SECTION 8. THERAPY

DOI: 10.46299/ISG.2023.MONO.MED.2.8.1

8.1 Modern view of the course of arterial hypertension in combination with type II diabetes and osteoarthritis

Today, arterial hypertension (AH) is one of the most important problems of the world population. Uncontrolled high blood pressure (BP) can lead to heart attack, stroke, kidney or heart failure, vision impairment, and other life-threatening complications. Therefore, blood pressure control is the most effective factor in preventing the occurrence of these complications. However, according to the results of many studies, blood pressure control in patients with hypertension in all countries of the world with different levels of economic and social development is insufficient [346].

In the message of the World Health Organization, obesity in the modern world is compared to an epidemic [347, 350]. A steady increase in the prevalence of obesity is observed in almost all countries of the world. In recent years, it has increased by an average of 60% in the world. Obesity leads to the development of insulin resistance (IR) of peripheral tissues, which plays a key role in the development of diabetes [350, 351].

Hundreds of millions of people suffer from diabetes in the world, more than a million in Ukraine [346, 349, 350]. The main cause of disability and mortality of patients with diabetes mellitus is cardiovascular disease, in the development of which hypertension plays a leading role, which, according to official statistics, is observed in 80% of patients with diabetes mellitus type II [351-353].

A similar situation is characteristic of osteoarthritis (OA). OA of the knee joints attracts special attention due to its high prevalence, progressive course and early disability, persistence of pain syndrome, impairment of motor activity and quality of life [346, 349, 352]. There is no doubt about the influence of obesity on the development and progression of OA.

OA is often pathogenetically associated with components of the metabolic syndrome (MS) (insulin resistance, type II diabetes, obesity, hyperlipidemia, arterial hypertension, and coronary heart disease (CHD). OA on the background of MS is an important medical and social problem even in economically developed countries [368]. Moreover, the presence of MS accelerates the rate of progression of joint pathology [352], in connection with which the study of the clinical-pathogenetic features of the combination of OA with MS is quite relevant [361, 365, 375].

The purpose of the study is to analyze the data of scientific works on the peculiarities of the course of arterial hypertension in combination with osteoarthritis, obesity and type II diabetes, as well as on their "early" biomarkers.

The materials were domestic and foreign literary sources of the last 10 years, published in specialized publications of Ukraine, Scopus and Web of Science databases, containing information about the peculiarities of the course of arterial hypertension in combination with osteoarthritis, obesity and type II diabetes, as well as about their "early" biomarkers. Analytical and bibliosemantic methods were used to analyze the results.

A number of population studies have shown a relationship between obesity, especially abdominal obesity, and the frequency of hypertension. According to them, blood pressure indicators increased in proportion to excess body weight [350, 351]. Vascular endothelium dysfunction also played a certain role in the genesis and development of hypertension. However, the influence of hypertension and its combination with obesity on the clinical manifestations and course of OA has not been sufficiently studied.

The basis of the development of hypertension during obesity is insulin resistance (IR). Many studies have found a positive correlation between the level of blood pressure and the concentration of insulin in the blood. Against the background of hyperinsulinemia, the reverse transport of sodium and water in the kidneys increases, which leads to hypervolemia. It is also believed that IR/hyperinsulinemia contributes to the development of hypertension due to abnormalities in the insulin signaling pathway and is associated with cardiovascular and metabolic disorders [374]. This

includes increasing the activity of the sympathetic and renin-angiotensin systems (RAS), reduces the synthesis of atrial sodium-uretic peptide, causes sodium retention with subsequent volume expansion, promotes the progression of kidney damage, cardiac hyperactivity, left ventricular hypertrophy, dyslipidemia, chronic hyperglycemia, and increases oxidative stress [357,358].

Abdominal obesity, which is a frequent companion of hypertensive patients with type II diabetes mellitus, contributes to the development of IR, hyperlipidemia, and hypertension. Adipose tissue synthesizes numerous biologically active substances, including leptin, tumor necrosis factor-α (TNF-α), IL-6, and IL-8. Recently, substances synthesized by adipocytes include angiotensin-II (A-II), plasminogen activator inhibitor-1 (IAP-1), transforming growth factor-β1 (TGF-β1), adiponectin, etc. It is believed that periarterial and periarteriolar adipose tissue can have the same properties as visceral fat, and therefore play a role in the development of vascular complications and IR. Most of the conducted population studies indicate a direct correlation between IR and obesity, however, IR may not be accompanied by excess body weight (BW). Thus, no association was found between obesity and IR in lipodystrophy, when there is no abdominal and visceral adipose tissue.

According to data from various studies, it can be assumed that the interaction between central obesity and hypertension may lead to a decrease in adiponectin, which more than likely increases the concentration of TNF-a. These altered adipokine patterns (low circulating adiponectin and high TNF-α) indicate that complications from obesity may progress more rapidly when hypertension is present and vice versa. However, the results of this study are specific to adult women, a similar study has not yet been conducted for men. Additional studies that would clarify the mechanisms of the origin of adipose tissue, including adipokines and cytokines, will help to understand the peculiarities of the occurrence, development and combination of the mentioned diseases and prevent severe consequences.

In addition, literature sources indicate that the concentration of leptin is increased also in the case of metabolic syndrome, probably due to resistance to leptin. At the same time, concentrations of anti-inflammatory cytokines (IL-10), ghrelin,

adiponectin, and antioxidant factors were, on the contrary, reduced, and were correlated with specific disorders within the cluster.

Therefore, the above-mentioned biomarkers are significantly correlated with the metabolic syndrome and can (provide minimally invasive means) be clinical and laboratory indicators for the early detection of the development of hypertension in combination with type II diabetes and OA against the background of obesity. Further studies are encouraged to determine the effectiveness of these biomarkers for early diagnosis and specific treatment of the mentioned diseases.

On the other hand, studies indicate the involvement of oxidative stress as an imbalance between pro-oxidant and antioxidant systems in the pathogenesis and progression of OA [362]. Intensification of lipid peroxidation (POL) leads to the release of pro-inflammatory cytokines, disruption of microcirculation, collagen structure and contributes to the progression of the degenerative process in joint tissues. Peroxidation products cause damage to the endothelium of vessels, vasospasm, and an increase in total peripheral resistance, which can cause an increase in blood pressure in patients with OA against the background of a decrease in the effect of hypotensive drugs. At the same time, the presence of hyperglycemia in patients with OA leads to the activation of the polyol pathway of glucose metabolism and non-enzymatic glucosylation of proteins, which causes damage to muscles and periaticular tissues. Hyperglycemia affects the course of OA both at the local and systemic levels: in particular, the local effects of oxidative stress and glycosylation of end products enhance cartilage damage, and the accumulation of toxic products of glycolysis can cause the progression of OA [365]. Dahaghin S. et al. [373] found an association of diabetes mellitus (DM) with hand OA in people aged 55 to 62 years, with a higher frequency of hand OA being noted in the subgroup of patients with a combination of excess body weight, DM and hypertension. Type II diabetes complicates the destructive processes in the tissues of the knee joints, which is why stage III OA is detected 2 times more often in its presence [354].

Data from the literature indicate that adiponectin, leptin and visfatin can affect both large joints and hand joints. These adipokines are involved in the regulation of

glucose and adipocyte metabolism, as well as immune and inflammatory responses. An increase in their level in blood serum is a predictor X-ray progression of OA of the joints of the hands [356, 367].

Adipose tissue contains macrophages that form a corona-like structure around hypertrophied adipocytes. Unlike the adipose tissue of lean people, which contains mainly anti-inflammatory M2 macrophages, in the case of obesity, the adipose tissue contains primarily pro-inflammatory M1 macrophages. In addition, the adipose tissue of obese people is rich in dendritic cells, T- and B-cells, neutrophils and adipocytes. During obesity, the production and release of pro-inflammatory cytokines and adipokines - leptin, resistin, lipocalin-2, RBP4, interleukins (IL)-6, 18, tumor necrosis factor-alpha (TNF-a) increases, which is accompanied by the occurrence of low-intensity systemic inflammation. The source of adipokines is also the own adipose tissue of the joints, in particular the infrapatellar adipose tissue (IPAT) of the knee joint. Due to its location, the IPAT can play an important role in local inflammation of the knee joints. Today, at least 3 cytokines are known, which are produced simultaneously by adipose tissue and IVT: IL-6, TNF-a, and VEGF (vascular endothelial growth factor) [347].

It has been established that a high level of some adipokines (IL-1, IL-4 and 6, leptin) is associated with the progression of articular cartilage damage in OA [359].

Therefore, the metabolic syndrome (MS) is a risk factor not only for the development, but also for the progression of OA, since there is a relationship between OA and metabolic changes that occur during obesity: both in one condition and in the other, increased circulation of systemic inflammatory markers is observed (C-reactive protein, IL-1 and TNF-a) [372]. In addition, leptin, produced by adipose tissue macrophages, is a key mediator of metabolic disturbances in OA. Leptin is able to induce the synthesis of metalloproteinases (MPPs) (collagenase, stromelysin, gelatinase, membrane proteinases, and metalloelastase), which cause cartilage damage during OA, and the degree of increased activity of these enzymes mostly correlates with the degree of cartilage tissue damage. Leptin enhances the synthesis of pro-inflammatory mediators (IL-6, IL-8 and prostaglandin E2) in cartilage in OA.

Thus, during metabolic syndrome, higher levels of insulin and leptin are also observed. The pro-inflammatory state of the immune system is illustrated by an increase in the content of C- reactive protein and IL-1. In the presence of metabolic syndrome, a more pronounced progression of joint damage is observed, which indicates a negative role of insulin resistance and adipokines (leptin, C-reactive protein, and interleukin-1) in the metabolism of articular cartilage during OA.

Hypertension plays an important role in the progression of OA, and the use of non-steroidal anti-inflammatory drugs (NSAIDs) for the purpose of anti-inflammatory and analgesic effects in patients with a history of heart disease increases the probability of hospitalization for heart failure by 10 times and leads to destabilization and progression of hypertension [353, 358].

In addition, NSAIDs can reduce the effectiveness of antihypertensive drugs, especially those whose effects are mediated through the renin-angiotensin system (angiotensin-converting enzyme (ACE) inhibitors, diuretics, angiotensin II receptor antagonists), the use of which reduced left ventricular hypertrophy (LVH) and arterial stiffness in patients with hypertension and diabetes [358, 370-372]. However, preference should be given to ARBs, because they reduce the mass of the LV myocardium the most, reduce the activity of angiotensin II, have fewer adverse reactions, and have a mild effect on renal hemodynamics.

According to the researchers, it should not be forgotten that the development of dystrophic changes in the vascular wall and articular cartilage, the progression of hypertension and OA can contribute to lipid metabolism disorders, which become a common pathogenetic mechanism of these diseases [364, 366]. Under conditions of dyslipidemia, oxidized low-density lipoprotein (LDL) reduces the activity of endothelial NO-synthase (NOS) and the bioavailability of NO [353]. Therefore, the analysis of the factors of endothelial dysfunction in patients with a combination of OA and hypertension against the background of obesity is fully justified.

To date, researchers have proven that the regression of the intima-media complex (IM) correlates with a decrease in the level of LDL [349]. At the same time, the risk of developing a stroke increases with an increase in the thickness of the intima-

media complex of vessels, and an increase in the TIM of the common carotid artery by 0.2 mm is associated with an increase in the risk of stroke from 33 to 43% [374]. In general, intima-media complex thickening is an independent predictor of adverse cerebrovascular prognosis. Based on this, the prescription of statins is mandatory.

Therefore, in the case of a combination of arterial hypertension and obesity as a result of vascular, metabolic and hormonal changes, the latter has an even more pronounced effect on the severity of clinical manifestations and functional insufficiency of joints in patients with osteoarthritis than arterial hypertension.

Hypertension in combination with type II diabetes is characterized by a high prevalence, more frequent and pronounced damage to target organs, a decrease in insulin sensitivity, which is accompanied by hyperinsulinemia, atherogenic dyslipidemia, a violation of the daily blood pressure profile, which significantly increases cardiovascular risk, and the activation of pro-inflammatory cytokines and growth factors not only enhances dysmetabolic manifestations, but also leads to the development of hypertrophy and fibrosis of the myocardium, causing its pathological remodeling.