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Correction of Lipid Metabolism Disorders in Hypertensive Overweight Patients Treated with Antihypertensives Combined with Statins

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Abstract

Protein-fat metabolism regulation disorder is one of the leading determinants in AH pathogenesis, which is closely associated with being overweight (there is an established relationship between AH and cell membranes lipid pathology, which leads to cationic pumps dysfunction, impairs calcium, sodium and other cations transport, and potentiates atherosclerosis development, which aggravates the course of AH). Thus, in overweight patients with AH and therefore dyslipidemia, a balanced antihypertensive and lipid-lowering drugs prescription is required, in particular involving sartans and statins combinations which reduce cardiovascular risks and delay acute heart or cerebral pathology development, hence improving patients life quality and expectancy.

Objectives: to evaluate dynamics of systemic inflammatory response, lipid profile, carbohydrate metabolism and systemic haemodynamics in overweight (BMI over 28±1.9 kg/m²) patients with stage II hypertension, risk 2-4, under combined therapy influence.

Materials and methods: Investigation of systemic inflammatory response, neurohumoral profile, lipid profile, carbohydrate metabolism and system haemodynamics indices dynamics under the influence of combined therapy (antihypertensive medications: fixed drug combinations – Ekvator (Amlodipine 5 mg and Lisinopril 10 mg) and Valodip (Amlodipine 5 mg and Valsartan 80 mg) during 120 days), to which Rosuvastatin (10 mg per day) was added, has been done in 64 hypertensive (stage II) overweight patients, medium age 59.0 [48.0; 63.0] years. The statin therapy influence on the general patients' state was estima-

ted by assessing systemic inflammatory response, neurohumoral profile, lipid profile, carbohydrate metabolism and system haemodynamics indices. General clinical, laboratory and instrumental testing was done in all patients for the purpose of diagnosis verification, complications and comorbidity evaluation.

Results. Inflammatory processes reduction, insulin resistance reduction and lipid, cholesterol metabolism and adipokines synthesis normalisation were observed, as evidenced by significant proinflammatory interleukins (IL-1β, TNF-α) decrease and anti-inflammatory IL-10, adiponectin and IL-1β/TNF-α ratio increase in both patients subgroups, significant decrease in indices representing blood compound atherogenic potential accompanied by antiatherogenic HDL cholesterol increase in both subgroups, positive changes of system haemodynamics in both subgroups: systolic and diastolic arterial pressure normalization and heart pump function increase.

Keywords: systemic inflammatory response, lipid profile, system haemodynamics, arterial hypertension, overweight patients.

Introduction

Excess visceral adipose tissue and its increased ratio to subcutaneous fat are associated with metabolic disorders and arterial hypertension (AH) development, cardiovascular remodeling processes, as well as the risk of cardiovascular and overall mortality [3, 10]. It has been shown that in outpatients without coronary heart disease (CHD) signs, the most common risk factors are hypertension (66.2%) and total plasma cholesterol > 5.2 mmol/l (68%) [6]. AH associated with obesity and insulin resistance (IR), contributes to the lipid profile shift, which, alongside hyperglycemia and hypertension, leads to early and rapid atherosclerosis development [8, 12, 14]. Therefore, the presence of hypertension on the overweight background increases the potential cardiovascular risk and encourages search for optimal therapeutic approaches for such patients, in particular the optimal statin therapy selection.

Protein-fat metabolism regulation disorder is one of the leading determinants in AH pathogenesis, which is closely associated with being overweight (there is an established relationship between AH and cell membranes lipid pathology, which leads to cationic pumps dysfunction, impairs calcium, sodium and other cations transport, and potentiates atherosclerosis development, which aggravates the course of AH) [5, 9].

According to the current European recommendations of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) for dyslipidemias treatment [11], and American recommendations of the American College of Cardiology (ACC) / American Heart Association (ANA) for the primary prevention of cardiovascular disease [1], statins are first-line drugs for the primary prevention of cardiovascular disease in patients with low-density lipoprotein cholesterol (LDL cholesterol) high levels, in high-risk patients with hypercholesterolemia and hypertriglyceridemia, which create additional condi-

tions for atherosclerosis progression [2, 15]. In particular, US guidelines indicate that in patients with clinical manifestations of cardiovascular disease associated with atherosclerosis, i.e. in people at highest risk, it is recommended to reduce LDL cholesterol levels with high-intensity or maximum tolerable statin therapy [1].

Statins are commonly used for cardiovascular disease and atherosclerosis prevention, which has been reported in many clinical studies, including METEOR (Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin) [13], GALAXY [7], ORION [4], ASTEROID (A Study To evaluate the Effect of Rosuvastatin On Intravascular Ultrasound-Derived Coronary Atheroma Burden) [4], SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) [7]. In these studies, significant reduction in LDL cholesterol level was observed against statins intake background accompanied by slowing progression and even regress of carotid and coronary arteries atherosclerosis as indicated by imaging methods. Thus, in overweight patients with AH and therefore dyslipidemia, a balanced antihypertensive and lipid-lowering drugs prescription is required, in particular involving sartans and statins combinations which reduce cardiovascular risks and delay acute heart or cerebral pathology development, hence improving patients life quality and expectancy.

The aim of the study is to evaluate dynamics of systemic inflammatory response, lipid profile, carbohydrate metabolism and systemic haemodynamics in overweight (BMI over 28±1.9 kg/m²) patients with stage II hypertension, risk 2-4, under combined therapy influence.

Materials and methods

64 overweight patients (average age 59.0 [48.0; 63.0] years) with stage II arterial hypertension (AH) were examined. They were undergoing inpatient treatment in the therapeutic department №1 of the industrial hospital SC "Motor Sich" during 2016-2018. All patients met the inclusion criteria and all examined groups were comparable in age and social status.

Study inclusion criteria were: male and female overweight (BMI over 28±1.9 kg/m^2) patients (45-65 years old); stage II hypertension diagnosed according to the Recommendations of ESH (European Society of Hypertension) / ESC (European Society of Cardiology), risk 2-4; patients with impaired carbohydrate tolerance, confirmed by biochemical methods; the known disease duration exceeds 5 years.

Study exclusion criteria were: permanent atrial fibrillation type cardiac arrhythmia, ventricular arrhythmias over class 2 according to B. Lown; coronary heart disease, acute myocardial infarction, progressive angina; exertional angina more than I class of NYHA (New York Heart Association Functional Classification) (IIa according to Strazhesko MD and Vasilenko VH); bronchial asthma; cardiomyopathy, myocarditis; decompensated heart defects; thyroid dys-

function; acute inflammatory or exacerbation of chronic inflammatory diseases; alcohol or drug addiction, mental illnesses; chronic renal failure; liver dysfunction; patients refusal to continue participation in the study.

The study was held according to Human Rights Declaration of Helsinki (1964), the Conference on Harmonization of Good Clinical Practice (GSP ICH), The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine of the council of Europe. All examined patients have signed an informed consent for participation in accordance with the protocol approved by the State Institute «Zaporizhzhya Medical Academy of Postgraduate Education of Ministry of Health of Ukraine» bioethics committee.

General clinical, laboratory and instrumental tests were done in all patients for the purpose of diagnosis verification, complications and comorbidity estimation.

Patients were randomised into two subgroups which were taking fixed antihypertensive drug combinations for 120 days. The first patient subgroup (n = 32) were prescribed combined medication "Ekvator" ("Gedeon Richter", Hungary) in a starting dose of 1 pill (Amlodipine 5 mg and Lisinopril 10 mg) per day, the second patient subgroup (n = 32) were prescribed "Valodip" (KRKA, Slovenia) in a starting dose of 1 pill (Amlodipine 5 mg and Valsartan 80 mg) per day. The dose has been corrected during the first two weeks if it was necessary. 10 (31.3%) first subgroup patients and 13 (40.6%) second subgroup patients didn't require dose correction, the others received the corrected dosage – "Ekvator" (Amlodipine 5 mg and Lisinopril 20 mg) 1 pill in a day and "Valodip" (Amlodipine 5 mg and Valsartan 160 mg) 1 pill in a day. The targeted arterial pressure level (130/85 mm Hg) was reached in 24 (75.0%) first subgroup patients and in 26 (81.3%) second subgroup patients. All patients were prescribed 10 mg Rosuvastatin ("Roxera", KRKA) per day.

The obtained data were presented as the median and Me [Q25; Q75] interquartile range. Distribution analysis has been performed according to each studied criterion. The study results were analyzed using parametric or non-parametric statistics, depending on the typical distribution using specialized computer programs ApacheOpenOffice (version 4.1) and PSPP (version 0.10.2). During statistical hypotheses testing, the null hypothesis was rejected at statistical significance (p) level below 0.05. During more than two independent variables comparison, variance analysis (One-way ANOVA) was used, followed by empirical tests. Equality of differences was tested using the Leuven test. In the case of differences equality in groups, the Scheffe test was used, and in the absence of differences equality, the T2-Tumhein test was used. In the case of non-normal data distribution, an analogue of the Kruskal-Wallis variance analysis was used, followed by post-hoc analysis using the Dunn test.

Results and discussion

The dynamics of systemic inflammatory response and neurohumoral status (Table 1) were obtained against the background of the proposed therapy in overweight patients with stage II AH in two subgroups with different treatment regimens before and after 120 days of treatment. An increase in pleiotropic proinflammatory cytokine IL-1β level which had no significant differences between the subgroups has been detected in both subgroups prior to treatment (Table 1). The IL-1β level has significantly decreased by an average of 16.39±0.58% and 16.34±1.14% in the first and second subgroups respectively after 120 days of combined therapy in both subgroups, hence confirming inflammatory processes reduction. Anti-inflammatory cytokine IL-10, which was reduced before treatment in both subgroups without significant differences, has significantly increased by 12.67±0.19% and 13.72±0.78%, respectively against the background of treatment, demonstrating immune response modulation promoting its cardioprotective function. Accordingly, IL-1β/IL-10 ratio, which did not differ significantly before the treatment, has significantly decreased by 33.31±0.82% and 35.74±3.3% respectively after the treatment in the first and second subgroups. Proinflammatory cytokine TNF-α level had no significant differences between subgroups before treatment. Inflammatory processes decrease, insulin resistance reduction and lipid metabolism, cholesterol and adipokine synthesis normalization were observed against the background of treatment, as evidenced by a significant decrease in acute inflammatory TNF-α protein level in both subgroups by 11.67±0.8% and 18.03±0.99%, respectively. Adiponectin level content had no significant differences between the first and second subgroups before treatment, however there has been a significant increase in its concentration by 2.95±0.21% and 2.56±0.21% respectively after the combined therapy. Such a significant increase on the background of decreased IL-1β and TNF-α levels was due to lipoprotein metabolism normalisation and inflammation reduction due to circulating chemokines binding and their pro-inflammatory activity inhibition. The obtained patterns are confirmed by a significant decrease in TNF-α/ADP ratio, which prior to the treatment did not significantly differ in both subgroups, and after it has significantly increased by 15.1±0.91% and 21.15±1.05% in both first and second subgroups (Table 1).

Overweight patients with stage II AH therapy with the combined drugs Equator and Valodip before and after 120 days of treatment with statins, namely Rosuvastatin (10 mg per day), had a positive effect on lipid spectrum and carbohydrate metabolism (Table 2) in two subgroups. Before treatment, total cholesterol level was above normal and did not differ significantly in both subgroups.

Table 1.
Systemic inflammatory, anti-inflammatory response and adiponectin indices in overweight patients with AH (stage II) subjected to combined therapy (Me [25; 75], n=64)

Index, units	Therapy subgroups	Before treatment	After 120 days	Δ %
IL-1β, pg/ml	(n = 32)	4.39[2.56;6.35] p_{3-4}=0.0001	3.79[2.11;5.57]	-16.16[-13.74;-19.53]
	(n = 32)	3.81[2.18;7.25] p_{3-4}=0.0001	3.22[1.93;6.43]	-15.97[-13.21;-17.59]
	p-level	p=0.39	p=0.78	p=0.39
IL-10, pg/ml	(n = 32)	3.21[2.19;3.87] p_{3-4}=0.0001	3.60[2.55;4.49]	12.71[11.84;13.42]
	(n = 32)	2.37[1.89;3.43] p_{3-4}=0.0001	2.73[2.18;3.94]	13.06[12.01;13.98]
	p-level	p=0.08	p=0.10	p=0.39
IL-1β\IL-10	(n = 32)	1.47[1.06;1.83] p_{3-4}=0.0001	1.14[0.77;1.40]*	-33.29[-36.53;-28.79]
	(n = 32)	1.74[1.30;2.85] p_{3-4}=0.0001	1.31[0.96;2.07]**	-32.41[-35.62;-30.05]
	p-level	p=0.36	p=0.33	p=0.91
TNF-α, pg/ml	(n = 32)	2.11[1.70;3.09] p_{3-4}=0.0001	1.90[1.55;2.74]	-10.66[-14.06;-8.31]
	(n = 32)	2.28[1.61;2.99] p_{3-4}=0.0001	1.91[1.30;2.53]	-16.38[-21.58;-14.69]
	p-level	p=0.79	p=0.50	p=0.0023
Adipo nectin, μg/ml	(n = 32)	3.87[2.65;6.35] p_{3-4}=0.0001	3.96[2.72;6.51]	2.75[2.11;3.58]
	(n = 32)	3.60[2.63;7.10] p_{3-4}=0.0001	3.69[2.67;7.32]	2.48[1.75;3.07]
	p-level	p=0.95	p=0.99	p=0.39
TNF-α / Adipo nectin	(n = 32)	0.63[0.26;0.87] p_{3-4}=0.0001	0.54[0.21;0.74]	-20.25[-24.54;-16.43]
	(n = 32)	0.67[0.33;1.02] p_{3-4}=0.0001	0.60[0.28;0.84]	-13.77[-17.12;-12.14]
	p-level	p=0.62	p=0.46	p=0.002

Notes (hereinafter): * (at p<0.05), ** (at p<0.01), *** (at p<0.001) – a significant difference after the conducted therapy

The treatment with Rosuvastatin addition has significantly reduced total plasma cholesterol by 5.04±0.2% and 4.92±0.11% respectively, which correlates with TNF-α levels and confirms lipid metabolism optimization by statin treatment. Atherogenic low-density lipoproteins (LDL) level has also significantly

decreased by 4.41±0.16% and 4.75±0.14% in both subgroups respectively. It should be noted that statistically significant differences between subgroups in the percentage reduction of total cholesterol and LDL were not detected. In contrast, antiatherogenic blood serum high-density lipoprotein (HDL) level has significantly increased by 7±0.15% and 6.9±0.16% in the first and second subgroups respectively. These lipid profile dynamics in the course of treatment indicate reduction of possible cardiovascular risks, in particular reduction of atherosclerosis, stroke, and coronary heart disease risks. The reduction of these risks is confirmed by a decrease in fasting blood glucose, which is a coronary heart disease predictor. Fasting glucose levels during therapy with fixed drug combinations with Rosuvastatin addition has decreased by 1.41±0.3% and 1.40±0.03% respectively. Thus, both treatment strategies with Rosuvastatin addition have shown a fairly comparable effect on the atherogenic lipoproteins reversal, lipid and carbohydrate metabolism disorders normalisation, and, consequently, cardiovascular risks associated with such conditions reduction.

Table 2.
Lipid and carbohydrate metabolism indices in overweight patients with AH (stage II) subjected to combined therapy (Me [25; 75], n=64)

Index, units	**Therapy subgroups**	**Before treatment**	**After 120 days**	**Δ %**
Total cholesterol, mmol/l	(n = 32)	5.41[4.80;6.59] p_{3-4}=0.0001	5.16[4.55;6.35]*	-5.36[-5.64;-5.02]
	(n = 32)	5.36[4.32;6.11] p_{3-4}=0.0001	5.08[4.11;5.84]*	-4.96[-5.37;-4.44]
	p-level	p=0.39	p=0.40	p=0.16
HDL, mmol/l	(n = 32)	1.31[1.23;1.50] p_{3-4}=0.0001	1.37[1.29;1.56]*	4.41[3.96;4.67]*
	(n = 32)	1.21[1.09;1.41] p_{3-4}=0.0001	1.27[1.15;1.47]*	4.74[4.08;5.24]*
	p-level	p=0.11	p=0.11	p=0.27
LDL, mmol/l	(n = 32)	3.44[2.81;4.22] p_{3-4}=0.0001	3.21[2.61;3.95]*	-6.84[-7.57;-6.38]
	(n = 32)	3.28[2.48;4.18] p_{3-4}=0.0001	3.07[2.32;3.87]*	-7.07[-7.46;-6.36]
	p-level	p=0.73	p=0.72	p=0.39
Blood glucose, mmol/l	(n = 32)	5.20[4.83;5.50] p_{3-4}=0.0001	5.13[4.76;5.43]	-1.36[-1.47;-1.29]
	(n = 32)	5.16[4.76;5.50] p_{3-4}=0.0001	5.09[4.69;5.43]	-1.38[-1.49;-1.29]
	p-level	p=0.784	p=0.784	p=0.40

Systemic haemodynamics indices also show positive effects of the therapy (Table 3) in overweight patients with stage II AH in the first and second subgroups before and after 120 days of treatment.

Table 3.

System haemodynamics indices in overweight patients with AH (stage II) subjected to combined therapy (Me [25; 75], n=64)

Index, units	Therapy subgroups	Before treatment	After 120 days	Δ %
SBP, mm Hg	(n = 32)	157.50[150.00;170.00] p_{3-4}=0.0001	135.00 [130.00;140.00]	-11.77 [-21.83;-11.11]
	(n = 32)	160.00[150.00;170.00] p_{3-4}=0.0001	130.00 [127.50;135.00]	-20.00 [-23.08;-16.62]
	p-level	p=0.60	p=0.10	p=0.048
DBP, mm Hg	(n = 32)	90.00[85.00;100.00] p_{3-4}=0.0001	80.00 [77.50;90.00]*	-12.50 [-13.39;-11.11]
	(n = 32)	90.00[90.00;100.00] p_{3-4}=0.0001	80.00 [75.00;85.00]	-14.29 [-17.65;-12.50]
	p-level	p=0.435	p=0.49	p=0.07
MAP, mm Hg	(n = 32)	112.50[108.00;122.00] p_{3-4}=0.0001	100.00 [95.83;103.33]*	-13.10 [-17.09;-11.79]
	(n = 32)	115.00[110.00;121.00] p_{3-4}=0.0001	97.50 [94.17;103.33]**	-17.05 [-20.01;-15.63]
	p-level	p=0.40	p=0.26	p=0.012
SO, ml	(n = 32)	63.80[51.20;78.50] p_{3-4}=0.0001	67.43 [55.19;81.65]	4.49 [3.61;6.94]
	(n = 32)	64.95[54.75;78.85] p_{3-4}=0.0001	69.47 [60.27;84.09]	7.86 [6.60;9.47]
	p-level	p=0.996	p=0.67	p=0.002
MV, l	(n = 32)	4.69[4.03;6.11] p_{3-4}=0.0001	4.91 [4.50;6.52]	6.82 [3.25;10.01]
	(n = 32)	4.39[3.79;5.67] p_{3-4}=0.0001	4.72 [4.17;6.40]	9.77 [5.04;11.96]
	p-level	p=0.52	p=0.0001	p=0.42
SI, l/min·m^2	(n = 32)	2.41[2.15;3.31] p_{3-4}=0.00032	2.46 [2.18;3.40]	2.24 [0.92;6.06]
	(n = 32)	2.33[1.94;2.92] p_{3-4}=0.00032	2.45 [2.07;3.13]	3.14 [1.65;10.38]
	p-level	p=0.40	p=0.57	p=0.39

Systemic haemodynamic indices had no significant differences in both subgroups prior to treatment. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels have significantly decreased on the therapy background in

both subgroups in overweight patients with stage II AH: CBP decreased by 16.91±1.3% and 19.93±0.83% respectively, and DBP decreased by 11.86±0.47% and 15.37±0.65% respectively. Mean arterial blood pressure (MAP) level has also significantly decreased both in the first subgroup by 14.04±0.63%, and in the second subgroup by 17.52±0.59%. At the same time, the stroke output (SO) level has significantly increased on the combined therapy background in both subgroups by 5.32±0.39% and 7.90±0.38% respectively. Other systemic haemodynamics indices which characterize contractile heart function, such as minute volume (MV) and systolic index (SI), had also significantly increased: in the first subgroup, MV increased by 7.87±1.05%, in the second subgroup – by 8.69±0.9%, and SI by 3.72±0.88% in the first subgroup and by 5.61±1.29% in the second subgroup. A significant difference in the value of SO level between the two subgroups after treatment has been also observed. Thus, the conducted antihypertensive therapy with both ACE inhibitors and sartans with statins addition has reduced inflammatory processes and insulin resistance, increased adipokines secretion, and, therefore, has been effective.

Conclusions

Combined therapy with antihypertensive drugs and statins in overweight patients with stage II hypertension leads to reduced inflammatory processes in cardiovascular system, and lipid metabolism and adipokines synthesis normalisation as evidenced by a significant decrease in proinflammatory interleukins (IL-1β, TNF-α) and anti-inflammatory IL-10, adiponectin and IL-1β/TNF-α ratio increase.

There were positive changes in systemic haemodynamics in both subgroups undergoing the treatment: the majority of patients developed SBP decrease by 16.91±1.3% in the first subgroup and by 19.93±0.83% in the second, DBP decrease by 11.86±0.47% and 15.37±0.65% respectively; target blood pressure levels were achieved in 75% of patients in the 1st subgroup and in 81.3% in the 2nd subgroup. Both patient subgroups demonstrated significantly increased left ventricle pumping function.

Atherosclerosis and CHD predictors (pro-inflammatory cytokines, cholesterol, LDL cholesterol, fasting glucose increase and HDL cholesterol, anti-inflammatory cytokines decrease) normalisation and cardiovascular risks reduction prove hypotensive therapy efficiency employing combined use of ACE inhibitors with statins, as well as sartans with statins.

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