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DRUG THERAPY FOR PROTEIN COMPOSITION CHANGES OF BLOOD IN HYPERTENSION AND IN CASES OF COMORBIDITY

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Background. *The binding function of serum albumin (BFSA) and its changes in various diseases in recent years are of interest to researchers. Hypertension (HT) in combination with comorbidities, including non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus (DM) can contribute to BFSA.*

Objective. *The aim of this study is to evaluate the relationship between quantitative changes in BFSA, protein fractions and indicators of endogenous intoxication (EI) in HT in combination with NASH and type 2 diabetes and to suggest drug therapy of the disorders revealed.*

Methods. *123 patients with stage 2 HT and degree 2-3 arterial hypertension were examined; they were divided into three groups: group 1 included 28 patients without concomitant diseases, 2 – 48 patients with concomitant NASH, 3 – 47 patients with NASH and type 2 diabetes. Groups 3 and 4 were divided into two subgroups (A and B): patients of the subgroup A received basic HT therapy and additionally Antral® 200 mg 3 times a day for 60 days, B – only basic HT therapy. All patients underwent a standard clinical examination, as well as for BFSA, total protein, albumin, globulins and albumin-globulin ratio, medium mass molecules (MMM) at 280 and 254 nm and erythrocyte intoxication index (EII). The comparison group consisted of 25 healthy individuals.*

Results. *It was found out that Antral® in patients with HT in combination with NASH and with NASH and type 2 diabetes with a statistically significant decrease in BFSA, total protein and albumin, as well as with increased indicators of EI (MSM_{254}, MSM_{280} and EII) caused significant improvement in BFSA, increase of total protein, serum albumin, reduce of MSM_{254}, MSM_{280}, EII and strengthening of all correlations.*

Conclusions. *Antral® therapy in patients with HT in combination with NASH as well as NASH and type 2 diabetes causes significant increase in BFSA, serum protein fractions and decreases EI.*

KEYWORDS: hypertension; non-alcoholic steatohepatitis; type 2 diabetes mellitus; binding function of serum albumin; Antral®.

Introduction

One of the important factors in the normal functioning of all organs and systems of the human body is the stability of protein content and their role in biological fluids. Albumin as the most common protein in the body is of particular interest of all the protein fractions. Normally, its content is about 55% of all proteins, so the importance of changing its content and function is not overestimated [1, 2]. The structure of the albumin molecule determines a number of its properties; the binding function of serum albumin (BFSA) is among them; BFSA is the ability to bind and transport a significant amount of biological substances of endogenous and exogenous nature: fatty acids, nitric oxide, chlorine and calcium ions, toxins, synthetic drugs and others. Violation of BFSA can have a negative impact on the body directly and reduce the effectiveness of drug treatment in various pathological conditions [3].

Endogenous intoxication (EI) is an important indicator of homeostasis. Development of EI indicates the presence of a pathological process in the body. Dysfunction of serum albumin, BFSA in particular, may directly affect the increase of EI. In diseases that are accompanied by endotoxicosis, a significant number of metabolites accumulate in the blood; most of them belong to the medium mass molecules (MMM) [4]. The accumulation of MMM as a marker of endotoxemia is a sign of intensification of the pathological process. In addition to MMM, another important indicator of EI is the erythrocyte intoxication index (EII), which evidences the permeability of erythrocyte membranes and may indicate signs of endotoxic damage to organs and tissues [5].

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Disorders of protein metabolism with the development of EI can be caused by many diseases. However, little is known about the possibility of such changes in cases of hypertension (HT) and related comorbid conditions, in particular when combined with non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus (DM) – a very common disease that causes systemic adverse effects on the whole body [6, 7]. In addition, they are associated with long-term use of various drugs that are mainly metabolized in the liver and can cause damage to this organ, which is the main source of protein synthesis and in particular albumin [8, 9].

Methods

The study included 123 patients with stage 2 HT and degree 2-3 hypertension in combination with diastolic heart failure FC 1–3 according to the NYHA. They were divided into three groups. Group 1 – 28 patients with HT without concomitant pathology (12 men and 16 women) aged 45-76, mean age (60.71±1.95) years. Group 2 involved 48 patients (21 men and 27 women) diagnosed with HT and concomitant NASH, aged 46-78, mean age (64.68±1.07) years. It was divided into two subgroups: 2A (27 patients) – undergoing basic HT therapy and additionally Antral® 200 mg 3 times a day for 60 days, 2B (21 patients) – only basic HT therapy.

Group 3 included 47 patients (21 men and 26 women) with HT combined with concomitant NASH and type 2 diabetes in the stage of subcompensation, aged 58-82, the average age was (68.72±0.86) years. It was also divided into two subgroups: 3A (27 patients) – in addition to basic treatment of HT and type 2 diabetes taking Antral® 200 mg 3 times a day for 60 days, 3B (20 patients) – only basic HT therapy. The comparison group consisted of 25 healthy individuals, comparable in age and sex (control group).

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 those 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.

The diagnosis of NASH was established according to 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, dated November 6, 2014) and 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 device by the SWEI method to determine the stiffness of the liver parenchyma, which averaged 8.42 kPA in the patients with NASH.

All patients were determined BFSA by the method of S. I. Chager, the content of MMM at wavelengths of 280 and 254 nm and EII by the method of N. I. Gabrielyan [10]. The content of total protein, albumin, globulins in the blood serum was studied by bochemical methods and the albumin-globulin coefficient was calculated.

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

Patients with type 2 diabetes were treated according to the unified clinical protocol of primary, secondary (specialized) medical care "Diabetes mellitus, type 2" (Order of the Ministry of Health of Ukraine No. 1118, dated December 21, 2012).

Analysis of the obtained digital data was performed by the method of parametric Pearson correlation. The correlation dependence was considered strong at r=0.7-0.99, medium at r=0.3-0.69, and weak at r=0.01-0.29. Statistica 10 and Microsoft Excel software were used.

Results

In the control group (almost healthy individuals) indicators of BFSA, protein fractions and EI were within norm. The analysis of the correlation of BFSA with serum proteins showed a positive relationship of medium strength with the level of albumin ($r=0.68$, $p<0.05$), total protein ($r=0.52$, $p<0.05$) and albumin-globulin ratio ($r=0.69$, $p<0.05$), as well as a negative relationship of medium strength with the content of globulins ($r=-0.68$, $p<0.05$). No significant correlations were observed between BFSA and endotoxicosis indicators ($p>0.05$) (Table 1).

In patients with HT without concomitant pathology (group 1), the values of BFSA and protein fractions were close to those in almost healthy individuals. At the same time, there was a significant increase in EII and MMM_{280} concentrations ($p<0.05$). The analysis showed a positive relationship between the average

strength of BFSA with the level of albumin (r=0.45, p<0.05), total protein (r=0.38, p<0.05) and albumin-globulin coefficient (r=0,49, p<0,05) and a negative relationship of medium strength with the content of globulins (r=-0,45, p<0,05). No significant correlations of EI indicators with the content of BFSA were observed.

In patients with HT in combination with NASH (subgroup 2A) before drug therapy, a significant decrease in BFSA, total protein and serum albumin was found. In addition, there was an increase in all studied indicators of EI (p<0.05). The presence of positive relationships of medium strength of BFSA with the content of total protein (r=0.69, p<0.05), albumin (r=0.63, p<0.05) and with albumin-globulin ratio (r=0.62, p<0.05), as well as a negative relationship of medium strength with the level of globulins (r=-0.6, p<0.05). At the same time, there were significant negative correlations between the mean strength of BFSA and EII (r=-0.46, p<0.05), the concentration of MMM_{254} (r=-0.48, p<0.05) and MMM_{280} (r=-0.41, p<0.05).

Similar changes were observed in the subgroup 2B, but the strength of the relationship between BFSA and albumin, globulins and albumin-globulin ratio were slightly higher than in the previous subgroup. Regarding the level of total protein, the correlation was almost the same. EI relationships in this subgroup were also similar, but the strength of the correlation of BFSA with MMM_{254} was slightly higher, and with EII, on the contrary, lower.

In patients with HT combined with NASH and type 2 diabetes (subgroup 3A) before correction there was even more pronounced decrease in BFSA, total protein, albumin, and albumin-globulin ratio. At the same time, there was a significant increase in all studied indicators of EI (p<0.05). The presence of a positive correlation between the average strength of BFSA and the level of total protein (r=0.63, p<0.05), albumin (r=0.54, p<0.05) and albumin-globulin coefficient (r=0.56, p<0.05), as well as a negative relationship of medium strength with the level of globulins (r=-0.56, p<0.05). There was also a negative correlation of the average strength of BFSA with EII (r=-0.63, p<0.05) and MMM_{254} (r=-0.60, p<0.05) and strong with MMM_{280} (r=-0,70, p<0.05). Similar changes were observed in the subgroup 3B, but there was an increase in the negative correlation with MMM_{254} compare to the previous subgroup.

Normalization of BFSA, total protein, albumin and albumin-globulin ratio was proved to be associated with Antral® in patients of the subgroup 2A. Also, a normalization of the concentrations of MMM_{254} and MMM_{280} and a significant decrease in the level of EII compare to subgroup 2B (p<0.05) were evidenced. A strong positive relationship of BFSA with the level of total protein (r=0.84, p<0.05) was noted

Table 1. Correlation coefficients between BFSA and indicators of protein composition of blood and EI in patients with HT combined with NASH and their correction by Antral®

Indicator	Control group (n=25)	Group I (n=28)	Group II (n=48)			
			Subgroup 2A (n=27)		Subgroup 2B (n=21)	
			Before treatment	After treatment	Before treatment	After treatment
Total protein	0.52 p<0.05	0.38 p<0.05	0.69 p<0.05	0.84 p<0.05	0.72 p<0.05	0.68 p<0.05
Albumin concentration	0.68 p<0.05	0.45 p<0.05	0.63 p<0.05	0.70 p<0.05	0.73 p<0.05	0.70 p<0.05
Concentration of globulins	-0.68 p<0.05	-0.44 p<0.05	-0.60 p<0.05	-0.66 p<0.05	-0.73 p<0.05	-0.74 p<0.05
Albumin-globulin ratio	0.69 p<0.05	0.49 p<0.05	0.62 p<0.05	0.67 p<0.05	0,71 p<0,05	0.72 p<0.05
EII	-0.07 p>0.05	-0.33 p>0.05	-0.46 p<0.05	-0.62 p<0.05	-0,31 p>0,05	-0.19 p>0.05
MMM254	-0.14 p>0.05	0.01 p>0.05	-0.48 p<0.05	-0.76 p<0.05	-0,62 p<0,05	-0.65 p<0.05
MMM280	-0.29 p>0.05	-0.07 p>0.05	-0.41 p<0.05	-0.64 p<0.05	-0,38 p>0,05	-0.25 p>0.05

Note. p – statistical significance of the correlation coefficient (p<0.05).

in association with Antral®, as well as a positive relationship of medium strength with albumin content (r=0.70, p<0.05) and negative medium strength with globulin content (r=-0.66, p<0.05). Compare to the subgroup without Antral® correction, the correlation of BFSA with the level of total protein was stronger, and with the level of globulins, on the contrary, slightly lower. In addition, negative correlations were found with EII (r=-0.62, p<0.05) and MMM_{280} (r=-0.64, p<0.05); compare to the patients undergoing no treatment it changed from negative weak to medium strength, as well as a negative relationship with the content of MMM_{254} (r=-0.76, p<0.05), which changed from medium strength to strong. In subgroup 2B, all indicators did not change significantly.

The patients in subgroup 3A had a statistically significant increase in BFSA, total protein and serum albumin during Antral® treatment. There was also a significant reduction in all indicators of endotoxicosis. An analysis of BFSA correlations revealed that statistically significant strong correlations with all protein fractions occurred in cases of Antral® treatment. Thus, there was a positive relationship with the level of total protein (r=0.76, p<0.05), albumin content (r=0.81, p<0.05) and albumin-globulin ratio (r=0.78, p<0.05), as well as negative – with the content of globulins (r=-0.81, p<0.05). Analysis of the relationship of BFSA with EI showed a strong negative correlation with the level of EII (r=-0.74, p<0.05), which was stronger than in the subgroup without correction, where it was moderate. In addition, medium-strength negative correlations with the content of MMM_{254} (r=-0.69, p<0.05) and MMM_{280} (r=-0.69, p<0.05) were revealed, which compare to the subgroup without treatment were also stronger, but not significantly. The correlations in the subgroup 3B did not change significantly.

Discussion

Therefore, in patients with HT and NASH and with HT combined with NASH and type 2 diabetes, there is a statistically significant correlation of BFSA with EII, MMM254 and MMM280, which may indicate development of endotoxicosis, not excluded due to liver cell damage and systemic pathological effects of comorbid diseases [12, 13].

Since the liver is the main organ that metabolizes many toxemia products, most of which belong to medium molecular weight peptides, damage to this organ leads to an increase in MMM. In addition, in cases of development of liver disease the accumulation of free radical forms of oxygen, which in addition to promoting the increase of EI products, cause damage to cell membranes that is manifested by an increase in EII. As we can see, the changes in protein composition and endotoxicosis and

Table 2. Correlation coefficients between BFSA and indicators of protein composition of blood and EI in the patients with HT combined with NASH and type 2 diabetes and their correction by Antral®

Indicator	Control group (n=25)	Group III (n=47)			
		Subgroup 3A (n=27)		Subgroup 3B (n=20)	
		Before treatment	After treatment	Before treatment	After treatment
Total protein	0.52 p<0.05	0.63 p<0.05	0.76 p<0.05	0.69 p<0.05	0.62 p<0.05
Albumin concentration	0.68 p<0.05	0.54 p<0.05	0.81 p<0.05	0.50 p<0.05	0.55 p<0.05
Concentration of globulins	-0.68 p<0.05	-0.56 p<0.05	-0.81 p<0.05	-0.51 p<0.05	-0.54 p<0.05
Albumin-globulin ratio	0.69 p<0.05	0.56 p<0.05	0.78 p<0.05	0.53 p<0.05	0.58 p<0.05
EII	-0.07 p>0.05	-0.63 p<0.05	-0.74 p<0.05	-0.65 p<0.05	-0.65 p<0.05
MMM254	-0.14 p>0.05	-0.60 p<0.05	-0.69 p<0.05	-0.68 p<0.05	-0.63 p<0.05
MMM280	-0.29 p>0.05	-0.70 p<0.05	-0.69 p<0.05	-0.64 p<0.05	-0.60 p<0.05

Note. p – statistical significance of the correlation coefficient (p<0.05).

their relationship with BFSA are more pronounced in patients with HT combined with NASH and type 2 diabetes, which can also be explained by the processes of glycolysis of proteins, and in particular albumin, which has a direct effect on BFSA. The severity of EI syndrome in these cases may be a marker of the severity of the pathological process [14].

Antral® treatment improves BFSA and serum protein composition, as well as strengthens significant correlations with all studied indicators of protein fractions and EI. These positive changes can be explained by the anti-inflammatory and detoxifying effects of Antral® on the whole body and in particular on the function of the liver as the main protein-synthesizing organ [15, 16]. The drug has a positive effect on hepatocytes by stabilizing cell membranes and lysosomal membranes and increasing the synthesis of phospholipids. By improving the energy supply and functioning of monooxygenase systems, Antral® restores the antitoxic effect of the liver. Due to its angioprotective action by improving capillary hemoperfusion, this drug can improve microcirculation in the liver and other organs, which has a positive effect on the whole body [17].

Conclusions

In HT without concomitant diseases an increase in EII and MMM_{280} and a decrease in the strength of correlations of BFSA with the concentration of protein fractions in serum take place.

In the conditions of HT combined with NASH as well as HT with NASH and type 2 diabetes a decrease in BFSA, total protein and albumin content and increase in EI, as well as a decrease in the correlation of BFSA with albumin, globulin and albumin levels, globulin coefficient and strength increase – with the content of total protein and EI, are evidenced.

Treatment of the patients with HT with concomitant NASH with Antral® normalizes BFSA and the content of total protein and albumin, as well as MMM_{254} and MMM_{280} and significantly decreases EII. In cases of HT with NASH and type 2 diabetes a significant increase in BFSA, the content of total protein and albumin in the serum and a decrease in EI take place with the drug. All studied correlations of BFSA are enhanced under the action of the drug in both comorbid states.

Prospects for further research. In the future, it is planned to identify other effects on the changes of BFSA and development of EI in comorbid diseases associated with HT, as well as to implement the data into clinical practice.

Conflict of Interests

Authors declare no conflict of interest.

Author's Contributions

Yurii R. Dzordzo – conceptualization, methodology, formal analysis, investigation, writing – original draft, writing – reviewing and editing; *Serhiy M. Andreychyn* – data curation, writing – reviewing and editing.

МЕДИКАМЕНТОЗНА КОРЕКЦІЯ ЗМІН БІЛКОВОГО СКЛАДУ КРОВІ ПРИ ГІПЕРТОНІЧНІЙ ХВОРОБІ В УМОВАХ КОМОРБІДНОСТІ

Ю.Р. Дзьордзьо, С.М. Андрейчин

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *Зв'язувальна функція сироваткового альбуміну (ЗФСА) та її зміни при різних захворюваннях в останні роки викликають інтерес у дослідників. Гіпертонічна хвороба (ГХ) при поєднанні з супутніми захворюваннями, зокрема неалкогольним стеатогепатитом (НАСГ) і цукровим діабетом (ЦД) 2-го типу може сприяти порушенню ЗФСА.*

Мета дослідження – *дати оцінку взаємозв'язків кількісних змін ЗФСА, білкових фракцій та показників ендогенної інтоксикації (ЕІ) при ГХ у поєднанні з НАСГ і ЦД 2-го типу та запропонувати медикаментозну корекцію виявлених порушень.*

Методи дослідження. *Обстежено 123 пацієнтів з ГХ II стадії зі ступенем артеріальної гіпертензії 2-3, які були розділені на три групи. До I увійшли 28 осіб без супутніх захворювань, до II – 48 пацієнтів із супутнім НАСГ, до III – 47 осіб із НАСГ і ЦД 2-го типу. II та III групи, своєю чергою були поділені на дві підгрупи (А та Б): хворі підгруп А – отримували базову терапію ГХ та додатково препарат Антраль по 200 мг 3 рази на добу протягом 60 днів, Б – лише базову терапію ГХ. Усі хворі пройшли стандартне клінічне обстеження, а також у них досліджували ЗФСА, вміст загального білка, альбуміну, глобулінів та альбуміно-глобуліновий коефіцієнт, молекули середньої маси (МСМ) при довжині хвилі 280 та 254 нм та еритроцитарний індекс інтоксикації (ЕІІ). Групу порівняння склали 25 практично здорових осіб.*

Результати. *Встановлено, що застосування Антралю у хворих з ГХ у поєднанні з НАСГ та з НАСГ і ЦД 2-го типу на тлі статистично достовірного зниження ЗФСА, вмісту загального білка та альбуміну, а також збільшення показників ЕІ ($МСМ_{254}$, $МСМ_{280}$ та ЕІІ) супроводжується істотним покращенням ЗФСА, зростанням вмісту загального білка, альбуміну, та зниженням – $МСМ_{254}$, $МСМ_{280}$, ЕІІ й посиленням усіх кореляційних зв'язків.*

Висновки. *Лікування Антралем у хворих на ГХ в поєднанні з НАСГ та з НАСГ і ЦД 2-го типу супроводжується істотним підвищенням ЗФСА, вмісту фракцій білка сироватки крові та зниженням показників ЕІ.*

КЛЮЧОВІ СЛОВА: гіпертонічна хвороба, неалкогольний стеатогепатит, цукровий діабет 2-го типу, зв'язувальна функція сироваткового альбуміну, Антраль.

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