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Pathophysiological Mechanisms of the Development of Arterial Hypertension in Obesity

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Annotation: In most countries of the world, arterial hypertension (AH) occupies a leading position in the structure of modifiable risk factors for cardiovascular diseases and their complications. One of the main reasons for this trend is the increasing prevalence of obesity, which is becoming an important risk factor for high blood pressure (BP). The results of numerous epidemiological studies have revealed the relationship between obesity, verified by body mass index (BMI), and blood pressure levels, as well as the prognostic role of BMI in relation to the development of hypertension. However, at present there is no consensus on the obesity criterion that most accurately predicts the risk of developing hypertension and associated complications. Data from prospective observational studies have confirmed the greater prognostic significance in this regard of indirect and direct assessment of abdominal and ectopic visceral adipose tissue. These facts formed the basis for numerous studies aimed at revealing the pathophysiological mechanisms of the formation of hypertension in patients with overweight and obesity, the review of which is devoted to this article.

Keywords: arterial hypertension, obesity, visceral adipose tissue.

Introduction.

In most countries of the world, arterial hypertension (AH) today occupies a leading position in the structure of modifiable risk factors for cardiovascular diseases and their complications [1], and its prevalence continues to increase steadily, currently reaching 45% among the adult population [2]. The Russian Federation, as shown by the results of the ESSE-RF epidemiological study conducted in 2012–2013, is also distinguished by a high prevalence (up to 50.2% among people aged 25 to 65 years) and an unsatisfactory level of control of hypertension (about 22.7% among all hypertensive patients). patients) [3].

Despite the progress achieved in the correction of individual cardiovascular risk factors, the number of people with hypertension predicted by 2025 will reach 1.5 billion people, which will undoubtedly lead to an increase in hypertension-related disability and death [1,2]. One of the main reasons for this trend is the increasing prevalence of obesity [4], which is becoming one of the leading risk factors for increased blood pressure (BP) [1]. In our country, according to the above-mentioned ESSERF study, body mass index (BMI) ≥ 30 kg/m2 occurs in a total of 26.9% of men and 30.8% of women, and an analysis of the prevalence of obesity over the past decade indicates a steady increase This indicator is predominantly among males [5].

The results of a number of epidemiological studies have revealed the relationship between obesity verified by BMI and blood pressure levels, as well as the prognostic role of BMI in relation to the development of hypertension [6]. Moreover, the association of obesity and hypertension is characterized by the absence of significant gender differences in the relative risk indicator (2.71 for men and 2.52 for women) [5]. According to Mendelian studies, it has been shown that a genetically determined increase in BMI by 1–2 units is accompanied by an increase in systolic and diastolic blood pressure levels by 0.7–0.9 and 0.5 mm Hg. Art. respectively [7, 8]. In general, 65–78% of people with hypertension have a BMI characteristic of overweight or obesity [9].

In addition, patients with hypertension and obesity are characterized by higher levels of cardiovascular morbidity and mortality [10], as well as treatment-resistant hypertension [11], which made it possible to classify obesity as a factor determining cardiovascular risk in hypertension [2]. Currently, in the

context of the pandemic of the new coronavirus infection COVID-19, this relationship becomes even more relevant in relation to predicting the severity of the infectious disease and creating correction algorithms to prevent the development of serious complications [12, 13].

However, currently there is no consensus on the obesity criterion that most accurately predicts the risk of developing hypertension and associated complications [14]. If in some populations the maximum prognostic value was characterized by BMI [15,16], then in others it was indirect indicators of visceral obesity [17,18]. Moreover, separate prospective observational studies that directly quantified abdominal visceral adipose tissue (AVAT) demonstrated an independent prognostic role for visceral adiposity [22]. hus, the volume of abdominal VAT, determined by magnetic resonance imaging, in the Dallas Heart Study was a more significant predictor of the development of hypertension compared to BMI and indirect markers of visceral obesity [19]. C. Sullivan et al (2015) identified a relationship between an increase in abdominal visceral adipose tissue, assessed over time using multislice computed tomography, and the development of hypertension [20]. The prognostic role of sonographic indicators of quantitative assessment of abdominal VAT in relation to increased blood pressure has also been confirmed in a number of studies [21, 22].

Finally, extremely interesting from the point of view of studying the pathophysiological basis of the association of obesity and hypertension are the results of studies assessing the prognostic role of ectopic BAT indicators [19, 22, 23]. In particular, M. Foster et al (2011) showed that patients with excessive deposition of visceral fat around the kidneys were characterized by a more than twofold increase in the risk of developing hypertension, including after taking into account BMI and the amount of abdominal visceral fat [23]. In the Dallas Heart Study, the maximum predictive value was the severity of retroperitoneal VAT [19]. There is evidence that epicardial fat tissue assessment, particularly echocardiographic epicardial fat thickness, has a high prognostic value in this context [22].

These facts formed the basis for numerous studies aimed at revealing the pathophysiological mechanisms of the formation of hypertension in patients with overweight and obesity, the review of which is devoted to this article.

The role of renal mechanisms in the formation of arterial hypertension in obesity

One of the main mechanisms of increased blood pressure in overweight and obese individuals is a change in natriuresis in the renal tubules, which is a consequence of both hyperactivation of the renal SNS, RAAS and mineralocorticoid receptors in an aldosterone-independent manner, and compression of the renal tissue by an excessive amount of visceral retroperitoneal adipose tissue and adipose tissue of the renal sinus [6, 30].

An increase in sodium reabsorption through the tubuloglomerular feedback mechanism leads to an increase in the secretion of renin by juxtaglomerular cells, a narrowing of the efferent and expansion of the afferent arteriole, an increase in intraglomerular pressure and the development of high grade albuminuria, which is the pathophysiological basis for the subsequent formation of glomerulosclerosis and a decrease in glomerular filtration rate [6,29] .

Expansion of renal BAT can extend into the renal medullary extracellular matrix, which is accompanied by the development of inflammation and remodeling of renal tissue, a decrease in blood flow in the renal tubules and an even greater increase in sodium reabsorption [17].

In addition, insulin has a direct effect on sodium reabsorption in the proximal renal tubules through activation of the third type sodium hydrogen exchanger [19].

Endothelial dysfunction and increased arterial stiffness

It should be noted that endothelial dysfunction and increased arterial stiffness are the earliest manifestations of hypertension developing in overweight and obesity [25]. Some studies have shown that obese individuals with higher values of arterial stiffness are characterized by a higher incidence of hypertension [23].

Hyperinsulinemia, through activation of the mitogen-activated protein kinase-mediated signaling pathway, is accompanied by the development of vascular inflammation, endothelial cell hyperplasia, and increased levels of endothelin-1 and adhesion molecules [26]. Selective insulin resistance is also manifested by a decrease in the implementation of vasodilating insulin signals mediated by phosphoinositol 3-kinase [14]. In addition to insulin, hyperleptinemia and selective leptin resistance, increased levels of interleukin-6 and plasminogen activator inhibitor-1, and decreased adiponectin levels are also important in the development of endothelial dysfunction and arterial stiffness [27].

Dysfunction of perivascular BAT plays a special role, leading to the release of pro-inflammatory adipokines directly into the vascular wall, which is accompanied by the development of inflammation and endothelial dysfunction, fibrosis of the extracellular matrix, hyperplasia and changes in the phenotype of smooth muscle cells underlying abnormally high arterial stiffness [18].

Natriuretic peptide system

In the development of hypertension and organ damage in obesity, the relative insufficiency of the natriuretic peptide system as a component of neurohumoral imbalance is also important [18]. Hyperinsulinemia developing in obesity is accompanied by an increase in the expression of type C receptor and neprilysin, which accelerate the clearance of biologically active forms of natriuretic peptides [14,28].

In addition, taking into account the numerous metabolic effects of natriuretic peptides, including stimulation of lipolysis, acceleration of the oxidation of free fatty acids, activation of the process of "browning" or "browning" of white BAT adipocytes, increased secretion of adiponectin, their relative insufficiency may be accompanied by an increase in BAT dysfunction and various metabolic disorders, potentiating the mechanisms of hypertension formation [31].

Other mechanisms of arterial hypertension formation in obesity

A manifestation of the imbalance of adipokines secreted by BAT adipocytes is a decrease in the level of adiponectin, which, along with the presumed selective adiponectin resistance in obese patients, contributes to the formation of hypertension, mainly due to endothelial dysfunction and increased arterial stiffness [25, 27].

The role of immune response dysfunction, manifested in hyperactivation of T cells and impaired polarization, is also discussed in the development of hypertension in patients with overweight and obesity. Type 1 T helper cells enhance proinflammatory reactions and promote the development of oxidative stress, increase tissue infiltration by M1 macrophages, and type 17 T helper cells and CD 8+ cells secrete interleukin-17, which is involved in the development of vascular remodeling. On the contrary, T-regulatory cells are a unique subpopulation of T-cells that suppress pro-inflammatory reactions, secrete anti-inflammatory cytokines and promote an increase in the proportion of M2 macrophages, which increase tissue sensitivity to insulin [26]. The shift in the ratio observed in visceral obesity towards predominant T-helper cells over T-regulatory cells contributes to the development of hypertension and vascular remodeling [28]. Hyperuricemia in visceral obesity also contributes to the formation of hypertension by influencing the expression of type 1 angiotensin II receptors in the vascular wall, the secretion of monocyte chemotactic protein-1, macrophage infiltration and the development of the pro-inflammatory status of BAT.

Hyperuricemia is accompanied by the deposition of collagen deposits in the kidney tissue, the expression of osteopontin, which increases the production of renin by juxtaglomerular cells and reduces the levels of nitric oxide in the macula densa [29].

The association of intestinal microbiota and hypertension in obesity, according to some authors, is based on a decrease in the species diversity of microorganisms and an increase in the Firmicutes/Bacteroides ratio, as well as metabolites of colon bacteria, including trimethylamine, short-chain fatty acids, secondary bile acids and those produced by gram-negative bacteria

lipopolysaccharides, leading to the development of a systemic inflammatory response, insulin resistance and metabolic disorders [32].

Conclusion

Thus, we can conclude that the main role in the development of one or another pathophysiological link in the development of hypertension in patients with overweight and obesity is played by dysfunctional visceral adipose tissue in the abdominal cavity and ectopic depots of visceral fat. and an imbalance of hypersecretion of adipokines against vasoconstrictor and anti-inflammatory mediators, which formed the basis of the obesity-based theory of the pathogenesis of arterial hypertension [22].

This approach allows us to talk about arterial hypertension that develops with visceral obesity, arterial hypertension, which has characteristic etiopathogenetic mechanisms, clinical features of the course, requiring appropriate methods of non-drug correction and the prescription of separate groups of antihypertensive drugs, and is considered one of the components of visceral obesity syndrome [24].

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