Izha Anna. Prospects for the use of “dry” carbon dioxide baths in patients with chronic viral hepatitis c with concomitant non-alcoholic fatty liver disease (literature review and own research). Journal of Education, Health and Sport. 2020;10(6):341-349. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2020.10.06.036
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.06.036
https://zenodo.org/record/3930929

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 29.05.2020. Revised: 02.06.2020. Accepted: 30.06.2020.

Prospects for the use of “dry” carbon dioxide baths in patients with chronic viral hepatitis c with concomitant non-alcoholic fatty liver disease (literature review and own research)

Anna Izha

State Institution «Ukrainian Research Institute of Medical Rehabilitation and Balneology of the Ministry of Health of Ukraine», Odessa, Ukraine

Abstract

The paper analyzes modern views on the etiology, epidemiology, pathogenesis, methods of treating patients with chronic viral hepatitis C with concomitant non-alcoholic fatty liver disease (NAFLD), discusses the possibility of using "dry" carbon dioxide baths (DCDB) in this category of patients. Our research was conducted to study the effectiveness of the integrated use of antiviral therapy (AVT) and DCDB procedures in patients with chronic hepatitis C with concomitant NAFLD. The authors of the study were the first to suggest using of DCDB in this category of patients. Based on the results obtained, for the first time, ideas about the specificity of the DCDB′s effect on the clinical course of the underlying and concomitant diseases, on the functional state of the liver, the dynamics of lipid metabolism, and ultrasonographic parameters of the liver were detailed. It is concluded that DCDB can be successfully used in the complex treatment of patients with chronic hepatitis C with concomitant NAFLD.

Keywords: chronic viral hepatitis C; non-alcoholic fatty liver disease; antiviral therapy; "dry" carbon dioxide baths.

Introduction. Liver disease is a major cause of disability and mortality worldwide. According to WHO expert estimates, the prevalence of HCV infection in the general population is 3%, 3-4 million people are infected with hepatitis C virus annually. Ukraine, according to the WHO, is one of the countries with a moderate prevalence of HCV infection, affecting from 1 to 2,5% of the population. Although, according to many scientists, the true incidence and prevalence of hepatitis B and C in Ukraine exceeds the official statistics by 5-8 times, as anicteric, erased, subclinical forms run behind the mask of another pathology and remain unrecognized [1, 2, 3, 4]. It is known that patients with chronic hepatitis C (CHC) are at high risk of liver cirrhosis and hepatocellular carcinoma. Cirrhosis of the liver develops in 10-20% of patients with CHC and is usually detected 10-20 years after the onset of the disease. According to some data, infection with hepatitis C virus increases the risk of hepatocellular carcinoma by 11 times. Annual mortality in patients with hepatocellular carcinoma increases to 80-90% in economically developed and developing countries, respectively [5, 6].

According to modern ideas, there are many factors that affect the natural course of CHC and the effectiveness of antiviral treatment. These factors include virus factors - HCV genotype, the degree of heterogeneity of the virus population, the amount of infected material and patient factors — age, sex, race, alcohol abuse, co-infection with other viruses and concomitant liver pathology [5, 6]. According to various studies, hepatic steatosis (HS) is observed in almost 50% of patients infected with hepatitis C virus. The possibility of developing steatosis in chronic HCV infection is significantly higher than in other liver diseases and is diagnosed 2 times more often than in chronic HBV- infection and autoimmune hepatitis. Among the main causes of HS are considered metabolic disorders (obesity, type 2 diabetes, hyperlipidemia), which lead to the formation of "metabolic" HS. At the same time, a significant proportion of patients with CHC often have fatty infiltration of the liver without the presence of metabolic syndrome, which allows to determine the role of the virus in the development of steatosis - the so-called "viral" HS [7, 8, 9].

It has been proven that the genotype of the virus affects the development of fatty infiltration of the liver. Thus, HS is most often diagnosed in patients infected with the 3rd genotype of HCV infection. Moreover, the severity of steatosis in these patients directly correlates with the level of viral load. This is due to the presence of steatogenic sequences in the genome of this genotype, which activate the suppressor of cytokine-7 signals and inhibit the activity of the insulin receptor-1 substrate. This results in impaired glucose transport in the cell and the development of insulin resistance (IR).

Also, the virus activates the signaling pathway of the SREBP-1 c protein, which enhances the intracellular accumulation of triglycerides. A number of researchers have shown that steatosis, which was initially detected in patients with the 3rd genotype of the virus, was reversible when achieving a stable virological response to therapy with pegelated interferon-alpha and ribavirin, however, with recurrence of infection in this category of patients again . In other genotypes of HCV infection, no association was found between the level of viremia and the severity of SP, as well as its regression when a stable virological response was achieved. This confirms the ability of the 3rd genotype to induce the development of hepatosteatosis in patients with CHC [10].

In the 1st genotype of HCV infection, metabolic factors (insulin resistance, abdominal obesity, serum triglycerides) play a major role in the development of HS. However, there are data that determine the direct effect of the virus on the formation of IR. Patients with HCV genotype 1 have been shown to increase cytokine-3 signal suppressor activity, impair insulin receptor-1 substrate function, and have difficulty transporting glucose to the cell. It was found that the replacement of the amino acid at position 70 of the core region of the 1st genotype of the virus is an independent predictor of the development of HS [11].

Although the accumulation of intracellular fat in hepatocytes occurs in HCV infection of different genotypes, the expression of core protein of the 3rd genotype leads to the accumulation of fat, three times more pronounced than in the 1st genotype. To further investigate the mechanisms by which different genotypes of hepatitis C virus may affect fat deposition in the liver in different ways, Jackel-Cram et al. [12], studied de novo lipid synthesis and triglyceride accumulation in hepatoma cell culture transfected with core genes of genotypes 3a and 1b to determine the effect of these genes on the expression of FAS ligand, which plays a major role in fatty acid synthesis. They showed that the activity of the FAS ligand was higher in genotype 3a compared to genotype 1b of HCV infection. It was found that phenylalanine at the 164th position in the core protein of the 3rd genotype may be key in determining the enhanced regulation of the FAS ligand and suggested that this molecular mechanism may be the basis of the direct steatogenic effect of the 3rd genotype [13, 14].

The mechanisms underlying the pro-inflammatory and profibrogenic role of both "viral" and "metabolic" HS remain incompletely studied. Hepatocytes have been suggested to become more sensitive to the damaging effects of various proinflammatory cytokines and free radicals, which are produced in large quantities in the liver due to HCV infection. It is oxidative stress and lipid peroxidation that occur in SP that cause the development of liver

fibrosis. In addition, fat-laden hepatocytes are more conducive to apoptosis, which is currently recognized as the main mechanism of liver cell death in chronic viral hepatitis.

It is proved that the severity of SP directly correlates with the degree of apoptosis of hepatocytes and, most interestingly, with the activity of Kupffer cells, which are one of the main sources of profibrogenic factors in the liver [15, 16]. Steatosis (regardless of its form - metabolic or virus-induced) worsens the prognosis of the rate of fibrosis in patients with CHC, but determining the form of steatosis in a particular patient can greatly help in choosing the right treatment tactics, which must be considered when prescribing therapy to such patients.

Antiviral therapy (AT) remains the basis for the treatment of patients with CHC, including NAFLD. For a long time, a combination of pegylated interferon alpha (peg-IFNα) and ribavirin was used as the standard of care for CHC. However, standard dual therapy was effective only in 40-50% of patients, in addition, it was often accompanied by severe side effects that complicate treatment. Advances in molecular biology in the study of hepatitis C virus have facilitated the development of direct-acting antiviral drugs (DAAD) for the treatment of CHC. Experience with the use of DAAD in real clinical practice has shown a high frequency of elimination of the pathogen, but CHC is a systemic disease that requires a special approach given the comorbid pathology of the liver [17, 18, 19]. The success of drug therapy for NAFLD has been linked to the administration of insulin-synthesizers and statins, ursodeoxycholic acid, essential phospholipids, drugs with antioxidant activity (vitamin E, vitamin D), and more.

Meanwhile, drug therapy involves significant risks: the development of serious side effects with prolonged use, allergic reactions, polypragmatism, and where any of them (vitamin E) can increase mortality from all causes, including hemorrhagic stroke and prostate cancer. In addition, the results of therapy are not always satisfactory in their effectiveness [20, 21].

Summarizing the above material, we can conclude that, despite the progress in the treatment of patients with CHC and NAFLD, many open questions remain. This stimulates the search for new non-drug technologies for the treatment of patients with CHC with concomitant NAFLD using preformed physical factors. Therefore, the issues of optimal combination of physical treatments and antiviral drugs, finding their synergy and potentiating the effects of effective stimulation of the body's adaptive capacity in combination with safety, good tolerability and high efficiency are very relevant and determined the direction of this study.

Dry carbonic acid gas bath (DCAGB) – a method of percutaneous therapeutic effect of carbon dioxide on the patient, whose body is up to the level of the neck in a special box. According to the current physical factor, the therapeutic use of SVR is attributed to carbogen therapy - a type of treatment with carbon dioxide (carbon dioxide, CO_2). CO_2 is an important physiological factor that affects metabolism, redox processes in the cell, hormonal regulation. A number of researchers note the positive effect of DCAGB on lipid metabolism. Under the influence of DCAGB increases lipid metabolism, reduces cholesterol and low-density lipoprotein in patients with atherosclerosis, increases the breakdown of fats and fat-like substances. The effect of carbon dioxide baths is manifested in the change of the functional state of the higher parts of the central nervous and autonomic systems by restoring the balance of nervous processes. Very important in the action of carbon dioxide baths is to increase the oxygen content in the arterial blood, resulting in tissues and organs receive more oxygen, enhance and improve all metabolic processes in the body (carbohydrate, fat, protein, electrolyte) [22, 23, 24]. Meanwhile, the possibilities of using DCAGB in the complex treatment of patients with CHC with concomitant NAFLD are almost undefined.

Aim of the research. Therefore, the aim of the study was to study the effectiveness of integrated use of antiviral therapy (AT) and procedures of "dry" carbon dioxide baths (DCAGB) in 40 patients with CHC with concomitant NAFLD.

Materials and methods. We formed 2 groups of patients with CHC (genotype 1b in the phase of replication, minimal and moderate activity) with concomitant NAFLD. The mean age of patients involved in our study was (48.12 ± 10.29) years, 23 women and 17 men. Patients of group I (20 people, control group) received a standard set of treatment (diet therapy that corresponded to the Mediterranean diet) [25], dosed exercise regimen, antiviral therapy - sofosbuvir (400 mg) and ledipasvir (90 mg) - 3 months), patients of group II (20 people, the main group) additionally received DCAGB procedures (daily 10 procedures for the first month of treatment, break of 20 days, 10 procedures for the second month of treatment, break of 20 days, 10 procedures for the third month of treatment). Evaluation of the effectiveness of treatment was performed 3 months after treatment. The study used such methods as anamnestic and clinical, performed research of general clinical, biochemical parameters of blood, serological markers of hepatitis C virus, HCV RNA PCR (qualitative and quantitative determination, genotyping), ultrasonographic examination of digestive organs, statistical methods.

Results and its discussion. The treatment in both groups was accompanied by a positive dynamics of most signs of the disease, however, a detailed analysis revealed

significant benefits in patients of group 2 with the use of DCAGB. In patients of group 2, a probable decrease in the manifestations of asthenic ($p < 0.05$) and pain ($p < 0.05$) syndromes was established as early as 1 month after the start of therapy, which was not observed in patients of control group 1, where probable changes were achieved only at the end. treatment. Regarding dyspeptic syndrome, its probable dynamics was observed slowly and was represented by the leveling of some signs of dyspeptic syndrome only at the end of treatment ($p < 0.05$). The study of indicators of the general analysis of blood in 3 months from the beginning of treatment defined probable ($p < 0,001$) normalization of level of ESR and lymphocytes at patients with initially raised level of these indicators. There was also a probable ($p < 0.001$) decrease in the number of patients with monocytosis.

The analysis of biochemical parameters determined the probable ($p < 0.05$) elimination of signs of cytolytic and cholestatic syndromes, normalization of the level of thymol test ($p < 0.05$) in patients of both groups at the end of 3 months of treatment. Regarding the normalization of lipid metabolism, a significant advantage was found in patients who additionally received DCAGB. Thus, in patients of group 2 a probable ($p < 0.001$) decrease in the concentration of CX, triglycerides, LDL, HDL, atherogenic factor was determined, in contrast to patients in group 1, where only a tendency ($p > 0.05$) to decrease total cholesterol. The study of the dynamics of carbohydrate metabolism in patients of both groups showed a slow dynamics in the normalization of the HOMA-IR index (5.35 ± 0.42) - at the beginning of treatment and 4.03 ± 0.32 - at the end of treatment), a probable decrease in insulin and glucose.

Analysis of the results of the study of the dynamics of qualitative determination of HCV RNA PCR, conducted 1, 2 and 3 months after the start of treatment, determined the presence of virological response in all subjects. At the end of treatment there was an improvement in the ultrasound picture of the hepatobiliary system in all patients, namely a tendency to reduce the acoustic density of the liver parenchyma and reduce the size of inflammatory foci, improve echo in the deep layers of the liver, improve vascular imaging. No significant effect on the reduction of inflammatory symptoms in the gallbladder and pancreas was achieved ($p > 0.5$). Comparative analysis between patients of groups 1 and 2 shows in favor of the predominant therapeutic efficacy of the treatment complex with the addition of HCV RNA PCR, which allowed to achieve complete normalization of lipid metabolism at the end of treatment. Thus, the obtained results prove the feasibility of using DCAGB in the complex treatment of patients with CHC with concomitant NAFLD in order to restore lipid metabolism, improve ultrasonographic features, ie influence on the main

pathogenetic links of formation and progression of NAFLD to increase the effectiveness of treatment of the underlying disease.

Conclusions

1. In patients with chronic hepatitis C with concomitant NAFLD, before treatment, clinical signs of asthenic (82.50%) and pain abdominal (55.00%) syndromes were determined. All examined were diagnosed with signs of dyslipidemia and IR along with changes in ultrasound data - distal attenuation of the echo of the liver (100.0%) and hepatomegaly (72.50%).

2. The combined use of diet therapy, physical exertion, standard AVT, and DCDB procedures contributes to reliable ($p < 0.001$) elimination of clinical signs of the underlying and concomitant diseases, normalization of the functional state of the liver, especially lipid profile, restoration of the ultrasound picture of the digestive system, leads to a virological response in all patients.

References

1. Stanaway JD, Flaxman AD, Naghavi M. et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. The Lancet. 2016 Sep 10;388(10049):1081–1088. doi: 10.1016/S0140-6736(16)30579-7.

2. Bedogni G, Nobili V, Tiribelli C. Epidemiology of fatty liver: an apdate. World J. Gastroenterol. 2014 Jul 21;20(27):9050–9054. doi: 10.3748/wjg.v20.i27.9050.

3. Zhdanov KV, Kozlov KV, Sukachev VS, Zaharenko SM, Karyakin SS. Elimination of hcv-infection: a history with continuation. J Infectology. 2018;10(4):6–13. doi: 10.22625/2072-6732-2018-10-4-6-13.

4. Assessment of the viral hepatitis response in Ukraine - WHO. Mission report. 2017 June 6–9. https://www.euro.who.int/__data/assets/pdf_file/0007/372697/ukr-hepatitis-report-eng.PDF?ua=1

5. Ringehan M, Mc Keating JA, Protzer U. Viral hepatitis and liver cancer. Philos Trans R Soc Lond B Biol Sci. 2017 Oct 19;372(1732):20160274. doi: 10.1098/rstb.2016.0274.

6. Fukui, H. Gut-liver axis in liver cirrhosis: How to manage leaky gut and endotoxemia. World J. Hepatol. 2015 Mar 27;7(3):425–442. doi: 10.4254/wjh.v7.i3.425.

7. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016;65(8):1038–1048. doi: 10.1016/j.metabol.2015.12.012.

8. Kralj D, Jukić LV, ljević SS, Duvnjak M, Smolić M, Čurčić IB. Hepatitis C Virus, Insulin Resistance, and Steatosis. J Clin Transl Hepatol. 2016;4(1):66–75. doi: 10.14218/JCTH.2015.00051.

9. Satapathy S.K., Sanyal A.J. Epidemiology and natural history of nonalcoholic fatty liver disease. Semin. Liver Dis. 2015;35(3):221–35. doi: 10.1055/s-0035-1562943.

10. Adinolfi LE, Rinaldi L, Guerrera B, Restivo L, Marrone A, Giordano M, Zampino R. NAFLD and NASH in HCV Infection: Prevalence and Significance in Hepatic and Extrahepatic Manifestations. International Journal of Molecular Sciences. 2016 Jun;17(6):803. doi: 10.3390/ijms17060803.

11. Caligiuri A, Gentilini A, Marra F. Molecular pathogenesis of NASH. International Journal of Molecular Sciences. 2016 Sep 20;19(9):1575. doi: 10.3390/ijms17091575.

12. Jackel-Cram C, Babiuk LA, Liu Q. Up-regulation of Fatty Acid Synthase Promoter by Hepatitis C Virus Core Protein: genotype-3a Core Has a Stronger Effect Than genotype-1b Core. J Hepatol. 2007 Jun;46(6):999–1008. doi: 10.1016/j.jhep.2006.10.019.

13. Guo CH, Chen PC, Ko WS. Status of Essential Minerals and Oxidative Stressin Viral Hepatitis C Patients with Nonalcoholic Fatty Liver Diseasenternational Journal of Medical Sciences 2013;10(6):730–737. doi: 10.7150/ijms.6104.

14. Pinzani M. Fatty Liver Disease: co-factor of HCV and evolving disease entity. http://congress-ph.ru/common/htdocs/upload/fm/gepatology/2016/prez/2-1-1.pdf.

15. Patel A, Harrison SA. Hepatitis C virus infection and nonalcoholic steatohepatitis. Gastroenterology & Hepatology. 2012 May;5(8):305–312. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3424424/.

16. Dulai PS, Singh S, Patel J. et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology 2017 May;65(5):1557–1565. doi: 10.1002/hep.29085.

17. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2015. J Hepatol. 2015;63(1):199-236. doi: 10.1016/j.jhep.2015.03.025.

18. European Association for the Study of the Liver. Electronic address eee.EASL recommendations on treatment of hepatitis C 2016. J Hepatol. 2017;66(1):153–194. doi: 10.1016/j.jhep.2016.09.001.

19. Bailly F, Pradat P, Virlogeux V, Zoulim F. Antiviral therapy in patients with hepatitis C virus-induced cirrhosis. Dig Dis. 2015;33(4):613–23. doi:10.1159/000375359.

20. Konerman MA, Jones JC, Harrison SA. Pharmacotherapy for NASH: Current and emerging. J Hepatol. 2018 Feb; 68(2):362–75. doi: 10.1016/j.jhep.2017.10.015.

21. EASL-EASD-EASO Clinical Practice Guidelines for the management of nonalcoholic fatty liver disease. J Hepatology. 2016 Jun; 64(6):1388–1402. doi: 10.1016/j.jhep.2015.11.004.

22. Ezhov VV, Tsarev AY, Platunova TE, Application of dry carbon baths in clinical practice (scientific review). Vestnik Fisioterapii i Kurortologii (Herald of Physiotherapy and Health Resort Therapy). 2017;23(2):63–76. http://science.cfuv.ru/wp-content/uploads/2018/01/VFIK-2-2017.pdf. [in Russian].

23. Suceveanu M, Suceveanu P, Pop D, Sitar Taut A, Zdrenghea D, Hâncu N. Role of mofette тherapy in cardiovascular rehabilitation – the covasna model. Balneo Research Journal. 2015 May;6(2):69–74. doi: 10.12680/balneo.2015.1089.

24. Persiianova-Dubrova AL, L'vova NV, Badalov NG. [Carbon Dioxide Baths: State of the Art]. Vopr Kurortol Fizioter Lech Fiz Kult. 2010;(4):48–50. https://pubmed.ncbi.nlm.nih.gov/21089208//

25. Mayevskaya MV, Ivashkin V.T. Liver and Nutrition. An Optimal Diet for Non-Alcoholic Fatty Liver Disease/ Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2018;28(5):105–116. https://doi.org/10.22416/1382-4376-2018-28-5-105-116. [in Russian].