CORRECTION OF METABOLIC DISORDERS AND BLOOD LEPTIN WITH ATORVASTATIN AND URSODEOXYCHOLIC ACID

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S u m m a r y. Detection of blood leptin by ELISA and conventional lipid panel in 43 patients with hypertension in dynamics before and after a month of outpatient treatment with lisinoprilin combination with atorvastatin or ursodeoxycholic acid (UDCA) revealed that both drugs resulted in a significant decrease in atherogenicity of serum by reducing levels of total cholesterol and low-density lipoprotein cholesterol with an additional effect of lowering triglycerides influenced bystatin, and lowering elevated levels of leptin in a more pronounced with ursodeoxycholic acid. The decrease in total cholesterol of 6.06±0.18 mmol/L to 5.39±0.22 mmol/L, $p<0.001$; and 5.29±0.19 mmol/L to 4.95±0.20 mmol/L, $p<0.01$ and low-density lipoprotein cholesterol of 3.75±0.20 mmol/L to 3.16±0.23 mmol/L, $p<0.05$ and 3.30±0.19 mmol/L to 2.96±0.18 mmol/L, $p<0.05$ in the settings of moderate increase of high-density lipoprotein level ($p>0.05$ in both samples) was observed as a result of the treatment. Triglyceride concentration decreased significantly of 2.43±0.37 mmol/L to 2.05±0.22 mmol/L, $p<0.05$under the influence of atorvastatin, while the reduction in triglycerides was less pronounced when UDCA was administered ($p>0.05$). The study of the impact of cardiac drugs on synthesis of adipocytokinesin patients with cardiovascular damage is promising in terms of possible correction.
K e y w o r d s: atorvastatin, ursodeoxycholic acid, leptin, lipid panel

INTRODUCTION

According to recent studies, adipose tissue produces a number of adipokines that regulate carbohydrate and lipid metabolism, inflammation and immune homeostasis [1, 3, 4]. These include leptin associated not only with obesity but also arterial hypertension (AH) and insulin resistance [2, 7, 8]. The main mechanism of increased blood pressure (BP) under the influence of leptin is considered to be the activation of the sympathetic nervous system [4, 6]. Described in the literature leptin-dependent mechanism of hypersympathicotonia in hypertensive patients [3, 7, 9] in the settings of obesity changes and loses linear relationship, which is explained by the development of leptin and insulin resistance [1, 10, 12], increased secretion of angiotensin [3-5, 9]. However, the impact of drugs on the content of leptin is not understood, although it has been described that it decreased during treatment being more pronounced in men. This problem is of particular importance to those agents meant to be taken by patients for a prolonged period of time – for the first-line (statins) and second-line lipid-lowering drugs, which, include ursodeoxycholic acid (UDCA) according to recent data [2, 4, 6-8]. Therefore, the study of changes of leptin concentration along with changes in lipid panel is relevant and well-grounded task of modern science.

THE AIM OF THE STUDY

Objective: to study the dynamics of leptin concentration and lipid panel parameters in overweight hypertensive patients or those with obesity under the influence of atorvastatin and ursodeoxycholic acid.

MATERIAL AND METHODS

Detection of leptin level was conducted by ELISA (*DRG Leptin ELISA*, Germany) in 43 patients with hypertension stage 2, second degree, who were taking atorvastatin (10 mg/day) (n=23, 4 men and 19 women, aged 65.5±1.5, body mass index (BMI) 33.8±1.08 kg/m^2, waist circumference 100.0±2.0 cm, thigh circumference 115.5±2.4 cm) or ursodeoxycholic acid at 10 mg/kg of body weight per day [1, 5, 6, 10] (n=20; 5 men and 15 women, aged 63.4±1.9, waist circumference 99.3±1.4 cm, thigh circumference 108.8±2.3 cm, BMI 33.1±1.0 kg/m^2) for 4 weeks in addition to conventional treatment of hypertension with lisinopril (10-20 mg/day). Initially the formed groups were identical under studied parameters including office blood pressure, age and gender ratio, lipid panel parameters and blood glucose, leptin, endothelin-1 and arginine levels. The study was conducted in accordance with the Protocol, lipid panel parameters were determined by conventional methods. Results were calculated by parametric statistic, significance was determined by Student's t-test. As the study results of patients comprised the parameters of one population before and after exposure to a particular agent (atorvastatin, UDCA), the changes were assessed by nonparametric Wilcoxon criterion, i.e. Wilcoxon signed-ranks test for matched pairs (Wst), which is used for moderate amount of samples.

RESULTS AND DISCUSSION

It was established that the levels of blood glucose, endothelin-1 and arginine in dynamics were independent of the chosen lipid-lowering agent. The effect of both drugs on the parameters of lipid panel was an expected one, which was similar both in statin and in the settings when UDCA was used for 4 weeks – there was a significant decrease in atherogenicity of the serum. First of all, it was manifested by a significant reduction in total cholesterol (6.06±0.18 mmol/L to 5.39±0.22 mmol/L, $p<0.001$; and 5.29±0.19 mmol/L to 4.95±0.20 mmol/L, $p<0.01$ by Wst) and low density lipoprotein cholesterol (LDL-C) (3.75±0.20 mmol/L to 3.16±0.23 mmol/L, $p<0.05$ and 3.30±0.19 mmol/L to 2.96±0.18 mmol/L, $p<0.05$ by Wst) in the settings of moderate increase of HDL level ($p>0.05$ in both samples). At the same time, certain peculiarities were found. Thus, concentration of triglycerides decreased significantly as affected by atorvastatin (2.43±0.37 mmol/L to 2.05±0.22 mmol/L, $p<0.05$ by Wst), while lowering of triglycerides was less pronounced in the use of UDCA ($p>0.05$).

Thus, atorvastatin and UDCA reduced total cholesterol by 11.1% and 7.4% (both $p<0.05$), LDL-C –by 15.7% and 10.3% (both $p<0.05$), triglycerides – by 15.6% ($p<0.05$) and 8.6% ($p>0.05$), respectively. That is, the cholesterol-lowering effect of atorvastatin and UDCA was similar, but more pronounced in atorvastatin in relation to triglycerides. The results may indicate that statins prevail in lipid-lowering effect in case of disturbances of glucose metabolism, which is characterised by dyslipidemia with high level of triglycerides [9-11].

Cholesterol-lowering effect and normalization of lipid metabolism as affected by UDCA result from the decrease in the absorption of cholesterol in the intestines, inhibition of cholesterol synthesis in the liver, activation of cholesterol excretion into the bile and increased excretion of very low density lipoproteins [6, 7]. While these effects are generally known, they do not receive enough attention in the clinical picture [5]. It was described that UDCA also activates several mechanisms of lipid utilization, through the stimulation of farnesoid-X- receptor alpha: increase in the number of peroxisome proliferator-activated receptors (PPAR) and the number of tissue lipoprotein receptors to very low density lipoproteins, plasma lipoprotein lipase activation. Furthermore, UDCA forms liquid crystals in the intestines with cholesterol molecules preventing their absorption [1, 2, 8, 9]. First hypercholesteraemic action of UDCA was described about fifteen years ago by a group of researchers supervised by R. Poupon. Therefore, our results allow us to recommend UDCA as it normalizer of lipid metabolism, especially for hypertensive and overweight patients [3, 7, 11].

An important problem of treatment of hypertensive and overweight/obese patients is correction of hyperleptinemia, as elevated levels of leptin are associated with an increased risk of myocardial infarction and stroke in men and women independent of other major cardiovascular risk factors [3, 4, 7]. We studied leptin adipocytokine concentration dur-

ing the month of therapy with atorvastatin or UDCA and revealed that there is a difference in drug effects [2, 10-12]. Thus, the level of leptin as affected by atorvastatin decreased by 6.6% (240.2±27.3 ng/ml to 224.3±27.5 ng/ml), but the difference did not reach its significance ($p>0.05$), where as the reduction was more significant inpatients taking UDCA– 26.5% (225.48±32.28 ng/ml to 165.6±27.35 ng/ml, $p<0.05$ by Wst). Therefore, hypoleptinemic effect of atorvastatin and UDCA was similar, but significantly expressed only in UDCA (fig 1).

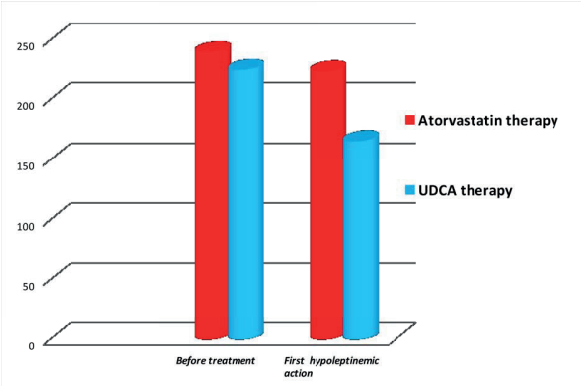

Fig. 1. Leptin concentration in hypertensive patients with obesity after 4 weeks of therapy with atorvastatin and UDCA

Normalizing effect of atorvastatin and UDCA on production of leptin has not been described; however, we believe it is carried out by the mechanisms of reducing the production of biologically active substances [7-9]. UDCA has a more pronounced effect through mechanisms of stabilization of membranes and restriction of oxidative stress due to increased levels of glutathione [7, 9] and through detergent effect on lipid components [10], membranes of mitochondria and endoplasmic reticulum [8, 9, 11]. Since chronic hyperleptinemia increases blood pressure resulting from the damage of depressor mechanisms and hyperproduction of endothelin-1, a vasoconstrictor that contributes to vascular remodelling, it means hyperleptinemic properties of UDCA, which we found, are an important aspect of the clinical use of the drug in the treatment of cardiac patients with overweight and obesity.

Determined correlation between leptin concentration after atorvastatin and arginine levels ($r=0.45$, $p<0.05$) is also considered to be important; however, its level decreased only slightly during treatment (108.2±6.0 mcmol/L to 97.1±6.8 mcmol/L, $p>0.05$). As arginine is a substrate of nitric oxide vasodilator synthesis, promotes membrane depolarization of endothelial cells, inhibits lipid peroxidation, regulates glucose metabolism and has antithrombotic effect, it suggests that through such connection leptin can also indirectly influence these processes that can be stimulated by atorvastatin but not UDCA, under administration of which such association was absent.

CONCLUSION

Adding atorvastatin or UDCA to conventional antihypertensive treatment for 4 weeks resulted in a significant decrease in blood atherogenicity with a decrease in total cholesterol and LDL-C, which was more pronounced in statin due to additional lowering of triglycerides and lowering of elevated leptin levels, which was more pronounced as affected by ursodeoxycholic acid. Therefore, it is better to begin the correction of metabolic disorders with UDCA in overweight or obese patients, while statin should be administered in the settings of related disorders of carbohydrate metabolism. It is perspective to study the impact of all drugs on the synthesis of adipocytokinesin patients with cardiovascular damage in terms of correction.

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