AI-02012 Paper-Obesity vs Hypertension

Owner	Ⓡ Rigel Arcayan
Tags	MD
Created time	@August 24, 2025 6:43 AM

This scholarly article from the *Clinical Kidney Journal* **examines the complex relationship between obesity and hypertension**, a growing global health concern. It **explores various physiological mechanisms** suspected of linking these two conditions, such as the **renin–angiotensin–aldosterone system (RAAS) overactivation, sympathetic nervous system dysfunction, altered adipokine levels, inflammation, and lifestyle factors**. The review also **discusses current and emerging therapeutic strategies** for managing obesity-associated hypertension, including **pharmacological treatments like GLP-1 receptor agonists and dual/triple agonists, as well as bariatric surgery and endoscopic interventions**. Ultimately, the text **aims to clarify the pathophysiological pathways and assess the effectiveness of different treatment approaches** in reducing blood pressure in obese individuals.

Obesity is a rapidly increasing global epidemic, affecting over 15% of the adult population and leading to significant clinical consequences and comorbidities, including hypertension, diabetes mellitus, cardiovascular and cerebrovascular diseases, and chronic kidney disease [1, 2]. There is a strong association between obesity and high blood pressure (BP) [1]. This review aims to evaluate the potential pathophysiological mechanisms linking hypertension and obesity and the effectiveness of various therapeutic approaches on BP [3, 4].

Pathophysiological Mechanisms Linking Obesity and Hypertension
Multiple underlying mechanisms are potentially involved [5]:

- **Renin–Angiotensin–Aldosterone System (RAAS) Overactivation**: Obesity can lead to elevated plasma levels of renin, angiotensin II, ACE, angiotensinogen,

and aldosterone, alongside upregulated renin receptors. This contributes to systemic vasoconstriction and increased tubular water and sodium retention, with adipocytes also potentially producing excess RAAS components. RAAS activation in obesity is driven by physical compression from fat accumulation (fatty kidney hypothesis) and increased sympathetic nervous system activity [1, 5, 6].

- **Fatty Kidney Hypothesis**: This concept involves intrarenal, perirenal, and renal sinus fat accumulation, which can cause kidney injury and metabolic dysfunction through inflammation, oxidative stress, and mechanical pressure. This pressure can activate the RAAS by compressing renal vasculature or depolarizing nerves, leading to increased BP and decreased renal function [1, 7, 8].
- **Sympathetic Nervous System (SNS) Overactivation**: Increased SNS activity is observed in patients with obesity, contributing to hypertension. Factors include baroreceptor reflex impairment, hyperinsulinemia, angiotensin II, and cytokine release from adipocytes, particularly leptin. SNS overactivation is especially evident in the renal and musculoskeletal systems [1, 8, 9].
- **Altered Adipokine Homeostasis**: Bioactive molecules produced by adipocytes, known as adipokines, have altered homeostasis in obesity.
    - **Leptin**: Circulating leptin levels positively correlate with BP, primarily by activating the SNS via the melanocortin 4 receptor (MC4R) [10].
    - **Adiponectin**: Adiponectin protects against high BP and cardiovascular events by promoting vasodilation via nitric oxide production and exhibiting anti-inflammatory functions. Lower adiponectin levels are associated with hypertension [10, 11].
- **Pro-inflammatory Status**: Obesity is characterized by a state of inflammation with high levels of circulating pro-inflammatory cytokines such as TNF-α, interleukin-6 (IL-6), and plasminogen activator inhibitor-1 (PAI-1), which may regulate BP [1, 12]. These cytokines can reduce NO-mediated vasodilation and influence endothelin-1 levels [12].
- **Obesity-associated Lifestyle**: A sedentary lifestyle and excessive intake of processed foods (often rich in salt) contribute to obesity and its association

with hypertension. Exercise has BP-lowering effects, and reduced food/salt intake is a mechanism of anti-obesity treatments [1, 13, 14].

Challenges in Hypertension Management in Obesity

Obesity is associated with a higher risk for hypertension and impaired response to pharmacotherapy or lifestyle interventions [15]. Mechanisms contributing to uncontrolled and resistant hypertension include:

- **Sodium Retention**: Sympathetic activation may contribute to sodium retention via upregulation of thiazide-sensitive sodium chloride co-transporter (NCC) and increased sodium–potassium–2 chloride co-transporter (NKCC2) activity in later stages of obesity, suggesting a need to target different transporters over the course of the disease [15, 16].
- **Treatment Non-adherence**: Obesity is a risk factor for non-adherence to lifestyle or pharmacological interventions [16].
- **Resistant Hypertension**: Defined as failure to reach target BP despite using three antihypertensive drugs from different classes (one being a diuretic) at maximum doses. Its mechanism in obesity is multifactorial, involving interactions of the nervous system, hormones, adipokines, and non-compliance. Excess aldosterone production by adipocytes has been proposed as a mechanism, and mineralocorticoid receptor antagonists (MRAs) are recommended in resistant cases [17].
- **Impact on Antihypertensive Medications**: Pharmacokinetic and pharmacodynamic properties of antihypertensive medications can vary in obese individuals due to increased volume of distribution, altered gastrointestinal transit, hepatic metabolism, and tissue distribution (especially for lipophilic medications) [18, 19]. However, a meta-analysis found no superiority of any specific antihypertensive drug group on cardiovascular risk in obese patients, except for slightly better protection with ACE inhibitors compared to calcium channel blockers [20].

Therapeutic Approaches

Weight loss is a fundamental part of hypertension management in obese or overweight patients, with an approximate 1 mmHg decline in systolic BP (SBP) per 1 kg decrease in body weight [21].

- **Pharmacotherapeutic Approaches**:

- **GLP-1 Receptor Agonists**: Medications like liraglutide, semaglutide, and orforglipron have been approved for obesity management. Liraglutide and semaglutide have shown significant BP reductions, often occurring prior to substantial weight loss and persisting with chronic therapy [22, 23]. Semaglutide, in particular, has demonstrated reductions in cardiovascular risk and major adverse cardiovascular events (MACE) [23-25]. The exact mechanism for BP reduction is unclear but may involve weight/fat loss, reduced salt intake, attenuation of RAAS activation, and natriuretic effects [26]. Orforglipron, an oral GLP-1 RA, also significantly reduced SBP [26].
- **Dual Agonists**: These include tirzepatide (GLP-1 and GIP receptors) and survodutide (GLP-1 and glucagon receptors) [27].
  - **Tirzepatide** has shown superior glycaemic control, reductions in body weight, visceral adiposity, and BP. BP reductions were partially attributed to weight changes but also involve increased adiponectin production, reduced pro-inflammatory cytokines, and release of vasodilatory substances [27, 28].
  - **Survodutide** may increase energy expenditure, decrease liver fat, and reduce BP [29].
- **Triple Agonists**: Retatrutide activates GLP-1, GIP, and glucagon receptors. It has demonstrated improvements in cardiometabolic risk factors, including SBP and DBP, and allowed a significant percentage of participants to be weaned off antihypertensive medications [30].

- **Bariatric Surgery**: This invasive procedure is generally offered to patients with a BMI > 40 kg/m2 or 35–40 kg/m2 with comorbidities, when other interventions fail [31]. Bariatric surgery can lead to remission of hypertension in a high percentage of patients (e.g., 84% in one study) and significantly reduces cardiovascular risk, including myocardial infarction, stroke, and overall mortality [31-33].
  - **Mechanisms beyond weight loss**: Significant BP reduction can occur as early as 1 week post-surgery, indicating non-weight loss-related contributors. These include reduced peripheral insulin resistance, decreased RAAS activation, systemic inflammation, improved comorbidities, reduced salt intake, increased incretins (GLP-1, peptide YY)

leading to natriuresis, and modulations of other adipokines (ghrelin, leptin, adiponectin). Pro-inflammatory cytokine levels also decrease [34].

- **Endoscopic Bariatric Interventions**: These include endoscopic sleeve gastroplasty and intragastric balloons. While more data exist on their weight loss efficacy, initial results show promise for metabolic parameters and BP reduction. Endoscopic sleeve gastroplasty has shown decreased body weight, HbA1c, SBP, and serum triglycerides, potentially via increased GLP-1 levels, altered bile acid secretion, decreased ghrelin, and improved insulin sensitivity [35]. Intragastric balloons have shown statistically significant decreases in diastolic BP (DBP) and SBP in some studies [36].

Future Perspectives

Ongoing clinical trials are investigating the efficacy and safety of new pharmacotherapeutic approaches (dual and triple agonists) and endoscopic procedures for weight loss and obesity-related complications like high BP [37, 38]. While GLP-1 receptor agonists have gained popularity due to being non-invasive and efficacious, comparing their long-term effects with bariatric surgery is still premature, with some studies suggesting advantages for bariatric surgery in certain cardiovascular outcomes and fatty liver disease, although these studies often don't include the most recent GLP-1 RAs [39, 40]. There is a clear need for future large-scale clinical studies comparing these therapeutic approaches to determine the optimal strategy for individual patients based on their baseline characteristics and comorbidities [40].