

The roles of perivascular adipose tissue in obesity-related hypertension

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ABSTRACT

Background: Obesity and hypertension (HTN) are two of the most prevalent and pressing current global health issues due to their associated morbidity and mortality. Obese individuals are more susceptible to developing HTN. Perivascular adipose tissue (PVAT) has been posited to be the fourth layer of the normal arterial wall. PVAT can modulate vascular tone, vascular endothelial function, and vascular smooth muscle cell growth and proliferation, contributing to HTN.

Results: In obesity-related HTN, PVAT exhibits abnormal vasoactive adipokine production and immune cell recruitment as well as enhanced inflammation, which exacerbate blood pressure elevation and lead to target organ damage. Distinct immune cell populations have been identified to infiltrate PVAT, which can become potential therapeutic targets.

Conclusion: This paper reviews PVAT dysfunction in obesity-related HTN, highlighting the vasoactive factor release, immune cell infiltration, and inflammation, as well as implications for therapeutic approaches.

 KEYWORDS

Obesity, Hypertension, Perivascular adipose tissue, Inflammation, Immune cells

1 | INTRODUCTION

1.1 | Overview of obesity

Obesity is a chronic and multisystem condition which is associated with increased morbidity and mortality worldwide. Excessive fat deposits generate unfavourable hemodynamic modifications, dysregulate fatty acid and glucose metabolism, trigger insulin resistance and inflammation, and eventually damage

several organs. (1) According to the World Health Organization (WHO), the global prevalence of adult obesity has more than doubled since 1990, and that of adolescent obesity has quadrupled. (2) In 2022, 43% of adults aged 18 and older (2.5 billion adults) were overweight, and 16% (890 million adults) were obese. Over 390 million children and adolescents aged five to 19 were overweight, including 160 million who were obese. Alarming, 37 million children aged

five and younger were overweight. If there are no breakthroughs in obesity management, the worldwide cost of overweight and obesity can reach three trillion US dollars per year by 2030.

Obesity is diagnosed by calculating the body mass index (BMI) that is weight (kilograms) divided by height squared (metres squared). Table 1 specifies the classification of whether a White, Hispanic, or Black individual is underweight, normal weight, overweight, or obese based on BMI as used by the National Institute of Health (NIH) and WHO. (3) As the cut-offs underestimate the obesity risks in the Asian and South Asian populations, an Asian and South Asian individual may be deemed overweight and obese with a lower BMI (BMI of 23-24.9 kg/m² to be overweight and BMI of more than 25 kg/m² to be obese). In 2019, higher-than-optimal BMI was estimated to result in five million deaths from noncommunicable diseases, comprising cardiovascular diseases (CVDs). (4) However, because individual variations exist, and BMI does not differentiate between lean muscle mass and adipose tissue mass, BMI is insufficient as the sole means of determining whether an individual is obese. (1, 3) Furthermore, an obesity paradox has been noted, whereby obesity evaluated by BMI may be benign rather than have pathological consequences. (1) Girth, which is abdominal circumference as evaluated by the waist/hip ratio, may be a better way to assess pathological obesity. This phenomenon manifests as a contrast between apples (increased abdominal circumference) and pears (increased hip circumference) – the former associated with cardiometabolic pathological conditions including CVDs, diabetes, and metabolic dysfunction-associated fatty liver disease (MAFLD), all leading to higher mortality.

1.2 | Overview of hypertension

High blood pressure (BP), systemic hypertension (HTN), or HTN is the leading risk factor for global disease burden and mortality. HTN causes chronic inflammation and predisposes to multiple detrimental complications in the cardiovascular system, kidneys, brain, and men-

tal health, including cognitive decline and dementia. (5) According to WHO's report on HTN in 2023, the number of individuals with HTN doubled from 650 million to 1.3 billion between 1990 and 2019. Among individuals aged 30 to 79 with HTN, only 54% have been diagnosed, 42% are being treated, and 21% are considered to have the condition controlled. If countries can mobilize to achieve WHO's goal of 50% population HTN control by the year 2050, 76 million cardiovascular deaths and 450 million disability-adjusted life years may be avoided. In addition, the economic benefits may be 18 times greater than business as usual.

HTN has been defined by the BP levels at or above which reducing BP will decrease the cardiovascular risks associated with elevated BP. (6) This threshold has classically been 140/90 mm Hg based on actuarial data from the insurance industry. Nevertheless, it is worth noting that among individuals aged 40 to 69, cardiovascular risks progressively rise from as low as 115/75 mm Hg with a two-fold escalation in death rates from cardiovascular causes for every 20/10 mm Hg increment. (7) Furthermore, the Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that hypertensive individuals at high risk of CVDs with systolic BP (SBP) of 130-180 mm Hg would benefit from reducing SBP to below 120 mm Hg. (8) Thus, the new threshold has been proposed to be 130/80 mm Hg for hypertensive individuals at high cardiovascular risk: chronic kidney disease patients, diabetic people, elderly people, and people with a Framingham Risk Score of 15% or higher. (6) In fact, the 2017 American Heart Association/American College of Cardiology guideline for HTN management has defined HTN for all individuals as BP at or above 130/80 mm Hg. (9) Although there is not a different BP cut-off for obese individuals, these people are 3.5 times more susceptible to developing HTN. (10) In fact, the Framingham Heart Study revealed 60-70% of HTN is caused by obesity.

1.3 | Adipose tissue, particularly perivascular adipose tissue, plays a role in obesity-related hypertension

Massive expansion and remodelling of adipose tissue in obesity exert differential impacts on specific adi-

Classification		BMI number
Severely underweight		Less than 16.5 kg/m ²
Underweight		Between 16.6 kg/m ² and 18.5 kg/m ²
Normal weight		Between 18.6 kg/m ² and 24.9 kg/m ²
Overweight		Between 25 kg/m ² and 29.9 kg/m ²
Obesity	Obesity class I	Between 30 kg/m ² and 34.9 kg/m ²
	Obesity class II	Between 35 kg/m ² and 39.9 kg/m ²
	Obesity class III (also known as severe, extreme, or massive obesity)	More than 40 kg/m ²

TABLE 1 Classification of whether a White, Hispanic, or Black individual is underweight, normal weight, overweight, or obese based on BMI as used by the National Institute of Health (NIH) and World Health Organization (WHO). (3)

pose tissue depots that have differential contributions to chronic systemic inflammation and HTN. (11) Initially thought to be exclusively an energy-storing organ, adipose tissue has been recognized to be highly dynamic and responsible for several processes, including metabolism and modulation of vascular tone. Adipose tissue can be categorized based on the cellular composition as white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue. During pregnancy, lactation, and post-lactation, subcutaneous WAT can transdifferentiate into pink adipose tissue. Adipose tissue can also be categorized based on the anatomical localization as visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), gluteofemoral adipose tissue (GAT), epicardial adipose tissue (EAT), and perivascular adipose tissue (PVAT). The focus of this paper – PVAT – is a heterogenous, metabolically active, endocrine organ surrounding most blood vessels, except cerebral and pulmonary ones. (12) Obesity is associated with an increase in PVAT mass and PVAT dysfunction, contributing to obesity-related HTN and target organ damage.

2 | DISCUSSION

2.1 | Obesity induces PVAT dysfunction

Obesity-induced PVAT dysfunction results from lipid spillover, hypoxia, and adipocyte apoptosis. Typically, the healthy PVAT consists of white-like and brown-like adipocytes, immune cells, stem cells, microvasculature, and nerves, but the exact phenotype depends on the anatomical location and may vary with the individual's health status.(12) Obesity is characterized by excess fatty acids stored in adipocytes that may be increased in number but mostly in size. (13, 14) Despite exhibiting some WAT histological properties, perivascular adipocytes are less differentiated and have less lipid storage capacity than white adipocytes. (15) Therefore, lipid spillover, ectopic fat deposition, and lipotoxicity occur after the storage capacity of perivascular adipocytes is exceeded. (13) Because the hypertrophic expansion of perivascular adipocytes is not supported by a similar rise in angiogenesis rates, some adipocytes are left outside of the existing vasculature's oxygen diffusion zone, resulting in hypoxia and vasoconstriction.(16) Oxidative stress is enhanced as nitric oxide

synthase uncoupling results in the production of superoxide instead of nitric oxide (NO). (14) Due to the increased reaction between superoxide and NO, vascular nitrotyrosine (a marker of peroxynitrite production) increases with nitration of proteins and leads to their dysfunction. Moreover, the aldosterone levels elevate in obesity, upregulating the expression of VCAM-1 (vascular adhesion molecule-1), PECAM-1 (platelet endothelial cell adhesion molecule-1), and ICAM-1 (intercellular adhesion molecule-1) as well as activating the NLRP3 (NLR family pyrin domain containing 3) inflammasome. (14, 17, 18) Consequently, dysfunctional perivascular adipocytes display abnormal Toll-like receptor signalling, vasoactive adipokine secretion, and immune cell recruitment. (13, 19) Adipocyte apoptosis happens when perivascular adipocytes can no longer tolerate the stress signals of nutrient overload and oxidative stress. (13) Despite evidence that brown-like adipocytes in PVAT may counterbalance the white-like ones and counteract obesity-induced cardiometabolic disorders, there is also evidence that BAT activation increases heart rate and becomes detrimental to cardiovascular health. (20, 21) Overall, obesity severely disrupts PVAT's homeostasis via various mechanisms involving NO production, vasoactive adipokine release, immune cell infiltration, and inflammation, thereby contributing to obesity-related HTN.

2.2 | PVAT produces vasoactive factors implicated in obesity-related hypertension

PVAT has been argued to be the fourth layer of the normal arterial wall (tunica adiposa) since the tissue is capable of modulating vascular tone, vascular endothelial function, and vascular smooth muscle cell (VSMC) growth and proliferation, leading to HTN. (12, 14) PVAT triggers both vasodilatation and vasoconstriction via endocrine and paracrine mechanisms. Multiple studies have shown that PVAT loses its anticontractile effects and potentiates vasoconstriction under certain pathophysiological conditions comprising obesity and HTN. (14, 22)

2.2.1 | Anticontractile PVAT-derived factors

PVAT-derived adiponectin, hydrogen sulphide (H₂S), angiotensin (Ang) 1-7, and NO have been the focus of many studies as vasodilators that protect against obesity-related HTN in animal models and humans. Adiponectin in different polymeric forms causes vasodilatation by acting on vascular endothelial cells and VSMCs, in addition to downregulating plasma glucose levels and impacting macrophage polarization. (23) H₂S also triggers vasodilatation via endothelium-dependent and -independent mechanisms besides mediating oxidative stress, macrophage polarization, and inflammation. (24) Ang 1-7, a member of the renin-angiotensin-aldosterone system (RAAS), induces vasodilatation via endothelium-dependent mechanisms and restores glucose tolerance. (25, 26) These anticontractile PVAT-derived factors stimulate NO production, which can directly elicit vasodilatation following diffusion to VSMCs or indirectly by increasing adiponectin. (22, 27) Based on animal models, other anticontractile PVAT-derived factors may include palmitic acid methyl ester and omentin; however, more research is needed. (28, 29) Regardless, all mentioned factors have been detected to decline in obesity and HTN.

2.2.2 | Pro-contractile PVAT-derived factors

PVAT-derived superoxide anion, aldosterone, Ang II, and prostaglandins counteract anticontractile PVAT-derived factors and cause vasoconstriction, resulting in obesity-related HTN. Superoxide anion is a free radical oxygen species, which enhances vasoconstriction in obese animal models by raising oxidative stress as well as lowering H₂S and NO bioavailability. (14) Superoxide anion production can be stimulated by aldosterone and Ang II, final mediators of the RAAS and in the case of Ang II, an antagonist of Ang 1-7. (18, 26, 30) Aldosterone and Ang II elicit oxidative stress generation, vasoconstriction, and immune cell recruitment in obese animal models and humans. These pro-contractile PVAT-derived factors have been documented to increase in obesity and HTN. On the other hand, prostaglandins – arachidonic acid-derived metabolites – assume different roles de-

pending on the individual's health status. For instance, prostaglandins augment serotonin- and phenylephrine-induced vasoconstriction of the aorta from obese mice but not lean ones. (31) The roles of chemerin and resistin in vasoconstriction and obesity-related HTN have also been suggested in animal models. Chemerin positively correlates with insulin resistance, more sympathetic nerve-induced vasoconstriction, and immune cell infiltration.(32, 33) Primarily secreted by macrophages, resistin attenuates insulin-related and endothelium-dependent, bradykinin-induced vasodilatation as well as promotes pro-contractile endothelin-1 (ET-1) expression. (34, 35)

2.2.3 | PVAT-derived factors exhibiting both anticontractile and pro-contractile properties

PVAT-derived leptin, hydrogen peroxide (H₂O₂), and catecholamines demonstrate anticontractile and pro-contractile properties via different mechanisms, depending on the individual's health status and the factor's concentration. In addition to controlling appetite, energy expenditure, and body weight, leptin causes vasodilatation by targeting vascular endothelial cells and VSMCs in animal models. (36) However, obesity-induced chronically high leptin levels trigger more ET-1 release, contributing to vasoconstriction and higher peripheral resistance. (36, 37) Similarly, H₂O₂ elicits vasodilatation by influencing vascular endothelial cells and VSMCs, but obesity-induced higher H₂O₂ levels lead to vasoconstriction in animal models and humans.(19) Human perivascular adipocytes can synthesize catecholamines de novo or take up and store catecholamines from the sympathetic nervous system, forming a reservoir of noradrenaline, dopamine, and serotonin that causes vasoconstriction. (38) In contrast, immune cells in PVAT of animal models can secrete catecholamines that enhance adiponectin and NO production, triggering vasodilatation. (39, 40) Recently, visfatin has been investigated for its potential roles in vasoconstriction, endothelial dysfunction, and stimulated VSMC proliferation in small resistance arteries of rats and humans but vasodilatation in large conduit arteries of rats.(41, 42) Higher visfatin levels are observed in hy-

pertensive obese individuals. (43)

2.3 | Immune cells in PVAT contribute to obesity-related hypertension

In response to obesity-induced inflammation, innate and adaptive immune cells in PVAT undergo several changes. As first confirmed in 2010 by Viel and co-authors, inflammation and the immune system play an essential role in HTN.(17) Immune cells interact with one another, crosstalk with perivascular adipocytes, and modify the vascular reactivity in obesity-related HTN.

2.3.1 | Innate immune cells

Neutrophils, mast cells, and dendritic cells (DCs) contribute to obesity-related HTN. Neutrophils are early responders to obesity: transiently rise in obese individuals and secrete elastase that enhances glucose intolerance and insulin resistance. (44, 45) Furthermore, obesity-induced higher levels of circulating neutrophils and accumulated neutrophils in microvasculature positively correlate with BP in animal models and humans. (44, 46, 47) Neutrophils regulate vascular dysfunction by generating superoxide anion, augmenting oxidative stress, and reducing NO bioavailability. Additionally, neutrophil extracellular traps (NETs) are created by neutrophil-derived extracellular DNA strings in mice upon Ang II stimulation. (44, 45) NETs promote endothelial damage and exert prothrombotic properties. As one of the first cell populations to migrate to inflammation sites, neutrophils facilitate the recruitment of DCs, macrophages, and lymphocytes. DCs significantly increase from negligible levels in the lean phenotype to levels comparable to macrophages in mice following a high-fat diet. (48, 49) The larger DC population in PVAT has been linked to oxidative stress, impaired anticontractile properties, and overproduction of proinflammatory cytokines. (50, 51) As antigen-presenting cells, DCs also play a critical role in activating T cells. Upon Ang II stimulation, DCs produce IL-23 that regulates the differentiation and maintenance of IL-17-producing T cells. Moreover, a subclass of DCs – plasmacytoid DC – causes vasoconstriction and HTN in response to PVAT-derived chemerin. (32) Nevertheless, because DCs and macrophages all express CD11b and F4/80, it has been complicated to iso-

late the roles of PVAT-derived DCs and macrophages in obesity and HTN. (48) The number of mast cells also increases in obese animal models and humans, and control of the mast cell population using pharmacological stabilizers can mitigate obesity in mice. (52) However, the specific roles of mast cells in obesity remain controversial. Some researchers believe that mast cells directly take part in insulin resistance and the onset of obesity, whereas others claim that mast cells play no essential roles in obesity. (52, 53) Regardless, mast cells are implicated in PVAT's mediation of the vascular tone by triggering local acute inflammatory responses in animal models. (45)

In 2005, De Ciuceis and co-authors were the first to identify the roles of a specific individual immune cell population – macrophages – in the development of experimental HTN. (54) Macrophages exhibit higher numbers and activation levels in obese and hypertensive patients via autocrine signals and interactions with other immune cell populations. (12) As previously mentioned, macrophages are the primary source of resistin that positively correlates with BP in humans. (35) Macrophage polarization assumes a crucial role in the proinflammatory shift in response to obesity. (55) Specifically, aldosterone, chemerin- and neutrophil-stimulated increase of M1 macrophages is associated with insulin resistance, atherosclerosis, and HTN as M1 macrophages induce oxidative stress, decrease H2S bioavailability, and release proinflammatory cytokines. (18, 24, 32, 44, 56) Meanwhile, adiponectin-, H2S-, and eosinophil-stimulated increase of M2 macrophages counteracts M1 macrophages and maintains PVAT's homeostasis via adipocyte turnover, lipid buffering, and modulation of sympathetic drive. (55, 57) Nevertheless, because macrophages are late responders to obesity, the significance of their interactions with other immune cell populations remains a matter of debate.

In contrast to other innate immune cell types, the number of eosinophils in mice declines in response to a high-fat diet. (58) Eosinophil-deficient mice have been proven to display impaired glucose tolerance, lose PVAT's anticontractile properties, and have high peripheral resistance, which may be rescued by eosinophil

reconstitution. (40, 45) Eosinophils maintain PVAT's homeostasis and elicit vasodilatation by producing interleukin (IL)-4 and IL-13 and sustaining M2 macrophage polarization. (39, 40, 57)

2.3.2 | Adaptive immune cells

Shortly following a high-fat diet, the total B-cell number as well as the cell numbers of the B-1 and B-2 subpopulations in mice all rise and correlate with Ang II-induced BP elevation. (59, 60) B cell-deficient obese mice are protected against obesity-related diseases in spite of weight gain. (61) Specifically, B-2 cells aggravate insulin resistance and atherosclerosis in mice by secreting atherogenic IgG antibodies and promoting proinflammatory T cells, whereas B-1 cells assume the opposing, protective role and attenuate glucose intolerance, vascular dysfunction, and inflammation in mice and humans by releasing atheroprotective IgM antibodies. (60, 61) How the two B-cell subpopulations act on vascular function is particularly interesting, considering that the B-1/B-2 ratio is ten-fold higher in murine PVAT than in the spleen and bone marrow.

The conventional alpha/beta ($\alpha\beta$) T-cell subpopulations undergo different changes in obesity: the frequencies of proinflammatory CD8⁺ cytotoxic T (T_c) cells, CD4⁺ helper T-1 (T_h1) cells, and CD4⁺ helper T-17 (T_h17) cells rise, while those of anti-inflammatory CD4⁺ helper T-2 (T_h2) cells and CD4⁺ or CD8⁺ regulatory T (T_{reg}) cells decline. (17, 30) T_c cells play an important role in both the initiation and maintenance of obesity, inflammation, and HTN in animal models and humans. (62, 63) CD8-deficient animal models have less glucose intolerance, proinflammatory cytokine production, and hypertensive responses to Ang II. Furthermore, it is well-known that T_h1 and T_h2 cells counteract and inhibit the cytokine secretion of the other. (45, 64) T_h1 cells release proinflammatory IL-2, interferon (IFN)- γ , and tumour necrosis factor (TNF)- α and support M1 macrophage polarization, whereas T_h2 cells produce anti-inflammatory IL-4 and enhance M2 macrophage polarization. (63, 64) Since the T_h1/T_h2 ratio increases in obese animal models and humans, proinflammatory cytokine secretion and M1 macrophage polarization by T_h1 are favoured, resulting in more vascular dysfunction and inflamma-

tion. (64) Meanwhile, more IL-17 is released by T_H17 cells in obese animal models and humans, contributing to and sustaining HTN as the proinflammatory cytokine augments oxidative stress and impairs vascular function. (45, 63) IL-17 can also be produced by the unconventional innate-like gamma/delta ($\gamma\delta$) T-cell population that is increased in obesity and promotes insulin resistance and inflammation. (45, 50, 51, 63, 65) Mice devoid of $\gamma\delta$ T cells are protected against Ang II-induced BP elevation, vascular dysfunction, and T-cell activation in PVAT. (66) CD28 is a co-stimulatory T-cell receptor that plays a role in $\gamma\delta$ T-cell survival and proliferation. (67) CD28-expressing δ T cells are elevated in PVAT of hypertensive mice and SAT of obese humans. The total T_{reg} -cell number is reduced in obese animal models and humans, along with their beneficial mediation of insulin resistance, vascular dysfunction, and immune homeostasis via cell-cell contact mechanisms and anti-inflammatory cytokine release. (17, 50, 63) In 2011 and 2012, the Schiffrin research group published two papers proving the protective roles of $CD4^+ T_{reg}$ cells against both aldosterone- and Ang II-induced vascular injury and HTN in mice. (56, 68) Although not examined in PVAT, $CD8^+ T_{reg}$ cells have recently been detected with higher percentages within the $CD8^+$ T-cell population in the circulation, VAT, and SAT of obese humans, possibly as a compensatory mechanism for the smaller $CD4^+ T_{reg}$ -cell population. (69)

2.4 | Therapeutic approaches to obesity-related hypertension

The non-pharmacological interventions to relieve obesity-related HTN are lifestyle modifications and bariatric surgery. The first recommended management strategy, lifestyle modifications, has been emphasized by different guidelines as a non-invasive, inexpensive, and sustainable method to alleviate obesity-related HTN. (9) In fact, lifestyle modifications are essential to support and maintain the effects of bariatric surgery and pharmacological interventions. Regular physical activity helps decrease perivascular adipocyte size and proinflammatory markers (e.g., leptin, $TNF-\alpha$) and immune cells (e.g., M1 macrophages) as well as enhancing anti-inflammatory markers (e.g., adiponectin, NO) and

immune cells (e.g., M2 macrophages). (19) Similarly, dietary interventions (e.g., DASH diet, Mediterranean diet, intermittent fasting diet) can improve the metabolic profiles and lower inflammation. (70) Therefore, PVAT inflammation is reversed, PVAT function restored, and blood glucose levels and BP normalized. (19, 70) However, lifestyle modifications can be insufficient as a stand-alone therapy because individuals may be unable to adhere to the exercise and diet regimen, requiring pharmacological and surgical interventions in addition. (71) Bariatric surgery is an invasive approach with some associated risks, especially for individuals in obesity classes II and III. (72) The success of the surgery necessitates the appropriate procedures, as well as a holistic and individualized treatment plan to consider the patient's nutritional and psychosocial attributes before, during, and after the surgery to avoid long-term complications (e.g., excessive weight loss, nutritional deficiencies, and gastrointestinal and renal problems). Successful bariatric surgery can reduce proinflammatory markers and immune cells as well as promote anti-inflammatory markers and immune cells, restoring PVAT function, normalizing BP, and improving metabolic control after six months. (73)

The main pharmacological interventions to ameliorate obesity-related HTN are the RAAS inhibitors, immunomodulatory drugs, and the more recently introduced glucagon-like peptide-1 (GLP-1) agonists (e.g., daily liraglutide or weekly semaglutide), double GLP-1 agonists, and glucagon inhibitory peptide (GIP) agents (e.g., weekly tirzepatide). (18, 30, 51, 71, 74) Firstly, it is worth noting that the effectiveness of anti-obesity medications in decreasing BP varies based on the drug's mechanism of action and the individual's characteristics. (71, 74) Weight-loss medications lead to insufficient BP lowering in most cases and should not be used for individuals with HTN in some cases. Consequently, anti-hypertensive medications are ultimately prescribed for obesity-related HTN. Anti-hypertensive medications include diuretics (especially long-acting ones), RAAS inhibitors, calcium channel blockers, all first-line agents, mineralocorticoid receptor antagonists, and adrenergic blockers. Anti-hypertensive medica-

tions targeting the RAAS (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and renin inhibitors, although the latter mostly abandoned) demonstrate a broad spectrum of benefits on HTN and the cardiovascular system. Additionally, ACE inhibitors and ARBs exert favourable influences on lipid and glucose abnormalities in obesity. Immunomodulatory drugs have recently received much attention thanks to advances in the understanding that immune mechanisms may be driving obesity and HTN. (18, 30, 51) Protection against obesity, HTN, and comorbidities by inhibition of cytokines and immune cells in experimental animal models suggests potential therapeutic approaches. Moreover, advances in technology (e.g., nanoparticles to deliver immunosuppressants) can support drug innovation and novel treatment strategies. (75) However, comprehensive knowledge of the immune mechanisms in obesity and HTN must be acquired before the available evidence from experimental animal models can be translated into various clinical HTN phenotypes.

3 | CONCLUSION

The complex interplay between obesity and HTN underscores the necessity for a multifaceted approach to prevention and treatment. Obesity predisposes an individual to HTN via several mechanisms, particularly involving the roles of PVAT. As a heterogeneous, metabolically active, endocrine organ surrounding most blood vessels, PVAT regulates vascular tone, vascular endothelial function, and VSMC growth and proliferation. In obesity-related HTN, PVAT becomes dysfunctional. The tissue exhibits abnormal vasoactive adipokine secretion and immune cell infiltration as well as augmented inflammation. Because lifestyle modifications can reduce obesity-related HTN but may be insufficient as a stand-alone treatment, pharmacological and surgical interventions may be required. Given the goals of simultaneously alleviating two conditions and that individual variations exist, therapeutic approaches should be made in a personalized way. Recently, immunomodulatory drugs have emerged as a promising therapeutic approach. However, further research on the immune mechanisms in obesity and HTN must be achieved to formulate effective

drugs and mitigate the pressing worldwide health and economic impact of obesity-related HTN.

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