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OBESITY-RELATED HYPERTENSION

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Abstract
Obesity is a globally expanding disorder and is the result of the interaction of genetic and environmental factors with the participation of social, behavioural, cultural, physiological, metabolic, and genetic influences. Obesity has profoundly negative effects on the health of the population and induces associated comorbidities such as hypertension, hyperlipidaemia, hyperinsulinemia / insulin resistance. There is ample evidence that obesity causes hypertension, cardiovascular disease, type 2 diabetes, cancer and chronic kidney disease, and the association of obesity with hypertension and other cardiovascular risk factors significantly increases the risk of cardiovascular events.
Keywords: *obesity, hypertension, hyperlipidaemia, insulin resistance, cardiovascular events.*

Abstract
Obezitatea este o tulburare în expansiune la nivel global şi este rezultatul interacţiunii dintre factorii genetici şi factorii de mediu, cu participarea influenţelor sociale, de comportament, culturale, fiziologice, metabolice şi genetice. Obezitatea are efecte profund negative asupra stării de sănătate a populaţiei şi induce comorbidităţi asociate ca HTA, hiperlipidemie, hiperinsulinemie/ rezistenţă la insulină. O multitudine de dovezi susţin că obezitatea produce hipertensiune arterială, boală cardiovasculară, diabet zaharat de tip 2, cancer şi boală renală cronică, iar asocierea obezităţii cu hipertensiunea arterială şi alţi factori de risc cardiovascular creşte semnificativ riscul de evenimente cardiovasculare.
Cuvinte cheie: *obezitatea, hipertensiune arterială, rezistenţă la insulină, evenimente cardiovasculare.*

Obesity has become a global public health problem, including in less developed countries, due to urbanization and adaptation to sedentary lifestyle. Obesity is currently estimated at over 65% overweight adults and over 36% obese adults (BMI over 30 kg/m^2) and even over 50% for men in underdeveloped countries. The WHO estimates published global obesity data in 2016 and reported 1.9 billion overweight adults, of whom 650,000,000 were obese; In addition, 350,000,000 children aged 5-19 and 24,000,000 children under the age of 5 were reported. The WHO estimates that if the trend



continues, the prevalence of obesity will reach 18% for men and will exceed 21% for women in 2025[1,2,3].

Obesity has major health consequences with the increasing prevalence of hypertension and a host of associated disorders, especially cardiorenal and metabolic disorders. Obesity-related cardiovascular disease has become one of the epidemic pathologies of the 21st century.

Excess weight gain is a major cause of hypertension (65-75% of cases of essential hypertension), obese people develop hypertension more than double than normal weight people, and obesity-related hypertension is one of the common causes of death in the world. The Framingham study estimated that 78% of essential hypertension in men and 65% in women is due to obesity[4,5,6,7]. However, recent clinical studies have shown that excess fat is not a determinant factor in the development of obesity-related cardiovascular disease and that abnormal fat distribution is a more important factor for morbidity. Clinical studies show that visceral obesity plays a major role in the development of hypertension, diabetes, hyperlipidaemia and atherosclerosis. The pathogenic mechanisms of obesity-related hypertension are still extensively studied, and its intimate mechanisms are still poorly understood and pharmacological treatment is unfocused[7,35].

Sympathetic NS activation, BP control via renal mechanisms and especially diuresis and natriuresis participate in the pathogenesis of hypertension; increased renal tubular reabsorption with primary sodium retention in the early stages of obesity with expansion of extracellular fluid volume is a major contributor to hypertension. In obesity there is a significant increase of the plasma renin activity, angiotensinogen, angiotensin II and aldosterone. Leptin and other neuropeptides also contribute to the development of hypertension in obesity.

Sympathetic activation in obesity has an essential role in the pathogenesis of hypertension in obese people. Increased caloric intake has been shown to increase plasma norepinephrine levels both at rest and after orthostatic stimulation. In addition, high-fat and high-carbohydrate food consumption stimulates α-1 and β-adrenergic receptors with increased sympathetic activity and hypertension.

Decreased parasympathetic activity is also blamed, which explains the persistent increase in heart rate in obese people. The best evidence of the association between obesity-related hypertension and the sympathetic NS is that the hypotensive effect with α/β-blockers is significantly higher in obese people compared to non-obese people[8].

The mechanisms of sympathetic NS activation in obesity are related to the dysregulation (reduction) of baroreceptor function, RAAS activation, renal functional and structural changes, insulin resistance, abnormal secretion of adipokines from adipose tissue. In addition, in some cases obesity is associated with **obstructive sleep apnoea** which produces intermittent hypoxia with activation of carotid chemoreceptors and reflex upregulation of the sympathetic NS activity[9,10,11,12].

The increase in sympathetic NS activity is uneven in various organs and mainly affects the kidneys and skeletal muscle, and the consequences of sympathetic activation in obesity are multiple:

- Hypertension: Sympathetic NS activation in the kidneys, heart, and skeletal muscle vascularity is associated with decreased **renal pressure natriuresis**, increased renin secretion, and sodium retention.
- Insulin resistance in obesity is linked to 3 possible mechanisms: sympathetic activation, vasoconstriction with decreased blood flow to the skeletal muscles and decreased **delivery** of glucose to the muscles.
- Thermogenesis and participation of the sympathetic NS in daily energy consumption.
- Renal disease: In obesity **renal pressure natriuresis** is decreased, intrarenal pressure is increased and glomerular filtration is initially increased, with a significant decrease in evolution. These renal pathophysiological disorders may be associated with the loss of nephrons and the onset of progressive renal disease progressing to renal failure. Thus, obesity contributes to the development and progression of renal disease, regardless of the presence of type II diabetes.

RAAS activation in obesity

The importance of RAAS in obesity-related hypertension is especially recognized in people with visceral obesity who frequently have increased plasma activity of renin, angiotensinogen, ACE, ANG II and aldosterone.

Renin secretion and ANG II formation are increased in obesity, although under normal conditions they are suppressed in case of salt retention, volume expansion and hypertension. The mechanisms that activate RAAS in obesity are multiple, renin secretion finally being stimulated by juxtaglomerular cells with compensatory increase of BP and of glomerular filtration rate[13,14,15,16,17,18,19,20]:

- the interaction between SNS and RAAS with renin production;
- further increase in SNS activity and renin secretion due to compression of the kidneys by excessive visceral fat;
- stimulation of renin secretion by decreasing tubular blood flow and Na supply;
- participation of local RAAS in adipose tissue: adipocytes produce significant secretion of angiotensinogen and ANG II and secrete factors that stimulate aldosterone secretion independent of ANG II.

In addition, activation of mineralocorticoid receptors (MR) via glucocorticoid hormones has been demonstrated due to decreased activity of 11β-SB type 2 (an enzyme that converts active cortisol to cortisone with low MR binding capacity).

RAAS activation increases the production of ANG II which is a potent vasoconstrictor agent and stimulates aldosterone secretion in the adrenal cortex; ANG II and aldosterone increase tubular Na reabsorption and water retention with intravascular volume expansion and hypertension. Thus, the

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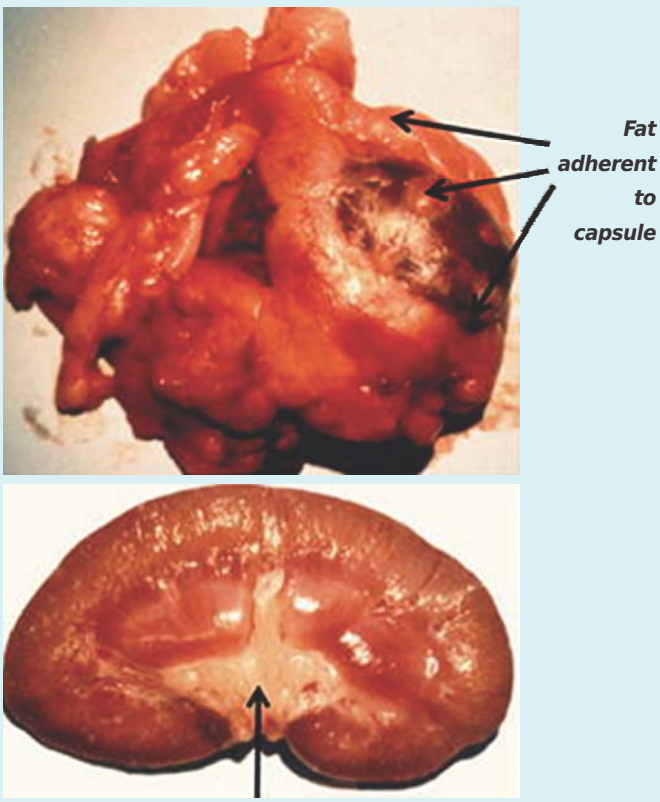
A. Obese Dog Kidney



Fat in renal sinus

B. Obese Mouse Kidney



Fat does not adhere to capsule

Figure 1. *A. Kidneys from an obese dog. The fat adheres tightly to the renal capsule, penetrates the renal capsule, and invades the renal sinuses*
B. Kidneys from a severely obese mouse. The kidney is surrounded by fat but the fat does not adhere to the kidneys[58]

activation of RAAS in obesity induces hypertension and contributes to glomerular injury with the loss of nephrons by increasing BP and its intrarenal effects. Knowledge of these mechanisms explains the major benefit of blockade with ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, with a significant decrease in BP in obese patients.

Renal functional and structural changes initiate and maintain obesity-associated hypertension, and progressive decline in renal function is associated with treatment-resistant hypertension. In such cases with obesity accompanied by hypertension and metabolic abnormalities, RAS and Na retention are additionally activated[21, 22, 23, 24]. Increased renal sodium reabsorption plays a major role in increasing BP in obesity through **renal-pressure natriuresis** dysregulation (obesity requires a higher than normal BP to maintain a sodium balance). Increased renal Na absorption with **renal-pressure natriuresis** dysregulation, volume expansion and hypertension are correlated with:

- mechanical compression of the kidneys caused by retroperitoneal adiposity
- accumulation of peri-renal fat that induces inflammation and expansion of the medullary extracellular matrix with compression of the renal medulla.
- activation of RAAS and mineralocorticoid receptors
- upregulation of renal sympathetic NS activity stimulates the reabsorption of Na directly or indirectly by activation of RAAS.
- relative deficiency of natriuretic peptides has been suggested to contribute to the reduction of excretion of salt and water in hypertension in obese people[25,26,27].

Systemic and renal hemodynamic changes are involved over time in the evolution of hypertension in obesity. Early glomerular hyperfiltration in obesity is gradually being replaced by decreased glomerular filtration due to nephron injury and loss. Expansion of extracellular fluid volume and increased blood flow to many tissues increases venous return and cardiac output, but reserve and exertion blood flow are reduced. Endothelial dysfunction, vascular thickening, additional increase of BP and the process of atherosclerosis in visceral obesity worsen the evolution of hypertension[28,29,30,31,32,33,34].

Renal structural changes and progressive loss of nephrons are related to the accumulation of visceral adipose tissue with physical compression of the kidneys, nephron stress due to increased Na retention and increased blood pressure, SNS response to hypoxia in obese patients with sleep apnoea.

Chronic kidney disease amplifies the effects of obesity on hypertension and makes it more difficult to control. Progressive glomerular sclerosis and progressive loss of nephrons are associated with decreased glomerular filtration rate, progressive decline in renal function, and treatment-resistant hypertension. The consequences of obesity on chronic kidney disease are obvious in the case of the association of obesity with type II diabetes and hypertension, which represents >70% of end-stage renal disease. In addition to hypertension and diabetes, other mechanisms by which obesity causes renal injury have been proposed: inflammation, oxidative stress, mitochondrial dysfunction, dyslipidaemia, and lipotoxicity caused by fatty infiltration of the kidneys[35,36].

Hormonal mechanisms

The role of insulin in hypertension in obesity

Obesity is characterized by decreased glucose tolerance, increased circulating insulin levels



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and decreased sensitivity to the metabolic effects of insulin, i.e. insulin resistance. Insulin resistance and hyperinsulinemia contribute to the pathogenesis of hypertension via multiple mechanisms[37,38,39,40]:

- Renal tubular retention of Na via the direct action of insulin in the renal tubules.
- Direct sympathetic-excitatory effect on the central NS (stimulates neurons in the hypothalamic paraventricular nucleus with a major role in regulating sympathetic output); in addition, insulin resistance produces β-adrenergic stimulation with vasoconstriction and decreased muscle blood flow. Sympathetic stimulation is also present in acute hyperinsulinemia in both normotensive individuals and those with borderline hypertension.
- Insulin also has vasodilating effects, however these effects are attenuated in chronic hyperinsulinism via β-adrenergic mechanism due to vascular trophic changes and altered vascular function with endothelial dysfunction.

Leptin

In obesity, an increase in leptin and the installation of leptin resistance have been shown. Hyperleptinemia and leptin resistance stimulate sympathetic NS activity centrally and have a depressant effect on the cardiovascular system, and increased Sympa-thetic NS activity induces sympathetically mediated hypertension, increased tubular Na reabsorption, and fluid retention. Leptin resistance is selective on metabolic effects, without influencing the action of stimulating sympathetic tone. In addition to sympathetic stimulation, hyperleptinemia produces cardiovascular effects via direct endothelial toxicity, and the long-term pressor effect is linked to altered endothelial production of nitric oxide (NO) with endothelial dysfunction[41,42,43].

NPY is a neurotransmitter with an orexigenic effect, reduces thermogenesis and causes downregulation of sympathetic neurons. NPY is involved in obesity-related hypertension, via sympathetic activation and its vasoconstrictor effects[44].

Adiponectin, a hormone derived from adipose tissue, helps regulate the energy balance and reduces the atherogenic process. In obesity, adiponectin deficiency is associated with insulin resistance and atherogenesis. Therefore, it is considered a responsible factor in cardiovascular pathology due to obesity[45].

Corticosteroids

Changes in adrenal function are common in obesity. The similarities between Cushing's syndrome and visceral obesity support the hypothesis that the hypothalamic-pituitary-adrenal axis participates in obesity-related

hypertension. Glucocorticoids increase food intake, reduce energy consumption and promote insulin resistance, fat accumulation and hypertension. In obesity, plasma glucocorticoid levels are normal. However, the action of glucocorticoids in adipose tissue is increased by increasing the level of 11β-hydroxysteroid dehydrogenase-1, an enzyme that generates active cortisol from inactive forms. Furthermore, it has been shown experimentally that in obesity the level of the enzyme 11β-hydroxysteroid dehydrogenase-2, which converts active cortisol to inactive cortisone, is greatly reduced in the kidneys and could be an additional mechanism by which cortisol contributes to mineralocorticoid receptor (MR) activation. Thus, the effects of obesity glucocorticoids are correlated with increased production of active cortisol and increased affinity of cortisol to bind to MR receptors. All of these mechanisms promote functional hypercortisolism and salt-sensitive hypertension in obesity[46,47].

Aldosterone

The interaction of aldosterone with adipose tissue has been shown by many studies. Obesity is often associated with excess aldosterone, and increased serum aldosterone is associated with arterial hypertension. Components of RAAS are present in adipose tissue and induce unfavourable manifestations, especially: insulin resistance, aldosterone secretion, hypertension, and after successful weight loss diets there is a decrease in plasma levels of RAAS components. All these data support the interrelationship between excess aldosterone and adipose tissue, suggesting that obesity is associated with increased aldosterone production, which in turn promotes metabolic syndrome.

The mechanisms of excessive aldosterone secretion in obesity are partially elucidated. Both the classical pathway and alternative mechanisms of mineralocorticoid receptor (MR) stimulation have been studied, including the direct influence of adipocytes on aldosterone synthesis or genetic predisposition.

Under physiological conditions, the main stimulus of aldosterone secretion is RAS and to a lesser extent ACTH and K levels. In obesity, additional mechanisms have been demonstrated to stimulate aldosterone secretion[48,49,50]:

- Hyperinsulinemia in obesity directly stimulates aldosterone secretion.
- Oxidation of endogenous fatty acids released from visceral fat deposits.
- Adipocyte-derived aldosterone releasing factors - ARFs. ARF secretion is mediated by dietary excess salt and in turn ARFs directly stimulate aldosterone secretion or indirectly via sensitizing adrenal cells to ANG-II.

In addition, in obesity, intense activation of mineralocorticoid receptors (MR) is demonstrated, either via glucocorticoid hormones or via cytokines in adipocytes that are being studied for the effect of alternative steroid receptor activators, including MR. Of these, the Rac1 protein, which activates the MR receptor signal both in the presence of aldosterone and independently of aldosterone, has been extensively studied. Rac1 is activated by excess salt, adipocyte-derived factors, ANG-II, hyperglycaemia.

However, the molecular basis of the relationship between increased adiposity and hyperaldosteronism remains unclear, and most obese patients do not have excessive aldosterone secretion. In these cases, in the presence of dietary excess salt, the alternative mechanism of activation of MR



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receptors via the action of adipocyte-derived factors (ARF, Rac-1) with aldosterone-like effects has been demonstrated: Salt-sensitive hypertension, heart failure, renal disease.

Excess salt is necessary for the onset of adverse effects of aldosterone in target tissues, promotes decreased insulin sensitivity and decreased glucose utilization, pro-inflammatory and pro-thrombotic effects, resistant hypertension, and finally metabolic syndrome; cardiac fibrosis occurs only in the presence of excess salt and is not evident during the low-sodium diet, and excess salt worsens proteinuria. Thus, excess aldosterone and dietary excess salt synergistically induce MR receptor activation, which in turn mediates renal injury and cardiac dysfunction (51, 52). In contrast, weight loss reduces plasma aldosterone and improves insulin sensitivity in both normotensive and hypertensive patients, and MR blockers reduce the expression of pro-inflammatory and pro-thrombotic factors in adipose tissue and reduce the metabolic and hemodynamic effects of aldosterone.

The conclusions of these observations concern the strategies needed to effectively reduce the incidence of hypertension:

- reduction of salt consumption in the current industrialized society;
- wider use of aldosterone receptor blockers for the treatment of hypertension.

Therapeutic solutions for hypertension in obesity

Obesity-related hypertension is generally a treatment-resistant form of hypertension for which ACEI and ARB are recommended as first-line antihypertensive therapy, given the role of RAAS in the pathogenesis of obesity-related hypertension. These drugs have the advantage of improving insulin sensitivity and have a nephroprotective effect in patients with diabetes. Aldosterone blockers are also recommended, based on studies of aldosterone involvement in hypertension in obesity. B-blockers are indicated due to sympathetic NS activation in this form of hypertension, but have the disadvantage that they promote weight gain and insulin resistance. Calcium channel blockers are recommended as second-line agents in combination with ACEI / ARD. The indication for diuretic treatment is useful in fighting volume overload, but has adverse metabolic effects that include dyslipidaemia and insulin resistance.

Simultaneously with antihypertensive treatment, the first target of treatment is weight loss as this reverses the pathophysiological mechanisms that support hypertension. The effect of weight loss on BP appears to be linear with a decrease in BP, around 1 mmHg per kg of weight lost. It is initially recommended to reduce weight by

non-pharmacological methods. All current guidelines recommend lifestyle change, reducing the intake of salt and saturated fats, physical activity, psychological support to reduce body weight[53,54].

For patients who do not obtain decrease in body weight and BP, pharmacological therapy is recommended. However, only a small number of patients are able to complete this program.

Surgical solutions are recommended for patients with resistant obesity or morbid obesity (BMI ≥40 kg/m^2) associated with hypertension or other comorbidities. Metabolic surgery (known as "bariatric") has become an unanimously recognized strategy for controlling BP in obese hypertensive patients, with an impressive number of procedures performed globally. Multiple international studies have shown that patients who have received bariatric surgery have experienced a significant decrease in body weight, decreased BP, reduced long-term mortality, and a decreased incidence of diabetes, hypertriglyceridemia, and hyperuricemia were obtained. Numerous studies suggest that metabolic surgery also has beneficial effects in patients with hypertension and cardiovascular disease. Thus, metabolic surgery has emerged as the most successful strategy for achieving substantial and lasting weight loss as shown by numerous randomized trials[55,56,57,58,59,60,61,62].

Conclusions

Obesity is a chronic medical condition that combines treatment-resistant hypertension and requires long-term treatment, and the association of obesity with hypertension and / or diabetes is an indication for more aggressive therapy. Early diagnosis of obesity, hypertension and other conditions, along with lifestyle changes can lead to early improvement in the health of the population. Specific guidelines for the treatment of obesity-associated hypertension include hypotensive treatment, but also weight loss via lifestyle changes or bariatric surgery. Metabolic surgery is currently the most effective treatment for prolonged weight loss and has been shown to be effective in patients with hypertension and cardiovascular disease. However, many future studies are needed to deepen the mechanisms of hypertension related to obesity and to develop more effective therapeutic strategies with minimal side effects.

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