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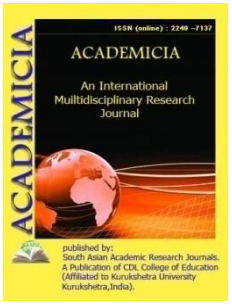

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FEATURES OF THE COURSE OF ARTERIAL HYPERTENSION ASSOCIATED WITH METABOLIC SYNDROME

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ABSTRACT

The article presents a review of the literature on metabolic syndrome, the dynamics of ideas, the relationship between insulin resistance and cardiovascular diseases; arterial hypertension as a component of metabolic syndrome, features of its development and course; features of hemodynamics and damage to target organs in arterial hypertension associated with metabolic syndrome. The second mechanism is the effect of hyperglycemia on the expression of the angiotensinogen gene in the renal tissue under IR conditions, which leads to increased renal hypersympathicotonia. The presence of a link between hypertension, obesity, impaired carbohydrate metabolism and gout was noted at the beginning of the last century by GF Lang [5] and E. Kylin [6], and subsequently by A. L. Myasnikov, D. M. Grotel and M.P. Konchalovsky. Thus, under conditions of chronic GI, active lipolysis occurs in fat stores and an increase in the concentration of free fatty acids (FFA) in the blood [12], an increase in the thickness of the muscular layer of blood vessels and myocardial hypertrophy, stimulation of the SNS, an increase in reabsorption and a decrease in sodium excretion and water [16], weakening of the vasodilating properties of insulin due to a deficiency in the production of nitric oxide [15].

KEYWORDS: *Syndrome, Hyperglycemia, Hypertension*

INTRODUCTION

The urgency of the problem. Cardiovascular disease (CVD) remains the most serious public health problem in many countries around the world. Experts from the World Health Organization (WHO) predict a further increase in CVD, as well as mortality from these diseases, in both developed and developing countries, due to changes in demographic indicators (aging of the population), an increase in noncommunicable diseases (NCDs) and characteristics and lifestyles.

According to the results of the Centers for Disease Control and Prevention, such a high prevalence of CVD, covering all countries and continents, leads to a decrease in the frequency of average life expectancy by 10 years, as well as to long-term disability of the adult population and requires colossal economic costs.

Target. To study the features of the course of arterial hypertension associated with metabolic syndrome on the basis of the results of clinical studies.

RESULTS AND DISCUSSIONS

Metabolic syndrome, dynamics of ideas, connection of insulin resistance with cardiovascular diseases

In the 21st century, cardiovascular diseases (CVD) associated with atheroscle-rosis (arterial hypertension, myocardial infarction, stroke) still occupy the first place among the main causes of death and disability [1]. Morbidity and mortality from ischemic heart disease (IHD), complications of arterial hypertension (AH) are associated with the presence and level of risk factors for their development [2]. Among them, the most significant are AH, dyslipidemia, obesity, diabetes mellitus (DM) and hyperinsulinemia (GI), which tend to combine [3]. The incidence of sudden death and the development of myocardial infarction, according to the PROKAM study, increases with a combination of two or more CVD risk factors [4].

The presence of a link between hypertension, obesity, impaired carbohydrate metabolism and gout was noted at the beginning of the last century by GF Lang [5] and E. Kylin [6], and subsequently by A. L. Myasnikov, D. M. Grotel and M.P. Konchalovsky. In 1956 J. Vaque noted an increased incidence of CVD in patients with abdominal obesity (AO) [23], and E. Gamus [9] in 1966 called the combination of these factors "metabolic trisyndrome". In 1989, N. M. Kaplan called the combination of AO, impaired glucose tolerance (IGT), hypertriglyceridemia, and hypertension a "lethal quart", meaning the extreme atherogenicity of this combination [14].

In 1988 G. Reaven [22] proposed the term “syndrome X” to denote a cluster of metabolic factors accumulating in one person: hypertension, dyslipidemia (an increase in the concentration of triglycerides (TG) in the blood, associated with a decrease in the level of high-density lipoproteins (HDL), IR and SD type II. Later, AO was added to these factors [22]. Since 1988, the MS criteria have undergone significant changes. A number of researchers have supplemented the concept of MS with new characteristics, such as hyperuricemia, microalbuminuria (MAU), left ventricular hypertrophy (LVH), hyperfibrinogenemia, ovarian sclerocystosis, etc. [14, 15].

Over the past decades, MS has come to be called the “epidemic of highly developed countries” due to its high prevalence. In the world, among the population over 30 years of age, its prevalence reaches 15–25% [12], in Russia among patients with hypertension - up to 74%, with IGT and diabetes mellitus - up to 90% [18].

In the classic sense according to the International Diabetes Federationmetabolic syndrome involves a combination of AO, IR, hyperglycemia,dyslipidemias, hypertension, disorders of the hemostasis system and chronic subclinical inflammation [18], which are based on complex neurohumoral and hormonal disorders [11].

IR is understood as a violation of insulin-mediated glucose utilization in organs (skeletal muscles and myocardium, adipose tissue and liver), where pathophysiological changes depend on the

nature of insulin action in a particular case [6]. At the same time, compensatory GI occurs to maintain the concentration of glucose in the blood at a normal level. Subsequently, NTG develops with the formation of MS.Until the end, the reason for the development of IR remains unclear. Even healthy peopledey insulin sensitivity can fluctuate widely, due tochanging 3-4 times [25].

The causes of IR can be a mutation of the codingheon (pre-receptor mechanism), autoimmunization with the production of antibodies tosulin and insulin receptors, a change in the insulin molecule,an increase in the number of insulin receptors, a change in their structure and affinityinsulin response [25], as well as the mechanisms of postreceptor action of insulinon (change in the structure of the glucose transport protein GLUT [15], hormonal and metabolic factors.

It is known that insulin is an anabolic hormone, the main function of which is the utilization of glucose and the synthesis of glycogen. Butits role in the regulation of metabolism goes beyond just the regulation of blood glucose levels. Insulin receptors are found in different tissues:

- ✓ skeletal muscles and myocardium, where glucose is utilized;
- ✓ adipocytes of adipose tissue, where, under the influence of insulin, lipolysis is inhibited;
- ✓ vascular smooth muscle cells, which proliferate with GIvascular endothelium, where insulin affects the synthesis of prostaglandins, nitric oxide, bradykinin (vasodilating effect);
- ✓ the kidneys, where insulin, acting on the renal tubules, enhances the reabsorption of sodium and water;
- ✓ sympathetic nervous system (SNS) - insulin stimulates the SNS, increasing cardiac output and peripheral vasospasm.

Thus, under conditions of chronic GI, active lipolysis occurs in fat stores and an increase in the concentration of free fatty acids (FFA) in the blood [12], an increase in the thickness of the muscular layer of blood vessels and myocardial hypertrophy, stimulation of the SNS, an increase in reabsorption and a decrease in sodium excretion and water [16], weakening of the vasodilating properties of insulin due to a deficiency in the production of nitric oxide [15]. Therefore, the presence of IR is closely associated with the risk of CVD associated with atherosclerosis: hypertension, coronary artery disease, stroke, which has been proven in numerous studies [22, 23].

Arterial hypertension as a component of metabolic syndrome,features of its development and course

Hypertension in MS is closely related to its other components. In 1985 M. Modan et al. in patients with hypertension, a higher level of insulin in the blood was revealed compared to normotonics. This relationship did not depend on the presence of obesity and IGT [19]. Later, E. Ferrannini proved the same with the help of the "clamp" test [8]. Patients with hypertension, on average, utilize 40% less glucose than those with normal blood pressure (BP) [10]. The relationship between AH and GI was independently confirmed by other researchers [15].

According to E. Ferrannini, there are three possible hypotheses that can explain the relationship between IR and AH. It is assumed that IR causes the development of AH, AH is the cause of IR,

and it is also possible that IR and AH are parallel consequences of a common cause [8]. The ARIC study found that GI was associated with hypertension and was its predictor when combined with metabolic disorders [23]. Other experimental studies have shown that a constant increase in blood pressure is accompanied by a decrease in peripheral blood flow and endothelial dysfunction, which can lead to a decrease in the sensitivity of skeletal muscles to insulin and the development of IR [12].

The assumption that IR is the result of hypertension seems unlikely [14]. In particular, it was shown that symptomatic hypertension is not accompanied by IR, and correction of blood pressure does not always lead to a decrease in IR [10].

It was also noted that AH and IR were most consistently observed in individuals with AO [15]. Back in 1956, J. Vaque drew attention to the relationship between excess body weight and the nature of fat distribution with the possibility of developing hypertension, diabetes mellitus, atherosclerosis and gout [23]. The relationship between hypertension and obesity has been confirmed in numerous studies. According to the Framingham study, newly diagnosed hypertension in 70% of cases is combinedmelts with obesity or overweight [16].

The Gothenburg epidemiological study not only confirmed the role of obesity as a risk factor for CVD, but also demonstrated their dependence on the typeobesity [17]. According to V.A.Almazov, in the group of patients with AH, AH and type II diabetes were more common than in the group with gluteofemoral obesity[18, 19]. The presence of abdominal obesity plays an important role in the association of hypertension and IR [15].

Thus, to date, there is no common understanding of both the etiopathogenesis of AH associated with MS, and the problem of the cause-and-effect relationship between AH and IR [14]. But there is no doubt that the pathogenesis of hypertension in MS is based on IR and thecompensatory GI in combination with concomitant metabolic disorders [2]. Chronic GI affects blood pressure through the following mechanisms:

stimulates the activity of the sympathetic-adrenal system (SAS), which leads to an increase in vascular tone, including renal hypersympathicotonia [19,20];

- stimulates the activity of the renin-angiotensin-aldosterone system (RAAS) [7]. Studies show that when AH is combined with IR, the activity of angiotensin-converting enzyme (ACE) is significantly higher,than in patients with hypertension without IR [10];

- blocks transmembrane ion exchange mechanisms (Na-K-ATPases andCa-Mg-ATPase), increasing the content of intracellular sodium and calcium anddecreasing the potassium content, which leads to increased sensitivityvascular wall to pressor effects [14, 17, 18];

increases the reabsorption of sodium in the proximal and distal tubules of the nephron, contributing to fluid retention, the development of hypervolemia and an increase in sodium and calcium in the walls of blood vessels [3,9];

- stimulates the proliferation of smooth muscle cells of the vascular wall due to direct and indirect mitogenic action, leading to narrowing of arterioles and an increase in systemic vascular resistance [7, 18].

Two more mechanisms are considered that are of great importance in the formation of hypertension in MS. The first is associated with leptin, a hormone synthesized in adipocytes of adipose tissue, which enhances the activity of SNS [20].

The second mechanism is the effect of hyperglycemia on the expression of the angiotensinogen gene in the renal tissue under IR conditions, which leads to increased renal hypersympathicotonia. Normally, insulin suppresses the stimulating effect of hyperglycemia on the expression of the angiotensinogen gene in the cells of the proximal renal tubules and prevents an increase in its secretion. With IR, insulin suppression of glucose-stimulated expression of the angiotensinogen gene in the cells of the proximal renal tubules does not occur, the gene expression is disinhibited, and the secretion of angiotensinogen increases [21].

Apparently, it is this mechanism that underlies the increase in the production of angiotensin II (AT II) in the glomerular and tubular cells of the renal tissue under the influence of hyperglycemia. The effect of AT II on AT1 receptors leads to an increase in renal hypersympathicotonia [12].

Under the influence of the above mechanisms, a constant increase in blood pressure is accompanied by a decrease in peripheral blood flow and endothelial dysfunction according to the principle of feedback, which enhances the phenomenon of IR. All this is more pronounced in hypertension associated with MS. First of all, the so-called insulin-requiring tissues - muscle (including myocardium), blood vessels - suffer.

Vessels are one of the main target organs that are affected in various diseases. The properties of arteries are impaired in hypertension, MS, diabetes mellitus, atherosclerosis, etc. Vascular lesion in hypertension is characterized by increased rigidity and stiffness, decreased elasticity of the wall of large arteries and, as a consequence, increased systolic and PAP, which accelerates arterial damage. An increase in the rigidity of the vascular wall occurs as a result of the rapid proliferation of vascular smooth muscle cells, elastic fibers and the accumulation of the extracellular matrix. This leads to an increase in the thickness of the intima-media layer and a decrease in the lumen of the vessel, to vascular remodeling [24].

A complex of neurohumoral factors (RAAS, SNS, vascular endothelium) is also involved in the remodeling process.

The process of remodeling involves the microvasculature, which leads to an increase in OPSS [13]. In MS, the process of vascular wall remodeling, in addition to hemodynamic and neurohumoral factors, is exacerbated by GI and IR [17, 18].

Based on the foregoing, it can be concluded that in MS due to a combination of disorders of various types of metabolism, the rigidity of the arteries increases and cardiovascular risks increase.

An increase in arterial stiffness, leading to an increase in SBP, PAP and OPSS, increases the load on the left ventricle. Hemodynamic load in combination with the specific effect of GI and IR on cardiomyocytes leads to LVH, which is one of the important manifestations of hypertension and isthe result of adaptation of the heart to an increase in afterload [12].

Having a compensatory character at the beginning of the disease, later on it acquires a pathological significance and is an independent risk factor for coronary artery disease, sudden

death and heart failure [13]. In particular, thickeningleft ventricular wall by 1 mm increases the risk of fatal complications7 times [21].

The issue of the association of hypertension and various components of MS with LVH has been insufficiently studied, and the available information on the role of insulin in the development of LVH is contradictory [15,20]. According to some authors, AH and obesity as components of MS are the leading determinants of LVH [14], which is apparently due to GI [21]. In other studies, obesity is considered the dominant factor regardless of fat distribution [17]. A predisposition to hypertension, obesity and LVH is also not excluded [24].

A number of studies have also shown that AH in MS is accompanied by more pronounced LVH than AH proceeding against the background of normal insulin metabolism [10, 14, 18], and LM Resnick even isolates LVH as a separate component of "generalized cardiovascular metabolic disease" [19]. The kidneys are one of the most vulnerable organs, both primary and secondary. AH is one of the main causes of end-stage chronic renal failure in 10–30% of patients [20].

Kidney damage in hypertension is manifold. An increase in systemic blood pressure is accompanied by an increase in pressure in the capillaries of the glomeruli, which leads to increased filtration of protein through the basement membrane, damage to the endothelium, and the release of cytokines and other mediators. As a result, this leads to the replacement of normal renal tissue with fibrous

In MS, kidney involvement, as well as damage to other target organs, is primarily associated with the action of metabolic disorders - IR, AO, hyperlipidemia, and hypertension. The initial changes in the kidneys are asymptomatic. The earliest marker of kidney damage (at the stage of functional disorders) and an unfavorable prognostic sign is MAU (urinary albumin excretion from 20-30 to 300 mg/day). It is a factor reflecting endothelial dysfunction and damage to the vascular system in general [27].

Some researchers consider the occurrence of MAU as an event of critical importance, indicating generalized damage to the vascular system and the progression of renal failure [22, 23].

MAU is more often observed in patients with a predominant increase in DBP, lack of adequate decrease in blood pressure at night, elevated PAP and BMI [12, 20, 26], LVH and biochemical signs of MS.

GI and IR are important metabolic factors of kidney damage, which are realized through specific mechanisms [22]:

- non-enzymatic glycation of renal membrane proteins, which disrupts their structure and function;

- direct glucotoxic effect through the activation of protein kinase C, which regulates vascular permeability, contractility, cell proliferation processes and the activity of tissue growth factors;

- activation of the formation of free radicals that have a cytotoxic effect;

violation of the synthesis of heparan sulfate, a decrease in the content of which leads to the loss of the basement membrane of the most important function

- the charge of selectivity, which is accompanied by the appearance of MAU, and further with the progression of the process and proteinuria. Intracellular hyperglycemia plays a certain role [23]. Another powerful nephrotoxic factor is hyperlipidemia, which promotes the development of nephrosclerosis similar to the mechanism of vascular atherosclerosis formation (structural similarity of mesangial and smooth muscle cells of arteries, rich receptor apparatus of LDL, oxidized LDL in both cases) [22].

Overweight, namely AO, also predisposes to the development of MAU. In the population study MONICA, it was found that AO is independent, including from other components of MS, as a predictor of MAU [23].

At the same time, MAU has a local toxic effect, leading to the development of aseptic inflammation. In the course of its development, the local synthesis of AT II is stimulated, the excess of which leads to an even greater spasm of the carrying artery, an even greater ischemia of the renal filter and, as a consequence, to an even greater loss of protein through the renal filter[28].

Thus, the multiple but common mechanisms underlying the development of MS lead to a more severe course of hypertension and damage to target organs. Given the close relationship between hypertension and target organ damage in MS, early diagnosis of such a combination will make it possible to identify patients with the most serious prognosis in the general population for a differentiated approach to treatment.

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