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The pathophysiology of hypertension in patients with obesity

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Abstract

The combination of obesity and hypertension is associated with high morbidity and mortality because it leads to cardiovascular and kidney disease. Potential mechanisms linking obesity to hypertension include dietary factors, metabolic, endothelial and vascular dysfunction, neuroendocrine imbalances, sodium retention, glomerular hyperfiltration, proteinuria, and maladaptive immune and inflammatory responses. Visceral adipose tissue also becomes resistant to insulin and leptin and is the site of altered secretion of molecules and hormones such as adiponectin, leptin, resistin, TNF and IL-6, which exacerbate obesity-associated cardiovascular disease. Accumulating evidence also suggests that the gut microbiome is important for modulating these mechanisms. Uric acid and altered incretin or dipeptidyl peptidase 4 activity further contribute to the development of hypertension in obesity. The pathophysiology of obesity-related hypertension is especially relevant to premenopausal women with obesity and type 2 diabetes mellitus who are at high risk of developing arterial stiffness and endothelial dysfunction. In this Review we discuss the relationship between obesity and hypertension with special emphasis on potential mechanisms and therapeutic targeting that might be used in a clinical setting.

Introduction

Epidemiological data indicate that the current global obesity epidemic began approximately 40 years ago;[1] however, some studies suggest that the rise in obesity rates started earlier, and that the progression of the epidemic has been somewhat irregular.[2–4] The causes of the obesity epidemic are most frequently ascribed to two factors: the combination of institutionally driven decreases in physical activity (for example, reductions in school physical education classes and the sedentary nature of most modern vocations); and over-nutrition resulting from modern food marketing practices and technology (such as inappropriately large portion sizes in restaurants and processed foods and the ready availability of inexpensive high-calorie fast food).[4,5] However, evidence also suggests that additional factors might contribute to the obesity epidemic, including sleep debt, endocrine

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disruptors and intrauterine and inter-generational effects, and these have been extensively reviewed elsewhere.[4,6] Obesity is a major public health burden in the USA and >300,000 deaths each year are attributable to obesity or being overweight.[7,8] In the USA, among the adult population of ~240 million individuals, >65% are overweight and, of these, half have obesity;[9] moreover, approximately 13 million US children are also estimated to have obesity.[10] Worldwide, in both developed and developing nations, one billion people are either overweight or have obesity, making this disorder a global epidemic.[11]

In 1967, a prospective analysis of data from the Framingham Heart Study highlighted the relationship between obesity and hypertension.[12] Indeed, the high prevalence of hypertension among patients with obesity (>60%) accounts for 78% of incident hypertension in men and 64% of incident hypertension in women.[13–15] The prevalence of hypertension increases in relation to BMI in both men and women after adjusting for age.[16,17] Estimates indicate that the increased risk of developing hypertension is 20–30% for every 5% increment in weight gain.[18] Even before the Framingham Heart Study data, researchers reported on the potential mechanisms of hypertension in patients with obesity by linking the cardiovascular and metabolic complications of obesity to adipose tissue that is distributed primarily at and above the waistline (that is, upper-body obesity).[19] Contemporaneous studies reported metabolic abnormalities associated with upper-body obesity, including insulin resistance and hypertriglyceridaemia.[20,21] This concept was further refined in the 1980s when researchers demonstrated that an increase in the waist-to-hip ratio was associated with increased risk of hypertension.[22–24] The clustering of abdominal obesity, hypertension, insulin resistance and hypertriglyceridaemia was, therefore, the key to later development of the concepts of the metabolic syndrome and cardiorenal syndrome (CRS).[25,26] Clinical trials have, for the most part, demonstrated that weight loss of ~10% of original body weight by calorie restriction and/or increased activity is an effective means to achieve clinically meaningful reductions in blood pressure and mortality from cardiovascular disease (CVD).[27,28]

Several other reviews have focused on specific factors contributing to obesity-associated hypertension.[29–37] In this Review, we present an integrated view of the pathophysiology of obesity-associated hypertension and discuss the relationships between the multiple factors contributing to this condition. We also discuss factors that contribute to obesity-associated hypertension, including incretin signalling, dysfunctional immunity and the gut microbiome, as well as specific antihypertensive therapies especially relevant to patients with obesity.

Obesity and hypertension

Progression from a normotensive to hypertensive phenotype results from a combination of genetic, environmental, behavioural and dietary factors (Figure 1). The combination of obesity and hypertension has two important consequences. Firstly, this combination is particularly insidious in that the population with obesity and hypertension have high morbidity and mortality from CVD, including coronary heart disease, congestive heart failure, sudden cardiac death, chronic kidney disease (CKD), end-stage renal disease and stroke.[29] Secondly, obesity increases the risk of treatment-resistant arterial hypertension, which therefore requires multiple medications and device therapy, such as renal sympathetic

denervation.[7,38] Conversely, in population studies, future weight gain is significantly higher in patients with hypertension than in normotensive individuals, indicating that hypertension *per se* contributes to the increased risk of obesity[12] and implying a further link between obesity and hypertension.

Before menopause women are protected against CVD, including hypertension, compared with age-matched men owing to the cardioprotective effect of estrogen;[39] however, in the setting of obesity or type 2 diabetes mellitus (T2DM) this protection is lost.[40–43] Population studies indicate that women who are premenopausal but obese have a substantially higher risk of developing hypertension (43–56%) than age-matched men with obesity (20–27%).[44] Weight loss of 5–10 kg in women with obesity substantially lowers the risk of developing hypertension by up to 25%.[45,46] Moreover, maternal and paternal obesity also seem to increase the risk of offspring to develop obesity and hypertension in early adult life.[32,47,48] Given the differences in cardiovascular physiology between sexes, women might require female-specific and more aggressive therapeutic and lifestyle management for obesity and its cardiovascular complications than men.[41]

Dietary factors

Fructose, fat and sodium

The current global obesity epidemic has primarily been ascribed to excess consumption of energy-dense foods, which are high in sugar, fat and sodium, in combination with an increasingly sedentary lifestyle.[1] The introduction of high-fructose corn syrup (HFCS) in 1967 in the USA, and its dramatic increase in consumption compared with other carbohydrates between 1970 and 1990, has been related to obesity, CRS and diabetes mellitus.[37,49,50] HFCS is more lipogenic than other sugars and increases the circulating levels of triglycerides, insulin, glucose and LDL cholesterol,[51] factors that increase the risk of progression to the metabolic syndrome and CVD. Increased HFCS consumption is also associated with elevated uric acid synthesis (a property that is unique among sugars[51]) and emerging evidence supports a role for uric acid in the development of hypertension and CVD.[37,52] However, the hypothesis that fructose and uric acid can induce hypertension is controversial. For example, in rodent studies, conflicting reports suggest that fructose consumption can lead to either no change[53] or an increase[54,55] in blood pressure. These differences might be attributable to the methodology used to measure blood pressure,[53,56] if fructose is dissolved in water (like in a sweetened beverage) or consumed in addition to high-fat or high-salt diets.[53,56,57] Results reported in clinical studies are equally controversial owing to differences between study design, treatment duration, variability of nutrient composition or form of fructose added to the diet (for example, fructose, HFCS, sucrose, or natural fruits).[57] Investigators have presented consistent evidence supporting the observation that reducing sodium intake can lead to reductions in blood pressure.[58,59] However, administering fructose with a high-salt diet leads to hypertension that persists even after removal of fructose from the diet.[54] Similarly, mice fed with a combination of high-fructose and high-fat diet for 6 months also develop hypertension.[56] These results suggest a synergistic deleterious effect owing to the interaction of fructose with either salt or

high fat content. Additional well designed prospective studies are, therefore, needed to determine the effect of HFCS in the development of obesity-associated hypertension.[50]

Cardioprotective nutrients

The undesirable dietary changes in the USA during the past 50 years might be further exacerbated by the imbalance in consumption of omega-6 and omega-3 fatty acids. Omega-3 fatty acids must be obtained from an individual's diet. Humans evolved on diets that contained fairly equal amounts of omega-6 and omega-3 fatty acids. However, in the past 50 years the US diet has become deficient in omega-3 fatty acid (ratio of omega-6 to omega-3 ~15:1) owing to increased consumption of plant-derived oils (soybean and corn oils) and red meat from grain-fed animals, which are rich in omega-6 but not omega-3 fatty acids.[60] Consequently, cold water marine fish have received much attention by dieticians due to their high content of omega-3 and more balanced ratio of omega-6 to omega-3 fatty acids. In meta- analyses, fish oil supplements lower blood pressure in patients with hypertension.[61,62] However, the reports that fish oils can prevent CVD in general are inconclusive.[63]

Combination diets, notably the Dietary Approaches to Stop Hypertension (DASH) diet,[64] which is rich in nutrients from fruits, vegetables and has modest levels of sodium, omega-3 and omega-6 fatty acids, have emerged as part of a balanced strategy for the management of hypertension. Approaches such as the DASH diet include green leafy (for example, cabbages, spinach and lettuces) and root (carrots and beets) vegetables that are rich in inorganic nitrate.[65] Beetroot juice, which also contains high levels of inorganic nitrate, can also lower blood pressure.[66,67] The nitrate content of these foods is likely to contribute to increased nitric oxide (NO) bio-availability, which has multiple beneficial pleiotropic effects in the vasculature such as vasodilation.[68]

Gut microbiota, obesity and hypertension

Emerging evidence suggests that changes in the gut bacterial microbiome, associated with genetic and dietary factors, can lead to metabolic disorders that result in obesity, insulin resistance, T2DM and hypertension.[69,70] In *ob/ob*[71,72] and *db/db*[73] mice, the number of caecal bacteria from the phylum *Bacteroidetes* (so called 'good bacteria') is reduced, which is accompanied by a proportional increase in the number of bacteria from the phylum *Firmicutes* (so called 'bad bacteria'). Bacterial-derived lipopolysaccharides are thought to regulate hormones such as apelin in adipose tissue that alter glucose homeostasis and inflammation.[73] Mice fed a high-fat diet have progressive increases in the number of *Firmicutes* suggesting that the quality of the diet can modulate the gut microbiome.[74] Changes in the gut microbiome lead to abnormalities in pattern recognition receptor function, immune and inflammatory responses, and insulin sensitivity.[75] These studies suggest that therapeutic manipulation of the gut microbiome (for example, by faecal transplantation or oral prebiotic or probiotic preparations) might potentially suppress immune and inflammatory responses and improve insulin sensitivity —a novel approach that might be used to manage obesity and hypertension in humans.[76,77]

Mechanisms of hypertension in obesity

The development of hypertension in patients with obesity is dependent on the interactions between dietary, genetic, epigenetic, and environmental factors (Figure 1).[78,79] Adipocyte dysfunction in patients with obesity contributes to vascular and systemic insulin resistance and the dysfunction of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS).[7,78] Structural and functional changes in the kidney, including activation of intrarenal angiotensin II (Ang II), are also important in the development of obesity-associated hypertension.[80] For example, some investigators have suggested that arterial hypertension in lean patients is mediated by an increase in peripheral vascular resistance, whereas hypertension in individuals with obesity is mediated, in part, by increased intravascular volume, cardiac output,[81] and proximal tubule sodium absorption in the kidney.[82] However, crosstalk between components of the intravascular RAAS, specifically Ang II and aldosterone, can also regulate vasoconstriction independently of renal control.[83,84] Accumulating evidence also suggests that uric acid might affect adipocyte function, and lead to vascular and renal injury.[37,85] Moreover, incretin signalling is also an important modulator of insulin resistance and immune function.[86]

The interplay between genetic and environmental factors (that is, epigenetic mechanisms) might also contribute the pathophysiology of obesity-associated hypertension.[79,87] Epigenetic mechanisms include changes in DNA methylation, histone modifications and microRNA (miRNA) regulation.[88] For example, the miRNAs miR- 142-3p and miR-140-5p are increased in patients with morbid obesity, and are biomarkers of the disease.[89,90] Epigenetic factors are also relevant to the development of obesity-related hypertension,[91,92] and might contribute to *in utero* epigenetic programming, which has been used to explain the origins of fetal and infant diseases.[93,94] Accumulating evidence suggests that environmental factors during early life might also program the development of obesity and hypertension, but these aspects are beyond the scope of this Review.[29,32]

Vascular injury

Endothelial dysfunction and arterial stiffness are thought to be the earliest manifestations of vascular dysfunction in obesity and precede the development of prehypertension and hypertension (Figure 1).[95–98] Increased arterial stiffness is seen in patients who are normotensive but have obesity and who are predisposed to develop hypertension; moreover, incident hypertension is more robustly predicted in patients who are in the highest quartile of arterial stiffness.[95–98] Changes in the extracellular matrix[99] and vascular smooth muscle dysfunction[100] contribute to arterial stiffness; however, accumulating evidence suggests that endothelial dysfunction also contributes to vascular stiffness, which is in turn strongly associated with insulin resistance.[98,101] Impaired vascular reactivity to insulin before the onset of hypertension is seen in spontaneously hypertensive rats,[102] suggesting that insulin resistance is an early event in hypertension development. In the vasculature two components of insulin signalling exist: metabolic and growth factor signalling. Metabolic signalling involves insulin receptor substrate-1 (IRS-1), phosphoinositide 3-kinase, protein kinase B (AKT), and endothelial nitric oxide synthase (NOS); growth factor signalling functions via the extracellular signal regulated kinases (ERK)1/2 and endothelin-1 (ET-1)

pathways.[84,103–105] In insulin resistant states, metabolism is impaired owing to serine phosphorylation of IRS-1, which leads to reduced NO bioavailability and impaired vascular relaxation.[103] Conversely, in this state, upregulation of the ET-1 pathway contributes to increased vascular contraction.[103] The imbalance in pathway-selective insulin signalling in obesity can, therefore, contribute to endothelial dysfunction and arterial stiffness.

In patients with obesity, metabolic changes in adipose tissue lead to altered secretion of bioactive molecules and hormones—collectively referred to as adipokines —such as angiotensinogen, aldosterone stimulating factor, dipeptidyl peptidase 4 (DPP-4), leptin, resistin, TNF and IL-6 (Figure 1). These factors can contribute to obesity-associated insulin resistance and hypertension.[106] Impaired adiponectin secretion also promotes insulin resistance.[78,107,108]

Renal injury

Abnormal renal function also leads to hypertension in patients who have obesity, as well as in animal models of obesity (Figure 1).[109] Obesity increases tubular absorption of sodium and promotes a compensatory shift in the pressure natriuresis curve towards higher blood pressure in response to elevated plasma sodium levels.[78,110] Moreover, these effects on sodium and pressure natriuresis can be caused by an increase in adipose tissue mass and extracellular matrix accumulation, which compress the renal medulla. Hyperinsulinaemia and inappropriate RAAS and SNS activation also contribute to increased sodium resorption.[78] Renal vascular remodelling, characterized by inflammation, endothelial dysfunction and vascular smooth muscle proliferation, is seen in humans and animals with hypertension.[111] Tubulointerstitial inflammation owing to a systemic immune and inflammatory response, elevated uric acid levels, tubulointestinal infiltration of immune cells, circulating proinflammatory immune cells and enhanced inflammation, oxidative stress and fibrosis collectively contribute to renal damage.[37,50,78,112]

The kidney regulates plasma glucose levels by reabsorbing almost all of the glucose filtered by the glomeruli (~162 g per day).[113] Glucose reabsorption is primarily localized to the S1 segment of the proximal convoluted tubule and functions via high-capacity, low-affinity sodium-glucose cotransporter-2 (SGLT2).[114] In humans with diabetes mellitus,[115] Zucker diabetic fatty rats,[116] and *db/db* mice[117] SGLT2 expression is increased in the proximal convoluted tubule, which correlates with glomerular hyperfiltration leading to increased glucose reabsorption.[117] This increased reabsorption leads to elevated plasma glucose levels and glucose toxicity, and sodium reabsorption, which also contributes to sodium retention.[118] In hypertensive rats, Ang II regulates the increase in SGLT2 expression via the angiotensin II type 1 receptor (AT_1R), supporting a role for SGLT2-mediated sodium reabsorption in the development of hypertension.[119,120] Moreover, *in vivo* data suggest that insulin is an agonist for this effect of SGLT2 in humans and is important for postprandial glucose and sodium reabsorption.[121] Emerging evidence also indicates that inhibition of SGLT2, with molecules such as dapagliflozin, in animal models or humans with T2DM induces a mild osmotic/ natriuretic effect that promotes modest reductions in blood pressure and body weight, which might reduce the risk of a future cardiovascular event.[122–124]

SNS overactivation

Obesity is associated with activation of the SNS in diverse tissues—including the heart, kidneys, and skeletal muscle—and with baroreflex dysfunction, leading to altered blood pressure.[33,34,125,126] Regardless of blood pressure, individuals who are obese have increased renal SNS activity compared with healthy individuals, indicated by an elevation in renal norepinephrine levels.[33] Interestingly, individuals who have obesity but are normotensive have suppressed cardiac SNS activity, whereas those who have obesity and hypertension have elevated cardiac SNS activity.[33] Increases in both renal and cardiac SNS activity might, therefore, be one mechanism that leads to the development of hypertension in obesity. The importance of SNS activation in the kidney to obesity-related hypertension is highlighted by evidence that renal denervation can lower blood pressure and increase sodium excretion in a canine model fed on a high-fat diet.[127] However, other studies suggest that SNS activation alone might not lead to the development of hypertension. Increased α-adrenergic-mediated vascular tone has been reported in overweight men, most of whom had hypertension;[128] however, hypertension, rather than body weight, might account for the increase in SNS activity reported in this study. In individuals who have obesity but are normotensive the observed increase in sympathetic outflow to the forearm musculature does not lead to an increase in peripheral sympathetic vascular tone.[129] The authors speculated that a dissociation between SNS activity and peripheral vascular tone can protect a subset of individuals with obesity from developing hypertension, which might explain the small population of individuals with obesity but normal blood pressure.[129] However, definitive evidence that hypertension in individuals with obesity is either initiated or maintained solely by a neurogenic mechanism has yet to be determined.[130]

Several factors have been suggested to promote obesity-associated hypertension by activating the SNS, including hyperinsulinaemia, hyperleptinaemia, RAAS activation (via Ang II), baroreflex dysfunction and obstructive sleep apnoea (OSA) (Figure 1).[131,132] However, evidence suggests that hyperinsulinaemia itself does not promote hypertension.[133,134] Increased leptin secretion from dysfunctional adipose tissue is also an important modulator of SNS activity.[131] Disruption of signal transducer and activator of transcription 3 (commonly known as STAT3) signalling in the arcuate nucleus leads to resistance to the anorexic effects of leptin and might result in weight gain.[135] Conversely, preservation of leptin sensitivity in the ventromedial and dorsomedial hypothalamus, involving activation of PI3 kinase and melanocyte stimulating hormone and its receptors, leads to enhanced renal sympathetic outflow.[131,132] Low adiponectin and increased apelin levels are linked to SNS activation, although their role in SNS regulation is unclear.[108,136]

Progression to a chronic hypertensive state in individuals with obesity might be preceded by a loss of nocturnal blood pressure dipping in the absence of elevated daytime blood pressure.[137,138] A non-dipping pattern of circadian blood pressure increases the risk of CVD and CKD.[137,139] The exact mechanisms for this non-dipping pattern of blood pressure are unknown; however, insulin resistance, autonomic nervous system dysfunction, increased SNS activity and increased inflammation can all contribute to the phenomenon.[137,140]

OSA and hypertension are typically associated comorbidities. 50–60% of individuals with OSA are hypertensive and half of individuals with hypertension have OSA.[141] Moreover,

the frequency of the association of these comorbidities is even higher in those with treatment-resistant hypertension.[142,143] OSA activates the SNS independently of obesity-related mechanisms[144,145] and, therefore, might be a major factor that promotes treatment-resistant hypertension in those who have obesity. Renal sympathetic denervation has led to positive improvements in blood pressure, OSA and glycaemic control in patients with obesity and treatment-resistant hypertension.[14,38,146] OSA is also highly prevalent among individuals with treatment-resistant hypertension and elevated aldosterone levels.[146] SNS activation and aldosterone production in response to non-classical adrenal stimuli might contribute to the increased aldosterone levels seen in patients with obesity (Figure 2).[146,147] Aldosterone regulates blood pressure via mineralocorticoid receptors in both the renal and vascular systems.[148] Treatment with a continuous positive airway pressure assist device and mineralocorticoid receptor inhibitors to limit the deleterious effects of elevated aldosterone levels can reduce the severity of OSA and normalize blood pressure (Figure 2).[146]

RAAS

In patients with obesity, inappropriate activation of RAAS modulates insulin resistance, SNS activation, dysfunctional immunity and abnormal renal sodium handling, which collectively contribute to cardiovascular and renal dysfunction (Figure 1).[40,78,84,108] In addition to the conventional circulating endocrine RAAS proteins, the heart, kidney, vasculature, adipose tissue, immune cells and brain express RAAS proteins as part of a tissue-specific local effect.[98,149–152]

Ang II synthesis by intravascular and intrarenal RAAS might directly regulate vascular stiffness, and endothelial and renal function.[98,153] Ang II also modulates vascular and renal function by inhibiting metabolic insulin signalling and enhancing ERK1/2 and ET-1 signalling.[84,104] Expression of RAAS components and increased expression and secretion of angiotensinogen by adipose tissue in obesity states supports a role for local RAAS activation in adipose tissue dysfunction.[152] Moreover, increased Ang II production by perivascular adipose tissue contributes to impaired vascular function.[154] This concept is further supported by studies in mice with an adipocyte-specific angiotensin knockout. When fed a high-fat diet, these mice have a lower blood pressure than wild-type control mice on an identical diet.[155]

Circulating aldosterone might also be involved in the development of hypertension in individuals with obesity. Obesity can be accompanied by elevated plasma aldosterone levels[156] and soluble factors derived from adipose tissue stimulate adrenal aldosterone secretion.[157–159] Endothelial dysfunction[160] and enhanced vascular smooth muscle reactivity have both been implicated in the modulation of vascular remodelling by aldosterone.[98] Patients with primary hyperaldosteronism can be insulin-resistant, and aldosterone levels have been correlated with BMI and insulin resistance in patients with obesity who are normotensive.[161] The precise role of aldosterone-induced vascular insulin resistance has not been fully elucidated; however, suppression of local inflammation and vascular stiffness by the mineralocorticoid antagonist spironolactone in rodent models of hypertension and insulin resistance has been reported.[98,162] Aldosterone activates nicotinamide adenine dinucleotide phosphate-oxidase (NADPH), which promotes oxidative

stress and decreases NO bio-availability.[163] Aldosterone also increases endothelial stiffness by modulating epithelial sodium channel expression on the endothelial cell surface and NO release.[163] Spironolactone can lower blood pressure in patients with obesity with elevated plasma aldosterone levels, although insulin resistance is unchanged in these patients.[161,164] Mineralocorticoid receptor antagonists might improve insulin resistance in patients with hyperaldosteronism in contrast to individuals with obesity in whom aldosterone levels are only moderately elevated.[164] However, insulin resistance in obesity can also develop via other pathways, including through the effects of overnutrition and SNS overactivation, meaning that mineralocorticoid receptor antagonists might not be appropriate in this context.[40,165] In this regard, eplerenone, a drug with higher binding specificity for the mineralocorticoid receptor than spironolactone, improved flow-mediated dilation in healthy individuals 55–79 years old.[166] Moreover, impaired endothelial function was improved in obese mice or exogenous-aldosterone-infused lean mice with an endothelial-specific mineralocorticoid receptor deletion.[167] A subset of individuals with obesity and hypertension might also have insulin-resistance-related hyperaldosteronism, for which mineralocorticoid receptor inhibitors might be useful to treat.[168]

Attenuation of Ang II-induced vascular damage by mineralocorticoid receptor antagonists suggests a crosstalk between the Ang II and aldosterone signalling pathways.[84,169] For example, Ang II-induced vascular smooth muscle contraction and hypertension are reduced in mice with a deletion of mineralocorticoid receptor specific to smooth muscle cells.[148] This study also suggests mineralocorticoid receptor-regulated blood pressure is independent of hypertension induced by renal mechanisms. Both the direct beneficial effects of mineralocorticoid receptor antagonists, and their role in reducing Ang II-induced pathology support the adjunctive use of mineralocorticoid receptor antagonists to manage resistant hypertension in obesity.[29,38]

Immune and inflammatory mechanisms

Accumulating evidence suggests that in patients with obesity, dysfunctional innate and adaptive immune and inflammatory responses contribute to vascular dysfunction and the pathogenesis of hypertension. However, the mechanisms and mediators of this relationship are still not well understood. Immune-mediated injury in obesity and hypertension can occur in the vasculature, central nervous system, kidney and adipose tissue, including perivascular tissue (Figure 1).[112,170,171]

Innate immunity—Macrophage infiltration into adipose tissue is associated with systemic insulin resistance.[172] Distinct macrophage phenotypes elicit either a proinflammatory (M1 macrophages) or an anti-inflammatory response (M2 macrophages).[172] Lipid-filled foam cells are a type of activated M1 macrophage that secrete proinflammatory cytokines within the vascular wall.[173] Proinflammatory cytokines secreted by macrophages, such as TNF and IL-6, contribute to insulin resistance by activating kinases that phosphorylate serine residues of IRS-1 and IRS-2 and lead to suppression of metabolic insulin signalling and promotion of growth factor signalling in the vasculature.[104]

Adaptive immunity—Accumulating evidence suggest that T-cell activation and dysregulation of T-cell polarization can affect the pathophysiology of hypertension. T helper (T_H) 1 cells mediate the proinflammatory response and oxidative stress, and promote infiltration of M1 macrophages into adipose and vascular tissues.[171] T_H17 cells secrete IL-17, which contributes to vascular injury in hypertension.[174] $CD8^+$ cells that are cytotoxic to the kidney and vasculature in hypertension also secrete IL-17.[112] T regulatory cells (T_{REG}) are a unique subpopulation of T cells [40] that suppress proinflammatory T-cell responses and promote polarization of M2 macrophages, which in turn leads to an anti-inflammatory response. Insulin resistance and impaired vascular reactivity are associated with depletion of T_{REG} cells and insulin sensitivity can be restored by T_{REG}-cell transfer and/or induction in rodents.[175] T_{REG} cells can also protect against insulin resistance and hypertension via secretion of anti-inflammatory cytokines such as IL-10, which can limit impaired insulin signalling caused by proinflammatory cytokines.[176] Moreover, IL-10 can inhibit NADPH-oxidase-mediated oxidative stress.[177] Finally, in patients with T2DM, an increase in proinflammatory T-cell ratio (that is, elevated levels of T_H17 cells and a decrease in levels of T_{REG} cells might contribute to vascular dysfunction thereby leading to hypertension.[178]

Inflammasome—Activation of the inflammasome by IL-1β might contribute to insulin resistance,[179] which is a response observed after pathogen exposure or danger-associated signal activation.[180,181] In obesity states, palmitate and ceramide lipid levels are elevated, which activates inflammasomes.[180] When fed a high-fat diet, mice deficient in central inflammasome molecules fail to become insulin resistant, which is accompanied by suppression of immune and inflammatory responses.[180,181] Mice fed a high-fructose diet become obese and develop hyperuricaemia, which is associated with inflammasome activation, suggesting that uric acid also contributes to an inflammasome response in obesity induced by a high-fructose diet.[182]

RAAS in the immune system—The role of RAAS-mediated immune cell activation in hypertensive states is supported by experiments in *Rag1*$^{-/-}$ mice, which have an absolute deficiency of T and B lymphocytes.[183] Adoptive transfer of T cells (but not B cells) can restore normal blood pressure, endothelial dysfunction, vascular remodelling and reactive oxygen species production.[183] Moreover, in rats, Ang II triggers the recruitment of T_H1 cells to renal and cardiovascular tissues, which is prevented by inhibitors of AT_1R.[40,112,171] Adoptive transfer of T_{REG} cells before Ang II infusion can attenuate blood pressure increases and improve vascular stiffness and impaired vasodilatory responses in young C57BL6 mice.[171] This improvement was associated with attenuation of infiltration of inflammatory monocytes, macrophages, and T_H1 cells, suppression of Ang II-induced NADPH oxidase activity, reactive oxygen species production, interferon γ (IFN)-γ, TNF, and IL-6 production, and an increase in IL-10 secretion.[177] Similarly, adoptive transfer of T_{REG} cells prevented aldosterone-induced vascular damage in vascular and renal tissues of young C57BL6 mice.[184]

RAAS-stimulated activation of the peripheral immune system—via the central nervous system—might also lead to immune-mediated hypertension in patients with obesity.[185,186]

Spleen and lymph nodes are extensively innervated by the SNS and norepinephrine also modulates T-cell activation.[187,188] In rats, intracerebroventricular administration of Ang II modulates lymphocyte proliferation and spleen cytokine secretion, and sympathetic denervation in the spleen can abolish these effects of Ang II.[189] These studies suggest that the modulation of blood pressure occurs via both peripheral and central immunomodulation in addition to the haemodynamic effects of RAAS.

Dietary fructose and uric acid

A high-fructose diet can lead to hyperuricaemia owing to decreased renal clearance, increased uric acid production by adipose tissue and increased hepatic production via the induction of fructokinase.[37] Interestingly, serum uric acid is independently associated with a non-dipping circadian pattern of blood pressure in patients with hypertension,[190] and 24-h ambulatory diastolic and daytime systolic blood pressure can be decreased by reducing serum uric acid levels with allopurinol.[191] However, these findings need to be confirmed by large-scale epidemiological and interventional studies.

Adipocyte dysfunction, maladaptive immune and inflammatory response, inappropriate activation of RAAS and enhanced oxidative stress all contribute to uric- acid-mediated induction of cardiovascular and renal injury.[57,192] Uric acid increased expression of monocyte chemoattractant protein-1, macrophage infiltration and adipose tissue proinflammatory responses in a murine model of CRS.[193] Uric acid can also contribute to an inflammasome response in obesity induced by a high-fructose diet.[192] Uric acid increases AT_1R levels in the vasculature, thereby contributing to Ang II-mediated endothelial dysfunction and vascular inflammation.[40] Uric acid can also lead to ischaemic renal injury owing to excess collagen deposition, increased macrophage infiltration and expression of osteopontin,[194] elevated juxtaglomerular renin production and reduced NO levels in the macula densa.[194] Ingestion of fructose can also increase salt and water resorption in the small intestine and kidney. Moreover, in rats, a high-fructose diet can induce synthesis of ET-1 leading to hypertension, which can be attenuated by administration of an ET-1 inhibitor.[57,195]

Incretins and DPP-4

Glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide are gut-derived hormones that enhance glucose-stimulated insulin secretion and suppress glucagon release, thereby modulating postprandial and long-term glucose homeostasis.[196] These incretins are rapidly degraded by the exopeptidase DPP-4, which circulates in the plasma and limits the half-life of these substrate hormones to ~2 min.[196,197] DPP-4 secretion from adipose tissue and inhibition of insulin-mediated glucose uptake in adipose and muscle cells by DPP-4 suggests that this exopeptidase has direct effects on insulin resistance (Figure 1).[198] In the past 10 years, DPP-4-resistant GLP-1 analogues (exenatide and liraglutide) and DPP-4 inhibitors (sitagliptin, vildagliptin, saxigliptin, linagliptin and alogliptin) have been approved in the USA for use in patients with T2DM to lower HbA_{1c} levels. Augmentation of GLP-1 levels using these drugs can improve cardiovascular outcomes in patients with T2DM,[196,197] suggesting that their effect extends beyond glycaemic control. Liraglutide and DPP-4 inhibitors can lower blood pressure in animal models of obesity and hypertension and

in humans with T2DM.[29,199,200] Linagliptin also has potent vasodilatory effects in *ex vivo* vascular ring preparations.[201] DPP-4 substrates other than GLP-1, such as stromal cell derived factor 1α and the natriuretic peptides,[202] might also contribute to the beneficial effect of DPP-4 inhibitors in the vasculature. Natriuretic peptide levels are low in patients with obesity[203] and, therefore, DPP-4 inhibitors might be used to extend the bioavailability of these proteins.

DPP-4 is also widely expressed in the kidney and $CD4^+$ and $CD8^+$ immune cells.[196,204] DPP-4 inhibitors can reduce the accumulation of M1 macrophages and increase levels of M2 macrophages in adipose tissue or atherosclerotic lesions.[205,206] Moreover, GLP-1 can enhance T_{REG}-cell function.[207] DPP-4 inhibitors might, therefore, be useful to treat immune-mediated mechanisms of hypertension in obesity.

Estrogen

In premenopausal women, estrogens can lower the risk of CVD; however, this cardioprotective effect is lost in premenopausal women who have obesity and diabetes mellitus.[1,208–210] Differences in sympathetic–adrenal nervous system regulation between men and women suggest that premenopausal women might have better control of stimuli that activate the SNS than men and are consequently protected from development of arterial hypertension, which correlates with results seen in lean hypertensive rats.[211–213] In these female patients, arterial stiffness is substantially higher than in age-matched men, which might explain why obesity limits the cardiovascular protection of estradiol in premenopausal women who have obesity.[214–216] Estrogen receptor-α and GPR-30 can also increase T_{REG}-cell function,[217] and insulin sensitivity is modulated by signalling mediated by estrogen receptor α in macrophages.[218] Whether these immune functions of T_{REG} cells and macrophages are modulated in premenopausal women who have obesity remains to be determined.

Estrogen modulates Ang II signalling differently under normal and high-salt diets. For example, estradiol suppresses Ang II signalling by reducing AT_1R expression,[98,219] whereas GPR-30 increases the expression of angiotensin converting enzyme (ACE) 2, decreasing AT_1R expression.[220,221] By contrast, estradiol can increase AT_1R expression when NO synthase is inhibited and under high-salt conditions,[222] which suggests that preventing estrogen suppression of Ang II signalling might decrease cardiovascular risk in women who have obesity. In the Framingham study, aldosterone levels were higher in women than in men, and were positively associated with markers of cardiac remodelling, such as left ventricular wall thickness in women but not in men.[210] These findings suggest that crosstalk between estrogen and mineralocorticoid receptors might contribute to altered immune and inflammatory responses, endothelial dysfunction and arterial stiffness relating to obesity and hypertension in women.

Therapeutics

Lifestyle modifications, including calorie restriction and exercise, are effective in limiting the effect of obesity on hypertension (Figure 2). However, many patients find weight loss programs difficult to maintain and high dropout rates occur during the initial years of such

programs.[223] Pharmacologic interventions are, therefore, useful when patients who have obesity are unable to comply with their weight reduction program or when weight reduction measures alone cannot reduce hypertension (Figure 2).

Targeting RAAS can potentially improve multiple pathophysiological components of obesity-associated hypertension, including increasing GLP-1 levels and modulating SGLT2 or SNS overactivation.[29,38,223] The angiotensin receptor inhibitor losartan can reduce serum uric acid levels, but a similar effect has not been seen with other such blockers.[224] DPP-4 inhibitors and GLP-1 analogues might also be used to manage hypertension as an add-on therapy in patients with T2DM.[29] Owing to the complex pathophysiology of treatment-resistant hypertension, the correct management of hypertension in patients who have obesity is of major concern to clinicians.[225] Aldosterone antagonists and control of inappropriate SNS activation by renal denervation are emerging as new modalities for the management of treatment-resistant hypertension (Figure 2).[7,40,226]

Conclusions

Hypertension related to obesity can occur via multiple mechanisms: insulin resistance; adipokine alterations; inappropriate SNS and RAAS activation; structural and functional abnormalities in the kidney, heart and vasculature; and maladaptive immunity. Hyperuricaemia associated with a high-fructose diet also contributes to vascular dysfunction, renal injury and immune activation. DPP-4-mediated incretin signalling can affect vascular function, immune responses and natriuresis in obesity states. Estrogen-mediated insulin sensitivity in premenopausal women who do not have obesity is compromised when they develop obesity. Alteration in the gut microbiome in obesity is another factor that contributes to insulin resistance and dysfunctional immunity. Treatment-resistant hypertension is more common in individuals with obesity than in those who do not have obesity, especially in patients with OSA, and is a major challenge in the management of hypertension. Adjunctive therapy with mineralocorticoid receptor antagonists and renal denervation are emerging as therapeutic measures to control treatment-resistant hypertension. Therapeutic strategies targeting obesity-associated hypertension are needed — mineralocorticoid receptor antagonists are especially promising in this context.[7,29] More studies focused on the clinical utility of treating hypertension in children with obesity are also necessary. Despite the positive therapeutic developments, obesity-related treatment-resistant hypertension remains a major issue in health care.

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Key points

- The incidence of hypertension is substantially increased in the population of people with obesity and affected individuals have increased morbidity and mortality from cardiovascular disease (CVD) and chronic kidney disease
- Adipokine alterations, insulin resistance, sympathetic nervous system and renin–angiotensin–aldosterone system activation, obstructive sleep apnoea, renal abnormalities, maladaptive immunity and gut microbiome changes all link hypertension to obesity
- Hyperuricaemia associated with a high-fructose diet is emerging as a key factor in the development of hypertension associated with diet-induced obesity
- Dysregulation of the dipeptidyl peptidase 4–incretin system contributes to the development of maladaptive immunity and associated hypertension in obesity
- Estrogen-mediated CVD protection is compromised in individuals with obesity, thereby underscoring the greater CVD risks associated with obesity in premenopausal women compared with those in age-matched men with obesity
- Adjunctive therapy with mineralocorticoid receptor antagonists and renal denervation is emerging as an additional therapeutic measure for management of obesity-related hypertension

Review criteria

MEDLINE and PubMed databases were searched for full-text English-language articles published between 1950 and 2014 with the following terms: “obesity”, “resistant hypertension”, “insulin resistance”, “obstructive sleep apnea”, “SNS activation”, “high fructose corn syrup”, “uric acid”, “endothelial dysfunction”, “DPP-4”, “tissue RAAS”, “aldosterone”, “adipose dysfunction”, “gut microbiome”, both alone and in combination. The reference lists of identified articles were also consulted for other relevant papers.

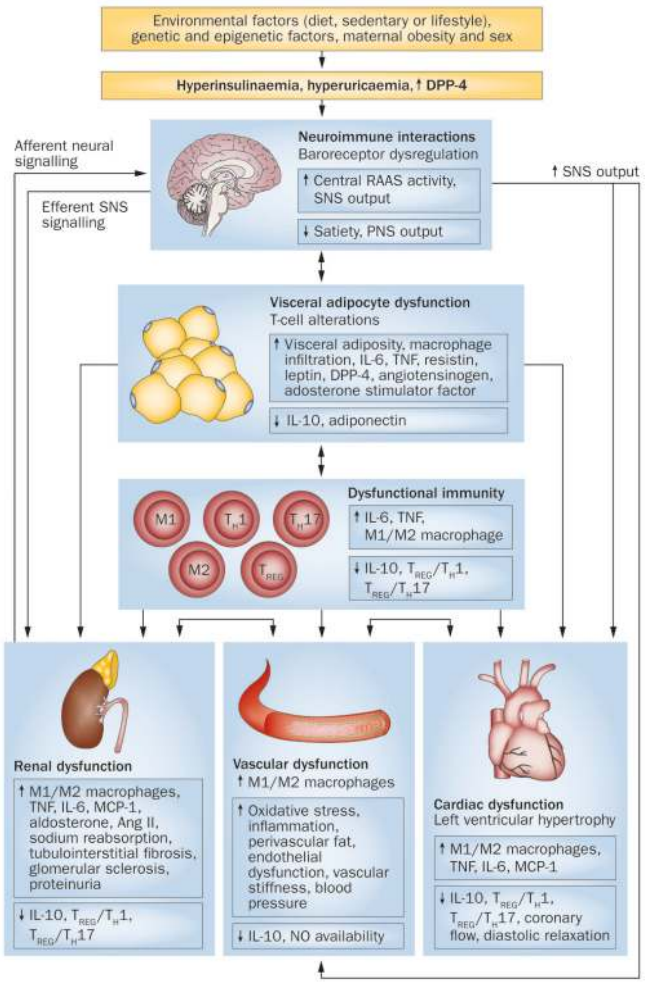

Figure 1.

Obesity contributes to the development of hypertension via the interaction of dietary, genetic, epigenetic and environmental factors. Visceral adipocyte dysfunction leads directly to renal, cardiac and vascular dysfunction, via an impaired immune or inflammatory response, and by affecting neuroimmune interactions that alter SNS signalling. Cardiac and/or renal abnormalities can lead to vascular dysfunction and vice-versa. Obesity-related hypertension is associated with structural and functional changes in the kidney, heart and vasculature. Hyperuricaemia might also affect adipocyte function and vascular remodelling, and cause renal abnormalities. Abbreviations: ↑, increased; ↓, decreased; Ang II, angiotensin II; DPP-4, dipeptidyl peptidase 4; MCP-1, monocyte chemoattractant protein-1; PNS, parasympathetic nervous system; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; T_H, T helper cell; T_{REG}, T regulatory cell.

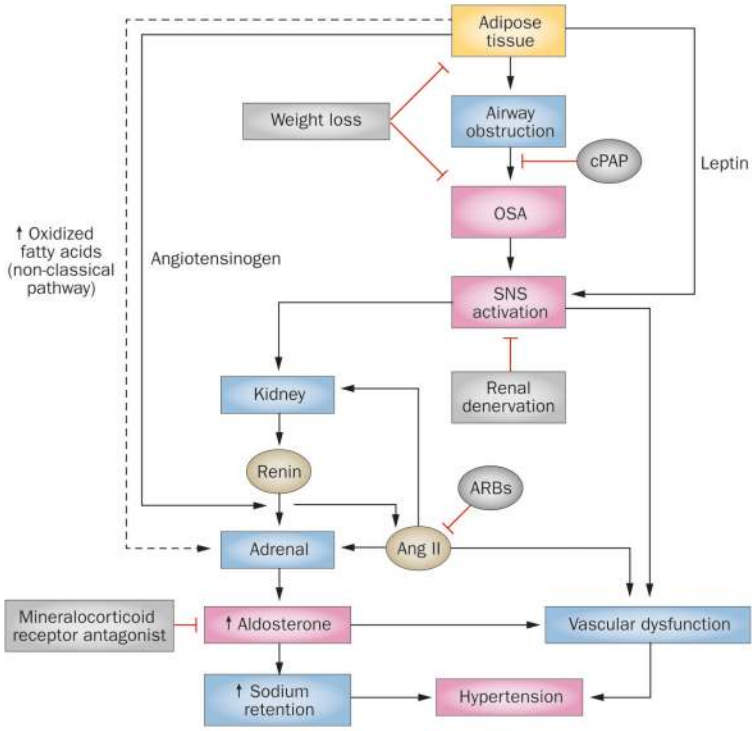

Figure 2.

Possible mechanisms of obesity-associated hypertension and therapeutic strategies. Adipose tissue releases leptin, angiotensinogen and oxidized fatty acids to stimulate adrenal release of aldosterone via activation of the classic RAAS, as well as a non-classical pathway mediated by oxidized fatty acids. Leptin stimulates the central SNS which in turn leads to renin release from the kidney. Activation of RAAS in other tissues contributes to renal and vascular dysfunction. Increased adipose tissue can lead to OSA, which can be treated by therapeutic weight loss or application of cPAP. OSA leads to activation of the SNS which activates RAAS in the kidney. Increased aldosterone can be reduced with mineralocorticoid receptor antagonists. Abbreviations: ↑, increased; ↓, decreased; ARBs, angiotensin type 1 receptor blockers; cPAP, continuous positive airway pressure; OSA, obstructive sleep apnoea; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.