, dysfunctional adipose tissue plays the central role as the "origin site." Its pathogenicity depends not only on its quantity but also on its type (white vs. brown/beige) and location (subcutaneous vs. visceral, perirenal, epicardial, perivascular). Through multiple intertwined pathways—including mechanical compression, endocrine/paracrine imbalance, local RAAS activation, and mediation of chronic inflammation and insulin resistance—dysfunctional adipose tissue forms a complex pathogenic network that ultimately drives sustained blood pressure elevation.

Nonetheless, research gaps remain. Most studies on adipose depots and hypertension are cross-sectional or preclinical; interventional and prospective studies that establish causal links are still scarce. Future research should focus on:

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1) Utilizing advanced imaging technologies (e.g., PET-CT, MRI) to precisely quantify fat volume and metabolic activity in different depots in humans, combined with long-term follow-ups to clarify causal relationships with hypertension.

2) Exploring the molecular details of "fat–organ crosstalk," particularly the role of neural regulation (e.g., perirenal fat innervation).

3) Translating basic findings into clinical strategies, investigating how lifestyle interventions, pharmacotherapy, or even biotechnological approaches may remodel adipose tissue health (e.g., inducing WAT browning), suppress harmful adipokine secretion, or block downstream signaling pathways.

A deeper understanding of adipose tissue dysfunction mechanisms is opening new doors. Future prevention and treatment of obesity-related hypertension may no longer rely solely on traditional antihypertensive drugs but shift toward targeting adipose tissue itself, aiming to restore its normal function. This paradigm shift offers renewed hope in addressing this global health challenge.

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