ON THE ISSUE OF METABOLIC DISORDERS AND THEIR CORRECTION IN CHRONIC HEPATITIS

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Abstract. *The aim of this study was to examine the state of the antioxidant system in patients with HCV and correction of pathogenetic therapy, taking into account changes in glutathione-dependent enzymes. Materials and methods. The paper presents the results of a survey 83 patients with chronic hepatitis C between the ages of 19 to 55 years, and 20 healthy people with a lack of hepatitis markers. Status of antioxidant protection was measured in terms of the activity of glutathione and glutathione-dependent enzymes: glutathione peroxidase (GP), glutathione reductase (GR), glutathione transferase (GT). Results. The results showed that the examined patients with HCV showed a significant suppression of the activity of glutathione-dependent enzymes and the decrease in total glutathione levels. For the correction of the system used in the preparation of glutathione "Glution" in doses ranging from 600 to 1200 mg per day for 10 days. Conclusion. Research has shown that patients with HCV decreased activity of antioxidant protection. Determine the feasibility of incorporating the complex pathogenetic therapy "Glution" the drug, taking into account the individual levels of glutathione deficiency.*
Keywords: *chronic hepatitis C, glutathione, glutathione-dependent enzymes.*

Relevance. The seriousness of the situation with viral hepatitis C is determined by the high frequency of formation of chronic forms, long-term asymptomatic course, manifestation of the disease in late stages (liver cirrhosis), and association with the development of hepatocellular carcinoma [15, 18, 5, 12, 6]. Antiviral therapy (AVT) is currently the international standard in the treatment of chronic hepatitis C. This is due, first of all, to the proven possibility of eliminating HCV RNA against the background of AVT, observed according to a number of authors in 60-80% of patients [19, 2, 13]. On the other hand, numerous studies have proven the resistance of the hepatitis C virus to AVT with the resumption of replication [14,10]. The development in a number of cases of initial resistance to AVT has also been proven, which currently determines that the patient has no chance of sanitizing the body from the virus and increases the role of pathogenetically oriented therapy, which allows preserving the liver [14,10,6].

Any pathological process, including viral hepatitis, is accompanied by increased formation of free radicals and an associated increase in lipid peroxidation processes, which is accompanied by a violation of the properties of biological membranes and disruption of cell functioning [2, 1]. The main protective function during activation of lipid peroxidation processes is performed by the antioxidant system of cells, the deficiency of which becomes one of the factors activating pro-oxidant reactions in the body. An important component of the antioxidant system is the glutathione-dependent link, which includes glutathione and its dependent enzymes – glutathione peroxidase, glutathione reductase and glutathione transferase [4, 1]. Solving the issue of pathogenesis of morphofunctional preservation of the liver from the position of the state of metabolic adaptation of the body in conditions of chronic hepatitis C will improve the effectiveness of therapy and the quality of life of patients.

The purpose of the study was to study the state of the antioxidant system in patients with chronic hepatitis C and the correction of pathogenetic therapy taking into account changes in glutathione-dependent enzymes.

Materials and methods. 83 patients with CHC in the reactivation stage aged from 19 to 55 years were examined. Of these, there were 30 (36.1%) men and 53 (63.9%) women. The diagnosis was established on the basis of clinical and laboratory data, as well as the results of PCR (HCV RNA) and ELISA (anti-HCV). The control group consisted of 20 practically healthy people with no markers of hepatitis. Patients by virus genotypes were distributed as follows: genotype 1 - in 46 patients (55.4%), genotype 2 - in 15 patients (18.0%), genotype 3 - in 22 patients (26.6%). The duration of the disease ranged from 5 to 15 years.

The state of antioxidant protection was determined by the activity of glutathione and glutathione-dependent enzymes. Total (GS) and reduced (GSH) and oxidized glutathione (GSSG) were determined according to V.G. Chernyshov. [14]. The activity of glutathione-dependent enzymes: glutathione peroxidase (GP), glutathione reductase (GR), glutathine transferase (GT) was determined by the method of S.N. Vlasova et al. [3].

The viral load and genotype of virus C were determined by real-time PCR RotorGene (CorbetResearch, Australia) using Ribosorb-amplification kits (Russia). Pathogenetic therapy included detoxification drugs: saline solution 0.9%, glucose solution 5%, rheosorbilact intravenous drip; hepatoprotective drugs: phosphogliv, essentiale, neo-strongeminophagen, hepa-merz, vitamin complex; choleretic drugs.

The research results were processed using the Statistica 6.0 Microsoft software package and using Student's t-test.

Results obtained and discussions. The results of studies of the levels of glutathione antiperoxide protection showed that in patients with chronic hepatitis C there is a significant disruption of the homeostatic function of the glutathione system. As can be seen from the data presented in table. 1, in the examined patients there is a pronounced decrease in the levels of GS and GSH - almost 2 times, GSSG indicators are 1.6 times lower than those in healthy individuals. Along with a decrease in glutathione levels, the examined patients showed suppression of the activity of glutathione-dependent enzymes. GP activity decreases in relation to healthy individuals by 1.8 times. The activity of HT decreases to the same extent. Significant changes in relation to the indicators of healthy individuals, but to a lesser extent, are also observed in GR activity (Table 1).

Table 1.

Indicators of the antioxidant system in groups of patients with chronic hepatitis C, n=83

Biochemical indicators	healthy, n=20	General group of patients, n=83
GS, μmol/ml.er.	45,3 ± 2,12	23,7±0,45*
GSH, μmol/ml.er.	43,2±2,14	22,2±0,45*
GSSG, μmol/ml.er.	2,15±0,15	1,51±0,04*
GR, μmol/NADPH/min/Hb	2,84±0,13	2,14±0,04*
GP, μmol/GSSG/min/Hb	583,5±28,28	332,3±6,17*
GT, μmol/GSH/min/Hb	2,44±0,11	1,35±0,03*

Note: * - presence of significant differences from the indicators of healthy individuals

The results of the studies led to our interest in the issue of the presence of levels of suppression of glutathione antioxidant defense. Analysis of the data obtained shows that of the three glutathione-dependent enzymes - GR, GP, GT, the GP enzyme is the most consistent in its relationship with the severity of clinical symptoms of intoxication - the leading clinical syndrome in the group of examined patients. Based on the degree of decrease in GP activity, 3 degrees of glutathione deficiency are conventionally distinguished: compensated – a decrease of up to 30% of control indicators, subcompensated – a decrease from 30 to 50% and decompensated – a decrease in GP indicators of more than 50% of control.

Taking into account the identified decrease in the activity of the glutathione system, to correct disorders in the glutathione system, we used “Gluthione” - a drug from Welfarm, produced in Spain, containing GSH. The heterogeneity of patients according to the degree of glutathione deficiency allowed us to divide patients into 3 groups: with a compensated degree of glutathione deficiency (group I), with a subcompensated (group II) and with a decompensated (group III) degree of glutathione deficiency. In each of the groups, we used the drug Gluthione® at a dose of 600 mg in saline solution intravenously for 10 days against the background of detoxification and symptomatic therapy.

During therapy with Gluthione®, a significant ($p<0.05$) increase in GS and GSH indices was noted in relation to both the indices before the start of treatment and the indices after the basic therapy (Table 2). It should be noted that in patients of group I with a compensated degree of glutathione deficiency, by the end of the course of treatment with Gluthione® the level of GP increased significantly ($p<0.05$) and at the same time differed from the indicators of patients who received basic therapy. The level of GH in patients of group I remained at fairly high levels regardless of the therapy. When analyzing these indicators in patients with subcompensated and decompensated glutathione deficiency (group II and III patients), an increase in GS, GSH, GR, and GP was revealed in both patients with subcompensated and decompensated glutathione deficiency, but there was no significant difference from the indicators before treatment. noted.

The results obtained allowed us to conclude that it is possible to achieve satisfactory correction of the LPO/AOS balance with Gluthione® 600 mg only in the group of patients with a compensated degree of glutathione deficiency.

Table 2.

The effectiveness of a 10-day course of treatment with Gluthione® (600 mg per day) in groups of chronic hepatitis C patients with varying degrees of glutathione system deficiency

Biochemical indicators	Healthy	Groups of examined patients							
		Stages of glutathione deficiency							
		Group I				Group II			
		Compensation				Subcompensation			
		Basic therapy		10-day treatment with Gluthione 600 mg		Basic therapy		10-day treatment with Gluthione 600 mg	
		Before treatm	After treatment n=11	Before treatm	After treatment n=13	Before treatm	After treatment n=12	Before treatm	After treatment n=13

		ent n=11		ent n=13		ent n=12		ent n=13	
GS, µmol/ml. er.	45,3± 2,1	28,8± 2,27*	30,8± 2,43*	28,8± 2,08*	38,2± 2,83* 1 3	23,1± 1,77*	23,7± 1,82*	22,1± 1,59*	26,4± 2,12* 2
GSH, µmol/ml. er.	43,2± 2,14	27± 2,2*	29,1± 2,3*	27± 1,95*	36,4± 2,69* 1 3	21,5± 1,62*	22,1± 1,7*	20,6± 1,51*	24,7± 1,99* 2
GSSG, µmol/ml. er.	2,15± 0,15	1,71± 0,15	1,70± 0,15	1,73± 0,16	1,80± 0,14	1,52± 0,13*	1,6± 0,13*	1,5± 0,11*	1,7± 0,13*
GR, µmol/N ADPH/m in/Hb	2,84± 0,13	3,36± 0,15	3,0± 0,13	3,2± 0,13	2,9± 0,12	2,28± 0,18*	2,09± 0,16*	2,1± 0,16*	2,11± 0,15* 2
GP, µmol/GS SG/min/ Hb	583,5± 28,3	441,6 ± 34,8*	466,1 ± 36,7*	437,4 ± 31,5*	526,3 ± 37,9	357,6 ± 27,3*	360,8 ± 27,6*	348,2 ± 25,1*	402,7 ± 29,0* 2 3
GT, µmol/GS H/min/H b	2,44± 0,11	2,16± 0,24	2,11± 0,15	2,1± 0,16	2,1± 0,15	1,25± 0,1*	1,3± 0,12*	1,19± 0,1	1,4± 0,13*

Note: * - reliability of differences from control; 1 - reliability of differences before and after treatment; 2 - reliability of differences between groups with compensation and subcompensation after treatment; 3 - reliability of differences between basic therapy and gluthione after treatment

The next stage of our research was to increase the dose of the drug to 1200 mg per day in patients of groups II (10 patients) and III (24 patients) of glutathione deficiency - subcompensated and decompensated. The results of the studies showed a significant increase in the activity indicators of GS, GSH and GP in patients in both groups II and III of patients in relation to the group of patients who received Gluthione at a dose of 600 mg/day, which made it possible to evaluate the indicators of group II patients as a compensated stage glutathione deficiency, and the indicators of group III patients actually began to correspond to the subcompensated stage of glutathione deficiency.

The biooxidant glutathione and its enzymatic redox system play an important role in cell metabolism [8, 10]. Glutathione and glutathione-dependent enzymes perform an important function in the integrative system of the body, promoting cellular adaptation to oxidative stress [10]. It is known that under pathological conditions the level of glutathione is largely determined by changes in the activity of enzyme systems that regulate the ratio of its oxidized and reduced forms [13]. Of particular interest in our studies is the dynamics of GH, the level of which in patients of group I - with compensated glutathione deficiency, remained at fairly high levels regardless of the therapy, which is considered as a positive adaptive tension of this enzyme link, aimed at maintaining the redox potential of the cell. This phenomenon, in our opinion, can be considered

as a functional stimulation of the glutathione system, the maintenance of which by the introduction of exogenous glutathione makes it possible to activate the important enzyme of antiradical defense - GP [8, 7].

Thus, the use of the drug Gluthione®, taking into account individual indicators of the degree of glutathione deficiency, makes it possible to maintain the functional activity of the glutathione system in the patient's body. This method will allow prescribing timely individual pathogenetically oriented therapy, increasing the economic effect by reducing the period of temporary disability and the length of the patient's stay in the hospital. The social significance of the proposed treatment method lies in reducing the disability of patients with chronic viral hepatitis C.

REFERENCES

1. Арипов О.А. Молекулярные механизмы клеточной гибели при гепатитах и пути их коррекции. Автореф. дис. … д-рамед. наук. Ташкент, 2010.
2. Буеверов А.О. Оксидативный стресс и его роль в повреждении печени// Российский журнал гастроэнтерологии, гепатологии, коллопроктологии. – Москва, 2002. – №4. – С.21-25.
3. Власова С.Н., Шабунина Е.И., Переслегина И.А. Активность глутатионзависимых ферментов эритроцитов при хронических заболеваниях печени у детей. Лабораторноедело. 1990; (8): 19-22.
4. Глушков С.И. Нарушение системы глутатиона и их роль в патогенезе острых интоксикаций ксенобиотиками с различными механизмами токсического действия. Автореф. дисс. … д-рамед. наук. СПб., 2006.
5. Даминов Т.О., Туйчиев Л.Н., Қодиров Б.А., Ходжаева М.А., Мўминова М.Т., Маматмусаев Ф.Ш. // Болалардаўткир В ва С вируслигепатитнингреконвалесценциядавридагепатобилиартизимдааниқланганўзгаришларнингклиник-лабораторхусусиятлари // O'zbekiston tibbiyoti Jurnali. – 2012. - №2. – С. 6-8.
6. Ивашкин В.Т., Ющук Н.Д., Климова Е.А и др. Рекомендации по диагностике и лечению взрослых больных гепатитом С//Москва, 2014. – 75 с.
7. Кротенко Н.В., Алифирова В.М., Иванова С.А. Параметры антиоксидатной защиты при рассеянном склерозе // Журнал неврологии и психиатрии. – 2009. – №7(2). – С. 53-56.
8. Кулинский В.И., Леонова З.А., Колесниченко Л.С., Малов И.В., Данилов Ю.А. Система глутатиона в эритроцитах и плазме крови при вирусных гепатитах // Биомедицинская химия. – 2007. – Т.53. – №1. – С. 91-98.
9. Лопаткина Т.Н. Хронический гепатит С: внепеченочные проявления, особенности клинического течения, диагностика//Вирусные гепатиты: достижения и перспективы. – 2009. - №2. – С. 5-8.
10. Нагоев Б.С., Понежева Ж.Б. Некоторые аспекты иммунопатологии при хронических гепатитах//Эпидемиология и инфекционные болезни. – 2009. - №6. – С. 45-49.
11. Октябрьский О.Н., Смирнова Т.В. Редокс регуляция клеточных функций // Биохимия. – 2007. - №72(2). – С. 132-145.

12. Приказ Министерство Здравоохранения Республики Узбекистан №5 от 05.01. 2012 года «О мерах по совершенствованию борьбы с вирусными гепатитами в Республике». – Т. – 2012. – 67 с.
13. Семененко Т.А. Клеточный иммунитет при гепатите С//Вирусные гепатиты. – 2000. - №1. – С. 3-9.
14. Собчак Д.М., Корочкина О.В., Соболевская О.Л. Оценка показателей медиаторов иммунного ответа у больных острым гепатитом С при комбинированной противовирусной терапии//Клиническая медицина. – 2006. - №12. – С. 47-50.
15. Таджиев Б.М., Алиев Б.Р. и др. Морфологические особенности HCV-инфекции в зависимости от генотипа вируса//IX Республиканский съезд эпидемиологов, гигиенистов, санитарных врачей и инфекционистов Узбекистана: материалы съезда (21-22 мая, Ташкент). – Ташкент, 2010. – С. 142-143.
16. Уразова О.И., Кравец Е.Б., Новицкий В.В., Рогалёва А.В., Васильева О.А., Кузнецова В.Н. и др. Активность перекисного окисления липидов и системы глутатиона в лимфоцитах крови у больных диффузным токсическим зобом // Бюллетень сибирской медицины. – 2008. - №4. – С. 47-51.
17. Чернышов В.Г. Определение восстановленного и окисленного глутатиона в эритроцитах беременных женщин. Лабораторноедело. 1983; (3): 31-33.
18. Шахгильдян И.В., Ершова О.Н., Михайлов М.И. и др. Современная характеристика острого и хронического гепатита С в России: Материалы международного симпозиума. – Брест, 2011. – С. 184–186.
19. Edeston A., Mondelli M. Lymphocyte cytotoxic to autologous hepatocytes in chronic hepatitis B virus infection//Hepatology. – 1999. – N2. – P 122-127.