KAPITEL 14 / *CHAPTER 14* [61]
CARDIOMETABOLIC EFFECTS OF COMBINED ANTIHYPERTENSIVE AND LIPID-LOWERING THERAPY IN HYPERTENSIVE PATIENTS WITH ABDOMINAL OBESITY

DOI: 10.30890/2709-2313.2025-38-03-027

Resume.

This study evaluated the changes in endothelial function, lipid metabolism, and insulin sensitivity in patients with arterial hypertension and abdominal obesity over a 6-month period of combined treatment with an ACE inhibitor (perindopril), a calcium channel blocker (amlodipine), and a statin — atorvastatin (Group I) or rosuvastatin (Group II). After six months, both treatment regimens led to improvements in endothelium-dependent vasodilation, reductions in total cholesterol and triglyceride levels, and enhanced HDL cholesterol. However, these effects were more pronounced in the rosuvastatin group, which also demonstrated a significantly greater reduction in the insulin resistance index (HOMA). These findings suggest a potential advantage of rosuvastatin in cardiometabolic risk reduction among hypertensive patients with features of metabolic syndrome.

According to Ukrainian, American and European guidelines, combination therapy is indicated for all patients starting from the 2nd degree of arterial hypertension (AH), and is also allowed (as an alternative to monotherapy) in the form of low-dose combinations even in the early stages of AH [1].

An important cardiovascular risk factor in hypertension is the level of cholesterol (especially low-density lipoprotein cholesterol) in patients' blood. It determines up to 70% of the attributable risk of developing cardiovascular disease complications [2]. Lipid metabolism disorders, such as hypercholesterolaemia and low high-density lipoprotein cholesterol (HDL-C), are reported in 40-85% of patients with HD [2]. Such a frequent combination of hypertension and dyslipidaemia may be associated with both a random combination of these common risk factors and common pathogenetic

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mechanisms underlying their development. Some researchers explain the frequent combination of hypertension and dyslipidaemia by the direct effect of hypercholesterolaemia and dyslipidaemia on peripheral vascular tone and, thus, on blood pressure [3]. There is strong evidence for the role of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) in the development of ED. Oxidised LDL is involved in the formation of foamy cells from macrophages/monocytes, which form, together with lipid inclusions, the core of the lipid plaque. Bioactive substances (tumour necrosis factor, interleukins, growth factor, etc.) released under these conditions are directly involved in the processes of migration and proliferation of vascular smooth muscle cells, enhancing collagen synthesis and breakdown. Under conditions of increased lipid load, these processes become pathological, causing ED with impaired endothelium-dependent vasodilation (EDV) and increased release of vasoconstrictors by the endothelium, the most studied of which is endothelin-1 [4]. Many studies have also demonstrated the association between dyslipidaemia and AD, which, along with hypertension, are the main components of the metabolic syndrome. According to the Framingham Study, the likelihood of developing hypertension and all cardiovascular pathology in obese people is 50% higher than in people with normal body weight. With an increase in the mass of visceral fat, a large amount of free fatty acids, 20-30 times higher than normal, enters the vascular bed through the portal vein system. This leads to disorders of carbohydrate and fat metabolism, as well as changes in the fibrinolysis system and endothelial function. Endothelial dysfunction caused by restricted synthesis and secretion of vasodilators by the vascular endothelium in the context of increased activity of the renin-angiotensin-aldosterone system and increased expression of vasoconstrictors, in particular endothelin-1, plays an important role in the progression of hypertension.

According to subanalyses of the EUROPA trial, patients treated with a combination of ACEI + ACEI + statins had a 71% reduction in the risk of cardiovascular death. The favourable effect of statins on prognosis, in addition to their hypolipidemic effect, is explained by their effect on endothelial function (anti-inflammatory effect - reduction of C-reactive protein, inhibition of metalloproteinase

synthesis; antithrombotic effect; inhibition of vascular myocyte proliferation; oxidative stress, effect on apoptosis), stabilisation and regression of atherosclerotic plaque, resulting in improved myocardial perfusion.

Hypertriglyceridaemia is a characteristic feature of dyslipidaemia in HD in patients with concomitant AD. These individuals are at increased risk of developing cardiovascular events, so maximal optimisation of treatment of this category of patients is a priority task of preventive cardiology practice. Of great interest is the study of the synergy of amlodipine and perindopril in relation to ED in patients with concomitant CAD, as well as the interaction of this combination with various lipid-lowering therapies. These studies may open new perspectives on the use of this combination.

The aim of the study. To study the dynamics of the main indicators of lipid, carbohydrate metabolism and vascular endothelial function as a marker of atherosclerosis in combined antihypertensive and different variants of lipid-lowering therapy (group I - atorvastatin, group II - rosuvastatin) in patients with hypertension and concomitant AD.

Materials and methods. We conducted a 6-month treatment of 164 male patients with stage II HD diagnosed in accordance with the recommendations [1], aged 60 to 85 years, on average (75±8.5) years with concomitant grade I AD. Exclusion criteria for the study: female sex, symptomatic hypertension, clinical and electrocardiographic manifestations of coronary heart disease, sinoatrial and atrioventricular conduction disorders of II-III degree, atrial fibrillation, frequent ventricular and supraventricular extrasystoles, HC of I and III stages, AH of II and III degrees, chronic heart failure of II-III stages, functional classes III-IV, fasting plasma glucose ≥ 6.1 mmol/l (patients with glucose homeostasis disorders were excluded), diabetes mellitus, chronic obstructive pulmonary disease, chronic diseases of the digestive tract and kidneys in the acute phase, endocrinological diseases.

Abdominal type I obesity was established at a waist-to-hip ratio of ≥ 0.95 with a body mass index (BMI) of 30.0-34.9 kg/m².

For optimal antihypertensive therapy in patients with hypertension with concomitant AD, a fixed combination of the ACEI perindopril and the ACEI

amlodipine was chosen.

It should be noted that fixed combinations significantly improve patient compliance, demonstrate benefits in many studies and are recognised as the optimal choice for patients with hypertension in all current guidelines.

84 patients received a fixed combination of the ACE inhibitor perindopril and the ACE inhibitor amlodipine in individually selected doses and lipid-lowering therapy with atorvastatin at a dose of 10 mg once daily. 80 patients were treated with the lipid-lowering drug rosuvastatin at a dose of 5 mg once daily in the same regimen against antihypertensive therapy. Lipid and carbohydrate profiles and vascular endothelial function were assessed before and 6 months after the start of therapy.

For the diagnosis of insulin resistance, the HOMA index (Homeostasis model assessment) was used, which was determined by the formula:

HOMA = fasting blood insulin level (mU/ml) multiplied by fasting blood glucose level (mmol/l) and divided by 22.5. A HOMA index of no more than 2.77 was considered normal.

Ultrasonography of the brachial arteries was performed using an ultrasound diagnostic scanner "LOGIQ 500" (General Electric, USA), diameter changes were assessed using a 7 MHz linear transducer with a phased array of the ultrasound system.

Statistical processing of the study results was performed using the methods of variation statistics using StatSoft "Statistica" v. 6.0. The vast majority of indicators had a non-normal distribution (the type of distribution was determined using the Shapiro-Wilks test), so in most cases we used non-parametric statistics methods. The results of the study are presented in the form of percentages that reflect the frequency of the feature in the sample and in the form of median and interquartile range. The comparison of relative values was carried out using the $\chi 2$ criterion. Comparison of quantitative values of dependent samples was carried out using the Wilcoxon test.

Results of the study and their discussion.

Endothelial vascular function was studied by visualisation of the brachial artery lumen using high-resolution ultrasound (Photos 1, 2).

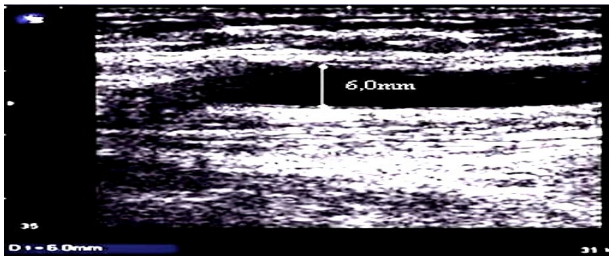

Photo 1: Brachial artery diameter in a patient with hypertension and abdominal obesity at rest

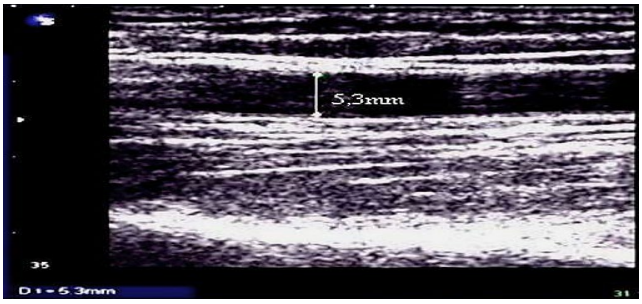

Photo 2: Brachial artery diameter in a patient with hypertension and abdominal obesity after reactive hyperemia test

The study was performed in the morning, on an empty stomach, after 15 minutes of rest. The brachial artery was echo-located in a longitudinal section 10-15 cm above the right elbow joint. The study was performed in triplex mode (B-mode, colour Doppler flow mapping, spectral analysis of Doppler frequency shift). The study of endothelial function was performed using reactive hyperaemia and nitroglycerin tests proposed by D.S. Celermajer. Transient ischaemia during reactive hyperaemia induces NO release, which causes local vasodilation of the artery (endothelium-dependent vasodilation, EDV). The latter is impaired not only as a result of endothelial dysfunction, but also due to structural changes in smooth muscle cells. To differentiate between these disorders, a nitrate test (endothelium-independent vasodilation, EIVD) was performed. Reactive hyperaemia was created by applying a pneumatic cuff for 4-5 minutes, into which air was pumped until the blood flow stopped (40-50 mm Hg above the actual systolic blood pressure). The results of the test were evaluated at 30 and 90 seconds after decompression (time of maximum arterial dilatation). After a 15-minute period of blood flow recovery in the brachial artery, a test was performed with

nitroglycerin (the drug acts through the formation of NO directly in the muscle cells of the vessels, and not through the endothelium), which was administered at a dose of 0.0005 g (1 tablet) sublingually. The results were evaluated at 3 and 5 minutes (the time of maximum nitrate action). The arithmetic mean was calculated from the four parameters and taken as the diameter of the artery.

Endothelial function, defined as endothelium-dependent and endothelium-independent vasodilation, was assessed as the percentage increase in vessel diameter from baseline to maximum during hyperemia and after nitrate administration. An increase in the diameter of the brachial artery by 10% after 90 s in the setting of reactive hyperemia and by 20% after 5 min after the nitroglycerin test was considered normal.

In addition, in all observation groups, we measured the blood flow velocity in the brachial artery at rest and against the background of a test with reactive hyperaemia (V, m/s).

The ratio of the change in blood flow velocity in the brachial artery after the test with reactive hyperaemia to its value at rest was determined.

The dynamics of the increase in the diameter of the brachial artery after the test with temporary compression in patients with hypertension under the influence of various hypolipidemic therapy regimens is shown in Fig. 1.

In patients with hypertension and AR, endothelium-dependent vasodilation significantly improved under the influence of combined antihypertensive and various hypolipidemic therapy regimens after three months of observation ($p<0.0001$ compared with baseline). After six months, the EWVD in the selected groups of patients increased by 63.1% under the influence of atorvastatin therapy, and by 97.9% with daily rosuvastatin ($p=0.036$ between groups, comparison was performed using the Mann-Whitney test).

The EWVD in patients with hypertension and arterial hypertension under the influence of different hypolipidemic therapy regimens did not change significantly during the entire observation period.

A significantly greater increase in EWVD with a slight increase in ENVD has been explained by some researchers by the fact that in the mechanisms of endothelial

function improvement, a lesser role is played by increased sensitivity (increased receptor density) to nitrovasodilators, and a greater role is possibly played by a decrease in intracellular oxidative stress and uncontrolled Ca2+ flux, which contributed to the formation of an abnormal vessel response to physiological stimuli.

It should be noted that the impaired normal vasodilator response to nitroglycerin in patients with hypertension makes it likely that the impaired response of vascular smooth muscle cells to nitrovasodilators may contribute to the development of endothelial dysfunction. Some researchers attribute this to the development of vascular "aging" with changes in vascular cytoarchitectonics.

The study demonstrated that in patients with hypertension with AR, the value of the endothelial shift in six months with the Perindopril+Amlodipine+Atorvastatin regimen increased by 22.5%, and with Perindopril+Amlodipine+Rosuvastatin - by 33.9% (p=0.033).

After six months of combined therapy in patients with hypertension, endothelium-dependent vasodilation remained impaired, despite the pronounced dynamics of its improvement in both groups of patients. In patients with hypertension and hypertension with AD, the addition of rosuvastatin to standard antihypertensive therapy was associated with a significant improvement in vascular endothelial function compared with patients whose treatment regimen included atorvastatin.

The baseline levels of total cholesterol (TC), triglycerides (TG), HDL cholesterol in both groups of patients did not differ and were 6.44+0.16, 2.61+0.14, 1.01+0.04 mmol/l in group I and 6.45+0.18, 2.59+0.13, 1.01+0.04 mmol/l in group II (M+m), p>0.05. Changes in blood lipid transport function under the influence of various lipid-lowering therapy regimens were analysed after 6 months.

When analysing the results of treatment in the study groups of patients, the levels of VLDL and TG were significantly lower with the use of antihypertensive and lipid-lowering therapy with rosuvastatin (group II). In addition, in group II patients, the levels of the antiatherogenic fraction, HDL-C, were significantly higher after 6 months, which undoubtedly has a positive effect on the prevention of cardiovascular complications in this category of patients.

Improvement of lipid profile and regression of endothelial dysfunction in patients at high cardiovascular risk is of fundamental importance, as dyslipidaemia, by promoting deeper remodelling of the vessel walls and increasing the expression of adhesive molecules on the surface of endothelial cells, forms a vicious pathological circle that initiates atheroma formation. Thus, inclusion in combined antihypertensive therapy with perindopril and amlodipine contributes to more effective prevention of atherosclerosis in patients with hypertension and AD.

The results of this study are supported by the data of many controlled clinical trials that studied the efficacy of rosuvastatin therapy compared with other statins, such as Comets, Lunar, Mercury-I, Solar, Stellar, which were part of the GALAXY programme. In general, patients taking rosuvastatin, compared with patients taking other statins (atorvastatin, simvastatin, fluvastatin, pravastatin), had a significantly more pronounced reduction in the levels of LDL-C, LDL-C, TG, an increase in HDL-C, and achievement of target LDL-C levels in a greater percentage of patients.

The results of determining changes in carbohydrate metabolism (Table 2) under the influence of combined antihypertensive and various hypolipidemic therapy regimens demonstrated a significant decrease in the NOMA index after 6 months of treatment only in patients with hypertension with concomitant CAD, in which rosuvastatin was included in the treatment regimen ($p<0.05$). The dynamics of changes in glucose and insulin levels in the selected groups of patients with hypertension and AD did not differ significantly and did not lead to a significant decrease in the above indicators over the 6-month observation period.

Impaired vascular endothelial function is pathogenetically associated with the development of insulin resistance (IR), which is observed in a significant number of patients with HD and underlies the metabolic syndrome. The cause-and-effect relationship between ED and IR also remains controversial. Many studies have demonstrated that ED is a consequence of the mechanisms underlying IR, such as hyperglycaemia, hypertension, and dyslipidaemia. Hyperglycaemia activates the enzyme protein kinase-C in endothelial cells, which increases the permeability of vascular cells to proteins and disrupts the ESMC. In addition, hyperglycaemia activates

lipid peroxidation, the products of which inhibit the vasodilator function of the endothelium. In hypertension, endothelial cell architecture is disturbed, vasoconstrictor endothelin-1 production increases, and vascular remodelling with a decrease in vascular elasticity occurs. Dyslipidaemia increases the expression of adhesive molecules on the surface of endothelial cells, which gives rise to atheroma formation. Thus, the above mechanisms, by increasing endothelial permeability and the expression of adhesive molecules, reduce EHVD. Other researchers believe that ED leads to the development of IR due to impaired transendothelial insulin transport. Undoubtedly, IR and ED, including nitric oxide production, are closely related and form a pathological "vicious circle" that leads to metabolic and cardiovascular diseases. Despite the fact that many cause-and-effect relationships in the pathogenesis of ED are still unclear, it is undeniable that ED is the first step in the development of atherosclerosis, which is associated with an increased risk of cardiovascular complications. It should be remembered that the therapy prescribed by a practitioner should undoubtedly be pathogenetically based to maximise the optimisation of treatment of patients at high risk of cardiovascular complications.

Conclusions.

1. In the group of patients with hypertension and concomitant abdominal obesity, significant dyslipidaemia is observed, with hypertriglyceridaemia being a characteristic feature. The addition of the lipid-lowering drug rosuvastatin to combined antihypertensive therapy (perindopril + amlodipine) contributes to a significantly more effective reduction in total cholesterol, triglycerides and high-density lipoprotein cholesterol levels compared with atorvastatin treatment.

2. Patients with hypertension and abdominal obesity are characterised by significant endothelial dysfunction and the inclusion of rosuvastatin in combination antihypertensive therapy with perindopril and amlodipine leads to a significant improvement in this dysfunction compared with the group taking atorvastatin.

3. In the group of patients whose treatment regimen included rosuvastatin, after 6 months of therapy, a decrease in the HOMA index was noted. Other indicators of

carbohydrate metabolism did not change significantly and did not differ from those in the group of patients treated with atorvastatin.

Prospects for further research may lie in studying the effect of rosuvastatin lipid-lowering therapy on other pathogenetic links of hypertension in order to optimise treatment and reduce dose-related adverse reactions of statins.