**The role of immunological disorders, endothelial dysfunction and hemostatic disorders in the genesis of arterial hypertension in the metabolic syndrome**

**Introduction.** Mortality from diseases of the circulatory system is an acute problem of modern health care. Every minute in the world from this nosology, 33 people die, оver the year - 32 million people. In this regard, the national health project aims to reduce cardiovascular mortality by 23% by 2024. Arterial hypertension continues to be an important risk factor for cardiovascular events and is highly prevalent [8,29].

According to statistics, 62% of the female population and 34% of the male population with hypertension have an excess body mass index, and a third of patients with hypertension are obese. In addition, patients with hypertension and overweight have impaired lipid, carbohydrate and purine metabolism, i.e. suffer from metabolic syndrome (MS) [7].

The pathogenesis of hypertension is currently being considered from the standpoint of multifactoriality. In conditions of metabolic disorders, the pathogenesis of hypertension certainly has certain features. Most authors agree that the development of hypertension in patients with MS is a consequence of immunometabolic processes that trigger the processes of endothelial dysfunction and disrupt coagulation system homeostasis.

An important role in scientific publications is given to the processes of chronic sluggish inflammation during the course and progression of hypertension in MS, and the development of cardiovascular catastrophes. In recent years, new data have been accumulating on the association of inflammatory markers detected in the blood with atherosclerosis and associated cardiovascular diseases. Interest in the cytokine system, the effect of the immune response, the establishment of the role of inflammatory mediators, and indicators of the hemostatic system as predictors of thrombotic complications is constantly growing [24].

**The aim of our study** was to systematize literature data on the study of the characteristics of the genesis of hypertension in patients with metabolic disorders in the light of immunological, endothelial and hemostatic disorders.

The spread of MS in patients with hypertension leads to damage to target organs, the progression of atherosclerosis and the development of cardiovascular complications. The main mechanism of hypertension progression in MS is insulin resistance (IR) and hyperinsulinemia [30]. The genesis of IR in MS can be laid at the genomic level and / or exacerbated by the degree of visceral obesity. It has been proven that the degree of severity of left ventricular hypertrophy (LVH) in metabolic disorders (MD) is higher than in individuals with hypertension without signs of MS [17,18,19]. Non-Dippers predominate among patients with MD, and a higher level of pulse blood pressure (BP) in this category of patients is associated with more pronounced risk factors for cardiovascular events [14]. Against the background of hyperinsulinemia (HI) and IR, proliferation of smooth muscle cells of the vascular wall increases, the endothelium becomes more sensitive to the effects of various biologically active substances due to an increase in the content of calcium and sodium ions in the arterial wall [6].

**The role of non-specific inflammation and immunological disorders in the genesis of hypertension.**

The importance of the study of hypertension in connection with MS is that MD are modifiable predictors of the development of cardiovascular complications. Visceral adipose tissue is the source of the production of biologically active substances such as adipokines, leptin, tumor necrosis factor (TNF-α), pro-inflammatory cytokines (interleukin (IL) -1, IL-4, IL-6, IL-10, IFN-Y), transforming growth factor β (TGF-β)), estrogens, angiotensinogen, etc. It is a known fact that chronic inflammation in MS is supported by both cellular and humoral immunity units against the background of weakened adaptive immunity [11].

According to the results of studies, in patients with hypertension and MS, the amount of leptin in the blood exceeded that level in comparison with the group of hypertension without MD. Leptin in individuals with hypertension leads to even greater stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), accelerating the progression of hypertension. Leptin starts the processes of fibrosis in the kidney tissue and stimulates the synthesis of endothelin-1, leading to endothelial dysfunction in the renal vessels [4]. Leptin also initiates the production of TGF-β by endothelial cells. Increased production of the cytokine TGF-β stimulates the growth of adipose tissue due to the fact that it is an inducer of preadipocytes. Excessive synthesis of TGF-β leads to fibroblast proliferation and vascular remodeling [10].

It is well known that various subtypes of T-lymphocytes are able to synthesize certain cytokines involved in various biological reactions [50]. Th1-subtype of lymphocytes generates the production of TNF-α, IL-2, IFN-Y; The Th2 subtype produces IL-4, IL-5, IL-10, IL-13, inhibits cell-mediated immunity, and stimulates B lymphocytes. The Th17 subtype of lymphocytes produces IL-17, IL-22 and is involved in the development of an autoimmune response [48]. CD8 + T lymphocytes are an additional source of synthesis of TNF-α and IFN-Y. In individuals with essential arterial hypertension, an increase in CD8 + T-lymphocytes and more pronounced renal and vascular remodeling were determined [53]. In addition, it has been proven that T-lymphocytes express on their surface a mineralcorticoid receptor involved in the development and progression of hyperonic disease. This receptor stimulates the production of IFN-Y CD8 + T-lymphocytes, causing damage to target organs. Preparations of the group of mineralcorticoid receptor antagonists inhibit the synthesis of IFN-Y CD8 + T-lymphocytes, slowing down the remodeling processes in hypertension [45,52].

IFN-Y and IL-17 are two powerful vasopressors for hypertension. IFN-Y increases the concentration of angiotensin II in the blood, indirectly affecting the production of angiotensinogen in hepatocytes and renal tubules. In addition, IFN-Y inhibits the production of nitric oxide, an important vasodilator [27,41].

IL-17 is independently expressed by various types of T-lymphocytes. Moreover, there are several subtypes of IL-17 (A, C, D, E, F). IL-17 is able to initiate the synthesis of TNF-α, IL-6, chemokines, metalloproteinases. The experiment proved the mechanism of increasing blood pressure and the development of vascular remodeling due to the activation of these cytokines [44,49].

Thus, cytokines are closely related to each other. An excess of IFN-Y cytokine in blood in patients with MS in combination with hypertension leads to stimulation of the production of macrophages that trigger the production of other pro-inflammatory cytokines (IL-1, IL-6, including TNF-α), and inhibits the production of anti-inflammatory mediators (IL-4, IL-10) [20]. It has been experimentally proven that one of the powerful participants in inflammation in MS is IL-6, which significantly increases the morning rise in blood pressure. It induces the production of C-reactive protein (CRP), apolipoprotein-α, fibrinogen, and complement components, which in turn close the vicious circle in stimulating local and systemic inflammation [24]. An increase in serum IL-6 level correlates with thrombotic complications in patients with MS due to procoagulant activity. A well-known fact is the effect of this cytokine on endothelial dysfunction. In hypertension and MS, the number of receptors for IL-6 also increases proportionally [54]. In this connection, it will be useful to use calcium antagonists in the treatment of hypertension, which can block IL-6 receptors on vascular endothelium [38].

Local overproduction of individual cytokines (IL-4, IL-10) leads to suppression of inflammation. In contrast, chronic activation at the systemic level leads to generalized immune responses [12].

The formation of IL-17, independently expressed by various subtypes of T-lymphocytes, the excess of which increases the stiffness of the vascular wall, completes the chain of immune responses [46]. The severity of the chronic subclinical inflammatory process aggravates the involvement of lymphocytes and monocytes in the immune response. Differences in the subpopulation composition of lymphocytes were revealed in patients with MS in combination with hypertension and in healthy individuals [51].

In patients with MS, an increase in serum CD25 +, CD4 + lymphocytes and CD36 + monocytes was detected. These subpopulations inhibit autoimmune processes in the body, causing suppression of the excess inflammatory process. The identification of a direct correlation between the increase in the body of CD4 + lymphocytes and the components of MS (systolic blood pressure, degree of obesity, impaired carbohydrate, purine and lipid metabolism) confirms immune inflammation in MS [2].

The role of B-lymphocytes in the development and progression of hypertension is also proved. In addition to the synthesis of antigen-specific immunoglobulins, B-lymphocytes are capable of producing a number of cytokines - transforming growth factor (TGF) -β, IFN-Y, TNF-α, IL-10, IL-35 [39,42]. The increased activity of humoral immunity in individuals with MS is manifested by an increased blood content of activated CD19 + CD23 + -B cells [35]. It is also known that the chronic inflammatory process is supported by the synthesis of the pro-inflammatory cytokines of CD14 + T cells by adipose tissue [57].

The experiment showed that B-lymphocytes increase the activation of macrophages and the production of immunoglobulins in individuals with hypertension [36]. According to foreign authors, an increase in the content of class G immunoglobulins in hypertension in combination with MD supports a chronic sluggish inflammatory process in the vascular wall and contributes to the development of atherosclerosis [45].

Visceral adipose tissue becomes the main source of TNF-α, the increase in the level of which in the blood serum indicates cell apoptosis and active lipolysis processes. Free fatty acids replenish the pool of atherogenic cholesterol, accelerating the processes of atherosclerosis in hypertension [25]. Excess TNF-α blocks insulin receptors and leads to the development of IR, the presence of which is only exacerbated in individuals with MD. The role of TNF-α in the development of endothelial dysfunction (ED) is to inhibit the production of nitric oxide and activate the synthesis of endogenous vasoconstrictor - endothelin [47]. In addition, TNF-α stimulates the production of adhesion molecules (GM-CSF, MCP-1, ICAM, VCAM) on the structural unit of the endothelium, resulting in an inflammatory reaction involving lymphocytes, monocytes, neutrophils [5].

Researchers have proven the relationship between the duration of hypertension and the level of CRP in plasma. A high level of CRP in the blood is associated with the development of cardiovascular complications in patients with hypertension and MS. It has been experimentally proven that CRP stimulates the expression of type 1 angiotensin II (AT II) on smooth muscle cells of the vascular wall, leading to remodeling processes [31]. Angiotensin II prolongs the synthesis of proinflammatory cytokines, adhesion molecules by endothelial cells, and increases the production of endothelin-1 [34].

**Endothelial dysfunction in hypertension and MS.**

Chronic non-specific inflammation in MS, supported by the cytokine system, is a trigger mechanism for triggering ED. The classic markers of ED are excess production of endothelin-1 and inhibition of nitric oxide production [16]. Immune damage leads to an imbalance in the production of vasoconstrictor and vasodilating, proliferative and antiproliferative factors by the endothelium. Activated parts of the immune system damage endothelial cells, causing structural and functional changes in the vascular wall, contributing to the progression of hypertension [9,21]. Elevated serum homocysteine ​​(HC) levels in patients with hypertensionand MD, identified as a marker for the early development of ED, are a predictor of thrombotic and ischemic events [13]. Excessive HC is associated with inhibition of nitric oxide synthesis and increased endothelin production. Other markers of endothelial dysfunction are sodium uretic peptide C, which is synthetically compensated for with nitric oxide deficiency, and a high level of lipoprotein (α). Lipoprotein (α), interacting with integrin Mas-1, promotes the attraction of monocytes into the vascular wall, activation of the transcription factor NFkB and the integration of the inflammatory process [1].

The role of the most powerful ED factor and the active component of RAAS, angiotensin II, is still undeniable. Angiotensin II blocks the synthesis of bradykinin and prostaglandins and, conversely, induces the synthesis of vasopressin, contributing to the development of vasoconstriction.

In the diagnosis of ED, there is a determination of the level of copeptin, which is a precursor of vasopressin, but having a more stable nature of secretion into the blood, in contrast to the hormone itself. Copeptin has clinical significance in risk stratification in patients with exacerbation of coronary artery disease, the development of heart failure, and death [28,56].

Under conditions of impaired lipid metabolism, the oxidation of low density lipoproteins (LDL) changes. Oxidized LDL suppresses vasodilating endothelial factors, increase endothelin synthesis, increase proliferation of vascular smooth muscle cells; stimulate the migration of monocytes into the endothelium, trigger the processes of thrombosis due to the induction of tissue factor synthesis by endothelium, and initiate platelet aggregation [15].

Of great interest is the determination in the blood of circulating endothelial cells (CEC) in relation to leukocytes, which are an indirect marker of ED, and a product of endothelial damage. A level exceeding 3 CEC per 300 thousand leukocytes in blood plasma increases the risk of developing atheroscherotic heart disease by 4 times in women under 60 years of age. And in the presence of coronary heart disease, the risk of coronary syndrome increases by 8 times [5].

Direct factors causing ED are actually high blood pressure and smoking. A dose-dependent relationship was established between the number of cigarettes smoked and the progression of ED. Nicotine not only reduces the content of nitric oxide and prostacyclin, but also promotes thrombosis by stimulating the expression of glycoproteins on the platelet membrane. Toxic substances in tobacco smoke directly damage the endothelial wall, which leads to an increase in CEC in blood plasma. The long-term effect of increased blood pressure on the endothelial wall disrupts its homeostasis processes, prerequisites for the development of atherosclerosis processes arise, and increased total peripheral vascular resistance contributes to the progression of hypertension [3].

A factor influencing the prognosis in patients with hypertension and MS is the determination of microalbuminuria (MAU). Chronic kidney disease is known to remain an independent risk factor for cardiovascular complications. Glomerular filtration rate of 30-50 ml / min automatically puts the patient in the group of high cardiovascular risk, less than 30 ml / min - in the group of very high risk. In this connection, MAU, as an early marker of ED in hypertension, has high diagnostic value in the initial stages of kidney damage [33,37,55].

**Changes in the hemostatic system in hypertension and MS.**

Under the conditions of IR and HI, the processes of hypercoagulation and hypofibrinolysis intensify, and the prerequisites for thrombotic complications in patients with hypertension and MS are created [22]. It has been experimentally shown that excessive synthesis of pro-inflammatory cytokines in individuals with MD introduces disturbances in the system of vascular hemostasis. Fibrinolytic changes are detected with increased activity of D-dimer, fibrin, fibrin-monomer complexes against the background of a decrease in plasminogen level and activation and an inhibitor of plasminogen activator type 1 (PAI-1) without gender differences. A positive linear correlation between the content of angiotensin II and PAI-1 was monitored [24]. Changes in plasma composition are associated with changes in indicators such as shortening of activated partial thromboplastin time (APTT), and an increase in the indicator of an external clotting pathway inhibitor (TFPI) in women with MS and hypertension. A reliable association of an increase in fibrinogen level with the degree of visceral obesity in men was determined. Having studied the studies on the effect of MD on the hemostatic system, it can be concluded that the activation of the fibrinolytic and plasma chains occurs the same in both men and women [32].

In women with signs of MS, compensatory stimulation of the anticoagulant hemostasis system is observed [26]. According to literature, an increase in the activity of blood coagulation factors (especially factor VII) in MS is mediated by hyperinsulinemia and IR [40].

Changes in the rheological properties of blood in MS are associated with an increase in the viscosity of blood plasma by 27%, an increased degree of aggregation of red blood cells by 63%, and a decrease in the efficiency of oxygen transport by 20%. Changes in the hemostatic system in individuals with hypertensionand MS are directly related to ED, due to the low production of prostacyclin [23].

**Conclusion.** Thus, the role of the interaction of various systems (immune, endothelial, hemostatic system) in the development, progression of hypertension and the formation of cardiovascular complications is shown. Modification of metabolic disorders, including a decrease in the degree of visceral obesity, can slow down the processes of chronic nonspecific inflammation, the development of ED, the progression of hypertension and the development of associated clinical conditions. Numerous clinical studies have proven the role of ED in the development of complications of hypertension. ED is an important predictor of the development of atherosclerosis and increased platelet aggregation abilities. The study of early markers of ED will help in determining the tactics of managing a patient with MD and hypertension, determining the intensity of treatment aimed at preventing the development of vascular accidents.

There is a lot of evidence linking the pathogenesis of hypertension with insulin resistance, a cascade of immuno-mediated reactions, a system of cytokines. The launch of immunometabolic processes contributes to the progression of hypertension, leads to more pronounced changes in target organs, and the resistant and aggressive course of hypertension. The role of HI and IR, angiotensin II in the activation of the hypercoagulation system, and the violation of the rheological properties of blood is proved.

Systematization of the available literature data on the issue under study can serve as the basis for determining prognostic criteria for the progression of hypertension and the risk of thrombotic complications.