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SEARCH FOR A WAY TO IMPROVE THE SERUM ALBUMIN BINDING FUNCTION AND THE FUNCTIONAL STATE OF THE LIVER WHEN HYPERTENSION COMBINED WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Summary. Recently, there has been a significant increase in interest in research on hypertension (HT), primarily due to its high prevalence. The interest in studying this problem is also exacerbated by the often insufficient effectiveness of existing treatments. The effect of

concomitant pathologies on HT, in particular non-alcoholic fatty liver disease (NAFLD), remains poorly understood.

The aim of the study – to evaluate the changes in the serum albumin binding function (SABF) and its relationship with the biochemical parameters of the blood when HT and HT combined with NAFLD and to suggest ways of medical correction of the detected disorders.

Material and methods. 76 individuals with stage 2 HT with degree 2–3 arterial hypertension were examined. They were divided into two groups. Group 1 included 28 patients with HT without concomitant diseases who received basic hypertension therapy, and group 2 included patients with concomitant NAFLD. The latter in turn was divided into two subgroups: 2a – 27 patients who in addition to basic HT therapy received additional Antral hepatoprotector 200 mg three times a day for 2 months, and 2b – 21 patients who received only basic HT therapy. All of them underwent a standard clinical examination, as well as SABF, protein fractions, and liver function indicators. The comparison group consisted of 25 healthy individuals, comparable in age and sex.

Results and Discussion. Patients in group 1 showed moderate changes in the functional state of the liver, but they did not exceed the norm, patients in group 2 – a significant decrease in SABF, as well as protein metabolism (decrease in total protein, albumin, albumin-globulin ratio and increase globulins) and liver function (increased activity of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltranspeptidase, thymol levels, alkaline phosphatase and total bilirubin). After treatment, the majority of patients in subgroup 2 had a statistically significant increase in SABF and a quantitative improvement in protein fractions and functional state of the liver. In subgroup 2-b, where hepatoprotective treatment was not performed, significant changes in most indicators did not occur. The results may be related to the positive effect of the drug on the liver, which leads to improved functional status of hepatocytes and their protein-synthesizing ability. In subgroup 2 b, where hepatoprotective treatment was not performed, significant changes in most indicators did not occur. The results may be related to the positive effect of the drug on the liver leading to improved functional status of hepatocytes and their protein-synthesizing ability.

Conclusions. Changes of the functional state of the liver are observed when HT without concomitant pathology. HT with NAFLD is accompanied by a significant decrease in SABF, changes in protein metabolism and the functional state of the liver. Prescribing Antral to such patients helps to increase SABF, normalize protein metabolism and improve the functional state of the liver.

KEY WORDS: hypertension; non-alcoholic fatty liver disease; serum albumin binding function; Antral; blood proteins; functional state of the liver.

Introduction . Hypertension (HT) remains one of the most common pathological conditions. According to some estimates, it affects about one billion people in the world [1]. In Ukraine, its prevalence covers about 30 % of the adult population [2]. Undoubtedly, this incidence leads to appropriate research. HT can cause the development of many complications that significantly impair the quality of life, and often disablement and even disability [2]. Recently, significant progress has been made in understanding the mechanisms of development of this disease, as well as in the treatment and prevention. However, despite significant advances in science, many aspects of the disease remain unexplored.

A special role in the course of HT belongs to comorbid states [3]. The understanding of impact of various liver diseases on it is of great interest. One of these diseases is non-alcoholic fatty liver disease (ALD), which is found in about 30 % of patients with hypertension [4]. Due to the modern way of life, NAFLD is becoming more common and causes significant liver dysfunction, which can have a graet impact on the pathogenesis of HT. Its protein-synthesizing function, in particular – the ability to produce albumin may decrease along with many disorders of the functional state of the liver [5].

Due to the structure, serum albumin regulates colloid osmotic pressure in blood plasma and other biological fluids, performs a transport function, having the ability to bind to fatty acids, hormones, nitric oxide, calcium and chlorine ions [6]. In addition, albumin transports many synthetic drugs, acts as an antioxidant, is a modulator of inflammation, removes exotoxins and endotoxins, has an effect on the coagulation hemostasis system [7].

Recently, the study of the serum albumin binding function (SABF) in various diseases is of great interest [8, 9]. Violation of SABF can reduce the effectiveness of drug therapies, due to the ability of albumin to bind to a large number of endogenous substances, as well as many drugs [10].

Studying the effects of HT combined with NAFLD on SABF will help to understand how to correct these processes and minimize the detrimental effects on the body of albumin dysfunction.

The aim of the study – to evaluate the changes in SABF and its relationship with the biochemical parameters of the blood in HT and HT combined with NAFLD and to suggest ways of medical correction of the detected disorders

Research methods. The study involved patients with stage 2 HT with degree 2–3 arterial hypertension in combination with diastolic heart failure FC I-III according to NYHA. Among the patients, 28 patients with HT without concomitant pathology (12 men and 16 women), aged 45–76, mean age (60.71±1.95) (group 1) were identified. Group 2 consisted of 48 patients (21 men and 27 women) who were diagnosed with HT with concomitant NAFLD, aged 46–78 years, mean age (64.68±1.07). It, in turn, was divided into two subgroups, subgroup 2a (27 patients) received basic HT therapy and additionally Antral 200 mg 3 times a day for 60 days, subgroup 2b (21 patients) – only basic HT therapy. The control group consisted of 25 healthy individuals of the same age and sex.

The duration of HT in patients ranged from 6 to 25 years. The study did not include patients with symptomatic hypertension, people who drink alcohol (more than 40 ml of ethanol per week for men and 20 ml for women), as well as patients who had at the time of examination or history of acute coronary syndrome, acute disorders of cerebral circulation, cancer, viral, drug and autoimmune hepatitis, mental disorders.

All patients received treatment according to the criteria of the unified protocol of medical care for patients with hypertension (Order of the Ministry of Health of Ukraine of May 24, 2012 No. 384) and the recommendations of the European Association of Cardiologists (ESC).

The diagnosis of NAFLD was established in accordance with the recommendations of the unified clinical protocol of primary, secondary (specialized) medical care "Non-alcoholic steatohepatitis" (Order of the Ministry of Health of Ukraine No. 826 of November 6, 2014), as well as the recommendations of the European Association for the Study of the Liver (EASL).

The functional state of the liver was examined by sonoelastography on the Ultima SM-30, SWEI method with determination of liver parenchymal stiffness (LPS), which averaged 8.42 kPA in patients with NAFLD.

All examined were determined SABF by the method of S. I. Chager [10]. The content of total protein, albumin, globulins, albumin-globulin coefficient, alanine aminotransferase (ALT) activity, aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), thymol test (TT), alkaline phosphatase (ALP) and total bilirubin were studied by biochemical methods.

Statistical analysis of the results was performed using the Statistica 10 software package and Microsoft Excel. The arithmetic mean (M) and its error (m) were calculated. The reliability of changes in the mean values of the results of the study between the groups was determined by the Mann-Whitney test.

Results and discussion. The analysis of laboratory parameters of SABF and protein fractions and indicators of the liver function in patients with HT without liver damage and with its damage was performed. As follows from the Table 1, the level of SABF in the group of patients with HT without concomitant pathology was slightly reduced compared to the control group – by 5.4 % ($p > 0.05$).

There were also some changes in protein metabolism, which, however, were statistically insignificant compared with the control group: a decrease in total protein concentration by 3.2 %, albumin fractions by 4.0 % and globulins by 2.5 % ($p > 0.05$). As for the albumin-globulin ratio, it did not differ in value from the control group, was 1.5 % less ($p>0.05$). The activity of aminotransferases was slightly increased compared to the control group: the level of ALT by 3.7 % ($p > 0.05$), and AST – by 6.4 % ($p>0.05$).

The change in GGT and TP was larger, which increased by 54.3 % ($p<0.01$) and 34.6 % ($p <0.001$), respectively. Thus, their change compared to the control group was significant, while the result was within physiological norms. There was also a significant difference in the activity of ALP of bloodserum, which was 17.0 % ($p <0.05$) was higher than the control level. The bilirubin index also increased by 36.5 % ($p <0.001$). However, these indicators were within the physiological norm.

The level of SABF in the group of patients with HT combined with NAFLD in subgroup 2a before correction was reduced relative to the control group by 14.6 % ($p<0.001$). There were also significant changes in protein metabolism: a decrease in total protein concentration by 13.7 % ($p<0.01$), albumin fraction by 9.4 % ($p <0.01$) and a tendency to increase the content of globulins – by 11.1 % ($p > 0.05$). The albumin-globulin ratio did not differ significantly from the control group.

There were pronounced changes in liver function. In particular, the activity of aminotransferases exceeded the indicators of the control group: AST – 2 times ($p <0.001$), ALT – 1.75 times ($p <0.001$). The largest was the change in GGT activity, which was increased by 3.21 times compared to the control group ($p <0.001$). In addition, there was a significant increase in TT, ALP levels and total bilirubin – by 40.0 % ($p <0.001$), 81.6 % ($p<0.001$) and 49.0 % ($p <0.001$), respectively.

In subgroup 2b there were changes similar to the previous subgroup in almost all indicators for the control group. No statistically significant difference was found between these two subgroups.

Table 1. Changes in biochemical parameters in patients with hypertension combined with NAFLD and their correction (M ± m)

Indicator	Control group (n=25)	Group 1 (n=28)	Group 2 (n=48)			
			Subgroup 2a (n=27)		Subgroup 2b (n=21)	
			Before treatment	After treatment	Before treatment	After treatment
SABF, g/l	48.44 ± 1.33	45.85 ± 1.053 p_1 >0.05	41.35 ± 0.649 p_1<0.001	46.05 ± 0.849 p_1>0.05	41.02 ± 0.702 p_1<0.001 p_2>0.05	40.77 ± 0.715 p_1<0.001 p_3<0.001
Total protein, g/l	74.4 ± 1.441	72.03 ± 1.24 p_1 >0.05	67.43 ± 1.466 p_1<0.01	73.47 ± 1.028 p_1>0.05	67.69 ± 1.569 p_1<0.01 p_2>0.05	68.25 ± 1.563 p_1<0.05 p_3<0.05
Albumin concentration, %	59.14 ± 1.997	56.78 ± 2.09 p_1>0.05	51.07 ± 1.003 p_1<0.01	56.12 ± 1.044 p_1>0.05	51.2 ± 1.237 p_1<0.01 p_2>0.05	51.54 ± 1.187 p_1<0.01 p_3<0.05
Concentration of globulins, %	39.68 ± 1.997	38.7 ± 2.13 p_1>0.05	44.1 ± 0.969 p_1>0.05	39.66 ± 1.062 p_1>0.05	44.02 ± 1.226 p_1>0.05 p_2>0.05	43.75 ± 1.224 p_1>0.05 p_3<0.05
Albumino-globulin ratio	1.49 ± 0.175	1.47 ± 0.176 p_1>0.05	1.16 ± 0.05 p_1>0.05	1.42 ± 0.069 p_1>0.05	1.17 ± 0.064 p_1>0.05 p_2>0.05	1.18 ± 0.064 p_1>0.05 p_3<0.05
ALT, U/l	25.26 ± 1.948	24.32 ± 0.781 p_1>0.05	44.22 ± 0.537 p_1<0.001	28.9 ± 1.663 p_1>0.05	44.38 ± 0.613 p_1<0.01 p_2>0.05	44.73 ± 0.692 p_1<0.001 p_3<0.001
AST, U/l	22.86 ± 1.285	24.32 ± 0.448 p_1>0.05	46.51 ± 2.16 p_1<0.001	30.11 ± 1.42 p_1<0.01	46.31 ± 2.166 p_1<0.01 p_2>0.05	45.83 ± 2.214 p_1<0.001 p_3<0.001
GGT, U/l	12.23 ± 1.686	18.88 ± 0.729 p_1 <0.01	39.31 ± 0.316 p_1<0.001	35.71 ± 1.765 p_1<0.001	39.5 ± 0.363 p_1<0.01 p_2>0.05	39.32 ± 0.406 p_1<0.001 p_3>0.05
TT, U/l	2,79 ± 0.126	3.76 ± 0.194 p_1<0.001	3.91 ± 0.068 p_1<0.001	3.56 ± 0.167 p_1<0.01	3.87 ± 0.059 p_1<0.01 p_2>0.05	3.59 ± 0.077 p_1<0.001 p_3>0.05
ALP, U/l	54.3 ± 1.702	63.54 ± 3.409 p_1<0.05	98.59 ± 2.007 p_1<0.001	87.86 ± 1.41 p_1<0.001	100.91 ± 2.554 p_1<0.01 p_2>0.05	98.67 ± 2.632 p_1<0.001 p_3<0.001
Total bilirubin, mmol/l	12.36 ± 0.929	16.87 ± 0.597 p_1<0.001	18.43 ± 0.418 p_1<0.001	17.12 ± 0.498 p_1<0.001	18.89 ± 0.5 p_1<0.01 p_2>0.05	18.55 ± 0.596 p_1<0.001 p_3>0.05

Notes:
p_1 – reliability of difference with respect to the control group;
p_2 – reliability of difference between groups before treatment;
p_3 – reliability of difference between groups after treatment.

In the group of patients with HT combined with NAFLD after correction with Antral there was a statistically significant increase in SABF compared with the subgroup without correction – by 13.0 % (p <0.001). Significant changes also occurred in protein metabolism.

Thus, the level of total protein increased by 7.6 % ($p < 0.05$) and the content of albumin by 8.9 % ($p < 0.05$), while the level of globulins, by contrast, decreased by 9.3 % ($p > 0.05$), respectively, significantly increased and albumin-globulin ratio – by 20.1 % ($p < 0.05$). In terms of total protein and globulins, the results almost reached the level of control.

Significant differences compared with the subgroup without correction were also noted in terms of liver function. The most significant changes occurred with the activity of aminotransferases, respectively, the ALT was lower by 35.4 % ($p < 0.001$), and AST – by 34.3% ($p < 0.001$). ALP activity decreased less significantly, but also reliably – by 11.0 % ($p < 0.05$). Regarding the TTindicator, no significant differences were found, but compared to the data before the correction, this indicator decreased by 8.9 % against the background of Antral ($p < 0.05$). There were also changes in total bilirubin. It was lower by 7.8 % compared with the subgroup without treatment ($p > 0.05$). However, the difference from the level before treatment was significant – 7.1 % ($p < 0.05$). The GGT content also decreased slightly – by 9.2 % ($p > 0.05$).

In the subgroup without correction after 60 days there were no significant changes in any indicator, except for TT, which was lower than the initial indicator by 7.2 % ($p < 0.05$).

As we can see, HT without concomitant pathology is not accompanied by significant changes in SABF, but there were changes in some indicators of liver function (GGT, TT, ALP and total bilirubin).

The results also indicate signs of decreased albumin transport capacity in patients with concomitant NAFLD, as well as liver dysfunction, most likely due to hepatocyte damage on the background of other metabolic changes. Restoration of SABF and liver function indicators occured against the background of taking Antral.

This effect of Antral on the liver can be explained by its anti-inflammatory effect due to its ability to stabilize lysosomal membranes, reduce cell migration to the site of inflammation, reduce the synthesis of prostaglandins and other inflammatory mediators, and reducing the degree of damage to the components of the nucleus of hepatocytes and Kupffer cells, which, in turn, stimulates the recovery of liver tissue [11, 12].

The drug also has the ability to activate the restoration of tissue respiration and oxidative phosphorylation by activating the cytochrome system, thereby stimulating the monooxygenase system of liver cells [13]. Antral, in addition, helps to suppress the processes of lipid peroxidation of tissues, as well as stimulates the body's antioxidant systems [14], thereby normalizing protein metabolism and other body systems.

Conclusions:

1. Stage 2 HT and degree 2–3 of hypertension without concomitant pathology is accompanied by an increase in GGT, TT, ALP and total serum bilirubin, which, however, do not exceed physiological norms.
2. When HT is combined with NAFLD, SABF disorders and significant deviations in protein metabolism occur, including a decrease in total serum protein, albumin and albumin-globulin ratio, and a simultaneous increase in globulin content. There are also typical changes that are characteristic of liver damage, namely: increased activity of AST, ALT, GGT, ALP levels of TT and total bilirubin.
3. Under the action of Antral in the conditions of stage 2 HT with degree 2–3 hypertension in combination with NAFLD there is a significant improvement in most of the studied indicators. In particular, the normalization of SABF, total protein, albumin, albumin-globulin ratio, which practically reached the level of control, as well as the activities of ALT, AST and ALP, which are significantly closer to those in healthy individuals, and ALT levels were normalized.

Prospects for research. In the future, it is planned to find out the relationship between changes in SABF when HT with other comorbid diseases, as well as to continue to improve the drug correction of these changes.

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