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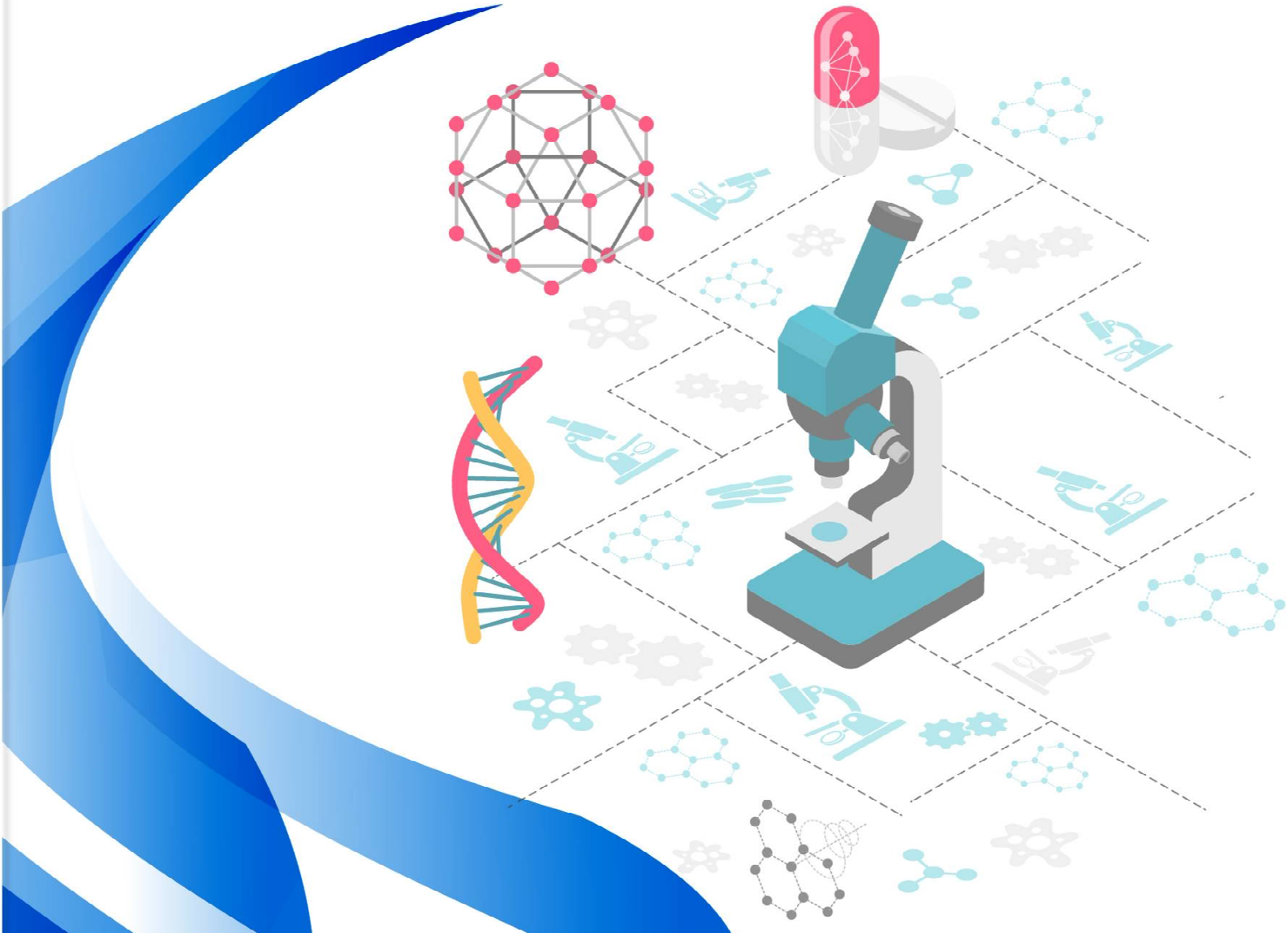

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INCIDENCE OF LIVER STEATOSIS IN DIFFERENT GENOTYPES IN CHRONIC HEPATITIS C AND THE EFFECT OF DAA THERAPY ON ITS OUTCOME

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Abstract.The terminology of non-alcoholic fatty liver disease encompasses a wide range of conditions, from simple accumulation of fat ("fatty liver" or steatosis) to non-alcoholic steatohepatitis, fibrosis and cirrhosis of the liver with its clinical consequences [21].*The incidence of non-alcoholic fatty liver disease among adults is 20-30% and higher in industrialized countries* [2].

Keywords: chronic viral hepatitis C, fatty liver, sustained virological response, direct-acting antivirals.

Introduction

Non-alcoholic fatty liver disease is asymptomatic in the most affected patients and is associated with obesity and features of metabolic syndrome, arterial hypertension proper, dyslipidemia, central obesity and insulin resistance or diabetes [15, 23]. Thus, hepatic steatosis against the background of chronic viral hepatitis C is an urgent problem of modern infectious diseases due to the high prevalence, severe consequences and negative impact on the effectiveness of antiviral therapy.

While patients with simple fatty liver disease live approximately the same future life expectancy for the general population, in people with non-alcoholic steatohepatitis, survival is impaired, primarily due to cardiovascular and liver-related causes. Despite its significant prevalence, only a small proportion of patients with non-alcoholic fatty liver disease have non-alcoholic steatohepatitis with a consequent increased risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma.

This concept was recently challenged by two long-term follow-up studies, which showed that severe fibrosis, but not the presence of non-alcoholic steatohepatitis (according to the diagnosis on the NAS scale) predicted all-cause mortality in patients with non-alcoholic fatty liver disease [3, 12]. This could be linked to the deficiencies in the NAS score, as the presence and degree of steatosis is disproportionately affected compared to lobular inflammation and abdominal distention, while portal inflammation is not included in the evaluation [6].

On the other hand, lobular inflammation and abdominal distention may be epiphenomena similar to simple steatosis, not associated with activation of fibrogenic pathways.

Liver steatosis is characterized by the accumulation of lipids in hepatocytes and is usually associated with metabolic factors, causing primary liver damage. In the past, the presence of hepatic steatosis was considered a benign condition. However, steatosis in synergy with another damaging agent can lead to the development of oxidative stress and increase the damage to hepatocytes [9, 20]. At present, the interests of researchers are focused on the pathophysiological mechanisms of the onset of steatosis in patients with chronic viral hepatitis C, and the existing data reflect the participation of viral and host factors in this process [14].

Fat accumulates in the liver in the form of triglycerides, and this occurs simultaneously with increased lipotoxicity due to high levels of free fatty acids, free cholesterol and other lipid metabolites: as a result, mitochondrial dysfunction with oxidative stress and the production of reactive oxygen species and mechanisms associated with stress endoplasmic reticulum are activated [10].

Along with this, altered intestinal flora leads to further production of fatty acids in the intestine, increased permeability of the small intestine, and thus increased absorption of fatty acids and increased levels of circulating molecules that promote the activation of inflammatory pathways and the release of proinflammatory cytokines such as IL- 6. and TNF-? [17].

In subjects predisposed to genetic factors or epigenetic modifications, all these factors affect the fat content in hepatocytes and the inflammatory environment of the liver, which leads to a state of chronic inflammation of the liver (Fig. 2) through heterogeneous pathways of hepatocellular damage with possible progression to hepatocellular death (for both direct toxicity and mechanisms of activation of apoptosis), activation of hepatic stellate cells and deposition of the fibrous matrix.

The diagnosis of non-alcoholic fatty liver disease remains one of the exceptions, and liver biopsy remains the gold standard for differentiating fatty liver from non-alcoholic steatohepatitis and for determining the stage of fibrosis, although several non-invasive markers have recently been introduced for the latter [8].

Long-term observations of patients infected with the hepatitis C virus make it possible to state a high incidence of liver cirrhosis and hepatocellular carcinoma in them. Over the past decades, significant advances have been made in the diagnosis and treatment of chronic liver diseases. The emergence of direct-acting antiviral drugs revolutionized the treatment of viral hepatitis C. The effectiveness of treatment with direct-acting drugs was 95-98%. Despite the success in the treatment of viral hepatitis C, many questions remain unresolved. One of these issues is the study of the influence of metabolic changes and hepatic steatosis as factors influencing the effectiveness of antiviral therapy and disease outcomes, especially considering that hepatic steatosis is often detected in patients with viral hepatitis C [1].

According to the results of various studies, fatty degeneration of hepatocytes is observed in almost 50% of patients infected with the hepatitis C virus [4, 5, 25].

In patients infected with HCV, steatosis is diagnosed 2.5 times more often than in the general population [13]. To understand the causes of hepatic steatosis and develop ways of influencing it in patients with chronic viral hepatitis C, two forms of steatosis should be differentiated: metabolic and HCV-induced. The possibility of metabolic steatosis is not directly related to HCV infection, however, as noted above, the combination of this form of steatosis and chronic viral hepatitis C may be associated with faster progression of fibrosis [7]. In this regard, patients with liver disease (steatosis or type 2 diabetes) should be periodically carefully examined clinically [11].

Another form of steatosis detected in patients with chronic viral hepatitis C is fatty infiltration caused directly by HCV [18, 19, 24]. Although the exact mechanism of HCV action on liver cells is not fully understood, the role of virus-induced steatosis as the only pathway of direct cytopathic action of the virus is recognized [16, 19]. According to many researchers, steatosis is one of the factors that accelerate the progression of the disease to the stage of cirrhosis, as well as reduce the likelihood of success of antiviral therapy [22, 24].

AIM OF THE STUDY.

The objectives of this study were formulated as follows:

- to determine the frequency and severity of liver steatosis in patients with chronic HCV infection with different HCV genotypes in the Uzbek population.

- to determine the association of steatosis with virological and metabolic factors.

MATERIAL AND METHODS.

The study was conducted at the Research Institute of Virology of the Ministry of Health of the Republic of Uzbekistan for the period 2019-2020. 75 patients with

chronic viral hepatitis C were examined, including 25 men and 50 women. All patients were over 18 years of age.

The median age of the patients was 47.9 years with an interquantile range (22-73 years). In terms of gender, the groups did not differ significantly.

The exclusion criteria for patients were: 1) the presence of concomitant liver pathology (liver cirrhosis, autoimmune hepatitis, alpha-1 antitrypsin deficiency, viral hepatitis B, primary biliary cirrhosis, Wilson-Konovalov disease, Budd-Chiari syndrome, hemochromatosis) or any liver disease in the stage decompensation; 2) the presence of diabetes mellitus and / or obvious clinical and laboratory manifestations of metabolic syndrome, incl. insulin resistance; 3) HIV co-infection; 4) regular alcohol consumption of more than 50 g / day for men and 25 g / day for women over the past two years; 5) the presence of a previous direct-acting antiviral treatment for chronic viral hepatitis C.

Biochemical parameters (bilirubin level, serum activity of alanine aminotransferase, aspartate aminotransferase, cholesterol) were measured on a Mindray BA-88A analyzer, Germany, using Human Diagnostics Worldwide reagents, Germany.

In addition to general clinical examination methods, all patients underwent a complete serological examination for markers of viral hepatitis B, C, D (for surface antigen HBsAg, anti-HDV, anti-HCV) by enzyme-linked immunosorbent assay (ELISA) on microparticles (DS, Nizhny Novgorod). All patients were positive for anti-HCV in the third generation ELISA test, as well as positive for HCV RNA in the blood. To measure the HCV RNA level, a real-time polymerase chain reaction was used with a PCR amplifier on Rotor-Gene Q (Corbett Research, Australia) for 36 wells, using AmpliSens-HCV-FL reagents for detecting hepatitis C virus RNA (lower threshold of sensitivity 50 IU / ml), AmpliSens-HCV genotype-FL for the detection and determination of hepatitis C genotypes (Russia), FBUN Central Research Institute of Epidemiology of Rospotrebnadzor, manufacturer of AmpliSens® reagent kits. Today FBSI Central Research Institute of Epidemiology of Rospotrebnadzor is the largest high-tech import-substituting biotechnological production of modern diagnostic drugs in Russia. Each patient was tested for HCV genotype and blood HCV RNA quantification.

All patients underwent ultrasound examination of the abdominal organs in the morning on an empty stomach after at least 10 hours of fasting, as well as fibroelastometry of the liver tissue. The diagnosis of hepatic steatosis and the degree of hepatic steatosis were made on the basis of the results of ultrasound examination (Philips clear Veu 350 device, with a convex multi-frequency transducer with 5-2 MHz) and transient elastography (FibroScan FS-502 device, Echosens, France) of the liver using the attenuation parameter ultrasonic wave (Controlled Attenuation Parameter - CAP) in decibels per meter (dB / m), which correlates with the degree of steatosis:

Level of steatosis	Activity of steatosis	Liver damage, in (%)	In dB/m
S0	no steatosis	-	≤228
S1	minimal steatosis	≤ 5% of hepatocytes with steatosis	229-268
S2	moderate steatosis	6–32% of hepatocytes with steatosis	269-301
S3	severe steatosis	33–60% of hepatocytes with steatosis	302-346
S4	very heavy steatosis or cirrhosis	61-100% of hepatocytes with steatosis	347≤ and upper

The diagnostic criteria were also altered biochemical parameters: increased activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, cholesterol.

For the statistical analysis of quantitative signs, the nonparametric t-Wilcoxon test was used to compare two dependent samples with each other in terms of the level of severity of the sign of steatosis with a significance level ? equal to 0.05, providing the probability of error $p < 0.05$, acceptable for medical research [1, 22]. So, the data was not evenly distributed, the rang sum test was used for the calculation. The confidence interval and the p value for the differences between the shares were obtained based on the calculation of the z criterion (Microsoft Excel, Biostat).

RESULTS AND DISCUSSION.

In most cases, hepatic steatosis is not accompanied by any clinical symptoms [1]. It is very difficult to determine fatty liver at the initial stage, when it may be asymptomatic, which makes it difficult to diagnose the disease. Hepatic parameters are usually within the normal range. However, these are not specific symptoms and can accompany other liver diseases. The diagnosis is made when the inflammatory process intensifies in the liver tissues and fibrotic changes appear, but then symptoms such as severity, pain in the right hypochondrium, bitterness in the mouth, flatulence, etc. appear [2]. Fatigue, malaise, abdominal discomfort, enlarged liver and spleen are common. Currently, one of the urgent problems is the identification of patients who require careful monitoring and differentiated treatment before, during and after antiviral therapy. This group includes patients with regression of hepatic fibrosis in chronic hepatitis after a sustained virological response, patients with liver cirrhosis, at risk of developing hepatocellular carcinoma, and patients with hepatic steatosis. Later, signs characteristic of liver failure may appear: lack of appetite, asthenic-vegetative manifestations. Usually, steatosis is detected by chance on ultrasound or when the biochemical parameters of the blood change. If you suspect liver steatosis, it is necessary to conduct laboratory and instrumental studies.

In the presented study, an attempt was made to reveal the factors associated with steatosis in patients with chronic viral hepatitis C. In this study, out of 75 patients with chronic viral hepatitis C, steatosis was detected in 70.67% of people (Table 1), of which in 29 (54.72%) people were found to be obese, an increased level of cholesterol in the blood in 19 (35.85%), which corresponds to the signs of metabolic syndrome.

Patients with female steatosis accounted for 67.92% of all patients with steatosis (36 cases), significantly older, often suffering from obesity and hypertension, and a larger waist.

According to our results, as in many studies around the world, HCV genotype 1 was dominant in patients [1, 2, 3]. The incidence of genotype 1 HCV was 66.67% of 75 patients (male / female: 16/34), genotype 3 - 21.33% (6/10), and genotype 2 - 12.0% (3/6). Other genotypes were not found during this study.

Liver steatosis was significantly more frequent in patients with HCV genotype 1 out of 75 - in 46.67% of patients, while in HCV genotype 3 it was observed only in 14.67% of patients, and in HCV genotype 2 - in 9.33 % of patients. If we look at the incidence of steatosis by genotypes within patients with hepatic steatosis, then genotype 1 also prevailed with 66.04% of 53 patients (35 cases), genotype 3 - 20.75% (11 cases), and genotype 2 - in 13.21 % (7 cases).

According to the results of the initial Fibroscan, the patients were divided into two groups: the first group - patients with hepatic steatosis exceeding 5% or more, the second group - without hepatic steatosis (lesion <5%). Comparison in the groups was carried out by gender, age, HCV viral load, inflammatory necrotic activity, and the presence of steatosis (Table 1). According to Fibroscan data before treatment, hepatic steatosis was observed in 53 (male / female: 17/36) patients with chronic viral hepatitis C, 29.33% (8/14) had no steatosis - S0.

When an ultrasound scan of the liver was done to patients with S4 degree of steatosis, they did not show signs of liver cirrhosis on the ultrasound scan, and therefore such patients were also included in the study as chronic viral hepatitis C.

Table 1. Characteristics of patients depending on the presence and severity of hepatic steatosis before the onset of direct-acting antiviral drugs.

Level of steatosis / Genotype	Without steatosis (S0) n=22	Patients with hepatic steatosis exceeding 5% or more n=53			
		Mild steatosis (S1) n=22	Moderate steatosis (S2) n=12	Severe steatosis (S3) n=12	Manifest steatosis (S4) n=7
n=25 (male/ femal	8/14	7/15	6/6	3/9	1/6
Age, year	44.41 ±17.59	49.92 ±17.08	52.96 ±14.04	52.58± 17.42	48.14 ±11.86
Genotype 1, 50	15	15	8	7	5
Genotype 3, 16	5	4	2	3	2
Genotype 2, n=9	2	3	2	2	0

Of the identified steatosis, 41.51% (7/15) had mild steatosis - S1, 22.64% (6/6) - moderate steatosis - S2, and 22.64% (3/9) had severe steatosis. - S3, and 13.21% (1/6) had steatosis with liver damage more than 70% of the total field - S4.

Taking into account that chronic viral hepatitis C passes without cytolitolytic manifestations, 53 patients with fatty liver on Fibroscan were prescribed biochemical blood tests. It should be noted that the increase in the parameters of the lipid spectrum and liver enzymes does not always depend on the severity of steatosis [27]

(Table 2). In the table below, you can see that the biochemical parameters were within normal limits or slightly increased with severe steatosis than steatosis with moderate or minimal activity. In the blood, the level of bilirubin increased in 10 out of 53 (18.87%), in 22 (41.51%) ALT, and in 17 (32.07%) AST. There was a moderate increase in cholesterol content in 17 (32.07%) patients, but the increase in triglycerides remained within the normal range, only in 13.21% of patients it was higher than normal.

Table 2. Laboratory characteristics of steatosis in patients before treatment with direct-acting antiviral drugs.

Level of steatosis / Genotype	Without steatosis (S0)	Mild steatosis (S1)	Moderate steatosis (S2)	Severe steatosis (S3)	Manifest steatosis (S4)
n=75	22	22	12	12	7
ALT	47,59 ±18,16	60,29 ±42,23	129,79 ±96,54	41,71 ±23,42	64,19 ±28,14
AST	47,86 ±28,21	40,75 ±29,81	96,67± 71,29	40,17 ±22,07	47,82 ±27,02
Bilirin	20,78 ±11,12	16,06 ±7,09	19,52± 13,19	20,6± 9,24	16,64 ±5,76
Cholerol	4,68± 2,71	4,72± 1,83	4,86±1 ,85	4,41± 1,13	4,58± 0,68

Note: n - is the number of observations; S-steatosis; ALT - alanine aminotransferase (normal value is: men - ≤35 U / l, women - ≤31 U / l); AST - aspartate aminotransferase (normal value is: men - ≤40 U / l, women - ≤35 U / l); RNA HCV - hepatitis C virus ribonucleic acid;

If liver steatosis is suspected, its identification and a differentiated approach to treatment are necessary, which determines the best results of antiviral therapy and disease outcomes.

Therapeutic measures were carried out in several directions: medicamental - antiviral therapy, with a simultaneous revision of lifestyle and nutrition. In general (regardless of the presence or absence of hepatic steatosis), antiviral therapy with DAAs was effective in all HCV patients (SVR was achieved in 75 people) (Table 3).

Analysis of SVR frequency depending on the presence / absence of hepatic steatosis showed that steatosis did not have a negative effect on the effectiveness of the antiviral response ($P<0.05$).

It is necessary to provide the fact that not only hepatic steatosis can influence the effectiveness of antiviral therapy, but also the opposite effect is observed [26]. Thus, as a result of effective antiviral therapy,

liver steatosis regressed to some extent and sometimes even completely disappeared in 20 patients (26.67%). After the course of DAA therapy, which ended with the achievement of SVR, hepatic steatosis (according to repeated Fibroscan data) disappeared in only one patient with 3 HCV genotype. Thus, with genotype 3 of the virus after a course of DAA therapy, the incidence of hepatic steatosis practically did not change from the initial 68.75% (11/16) to 62.5% (10/16) 6 months after the end of therapy (P>0.05) but its increase was also determined in three patients, while with genotype 1 HCV after completion of DAA therapy, the incidence of hepatic steatosis significantly decreased: the incidence of hepatic steatosis decreased from the initial 70.0% (35/50) to 32.0% (16/35/50) (P<0.05), but while in 12 out of 50 patients (24.0%), hepatic steatosis appeared and even progressed after DAA therapy with SVR.

As a result, when patients with chronic viral hepatitis C with hepatic steatosis were divided into two groups "before treatment" and "after treatment" (P>0.05), without dividing by genotypes, the result of calculating the outcome of the frequency of reducing steatosis after receiving DAA therapy with SVR according to the Wilcoxon T test did not give the desired response, that is, the effect of DAA therapy to reduce hepatic steatosis after SVR, as suggested at the beginning of the study (P>0.05) (Table 3).

Table 3. Correlation analysis to compare data from two groups of patients with HCV steatosis.

Average ue in the group efore treatment"	Average value in the group "After treatment"	Empirical value of the criterion	Significa nce level
261.44	263.107	1434.5	0.96

In those cases when hepatic steatosis did not disappear completely, its severity in an equal amount decreased in one group of patients and increased in another. And also, there are new cases of steatosis detection in patients after SVR, which had not been identified earlier. And this phenomenon occurred regardless of the type of HCV genotype.

CONCLUSION.

1.Chronic viral hepatitis C can induce hepatic steatosis through a variety of mechanisms.

2.In chronic HCV infection caused by 1 genotype of the virus, hepatic steatosis, compared with genotype 3 HCV, occurs in almost the same amount within each group. However, in the general population, hepatic steatosis occurs almost 3 times more than in HCV genotype 3, since the occurrence of genotype 1 is 3 times more than genotype 3.

3.The presence of hepatic steatosis in HCV genotype 3 is not a predictor of low response to DAA therapy. The effectiveness of DAA therapy in these patients remains high.

4.In addition, in the presence of SVR, hepatic steatosis does not always disappear in patients with HCV genotype 3 after receiving DAA therapy. Maybe this is due to the special food of the oriental cuisine.

References:

1.Целиковский А.В. и др. Влияние стеатоза печени на эффективность комбинированной противовирусной терапии хронического гепатита С// Современные проблемы науки и образования. - 2012. - № 6;

2.Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002; 346: 1221-31;

3.Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015; 149: 389-97 [e10];

4.Bjornsson E, Angulo P. Hepatitis C and steatosis. Arch. Med Res, 2007. Vol. 38. No. 6. 621-627;

5.Bondini S., Younossi Z.M. Non-alcoholic fatty liver disease and hepatitis C infection. Minerva Gastroenterology Dietol. 2006.-Vol. 52.-No.2.-P.135-143;

6.Brunt EM. Histopathology of non-alcoholic fatty liver disease. Clin Liver Dis 2009; 13: 533-44;

7.Bugianesi E., Marchesini G., Gentilcore E. et al. Fibrosis in genotype 3 chronic hepatitis C and nonalcoholic fatty liver disease: role of insulin resistance and hepatic steatosis / Hepatology, 2006.- Vol.44.- No. 6- P.648-655;

8.Buzzetti E, Lombardi R, De Luca L, et al. Noninvasive assessment of fibrosis in patients with nonalcoholic fatty liver disease. Int J Endocrinol 2015; 2015: 343828;

9.Castera L. Steatosis, insulin resistance and fibrosis progression in chronic hepatitis / / Minerva Gastroenterol. Dietol. - 2006. - Vol. 52. - P. 125-134;

10. Cusi K. Role of insulin resistance and lipotoxicity in nonalcoholic steatohepatitis. Clin Liver Dis 2009; 13: 545-63;

11.EASL Clinical Practice Guidelines 2016;

12.Ekstedt M, Franzen LE, Mathiesen UL, et al. Low clinical relevance of the nonalcoholic fatty liver disease activity score (NAS) in predicting fibrosis progression. Scand J Gastroenterol 2012; 47: 108-15;

13.Eugene J., Yoon and Ke-Qin Hu Hepatitis C virus (HCV) Infection and Hepatic Steatosis. Int J. Med Sci. 2006. Vol.3 No. 2. P.53-56;

14.Fartoux L., Poujol-Robert A., Guechot J. et al. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C // Gut. - 2005. - Vol. 54. - P. 1003-1008;

15.Hassan K, Bhalla V, El Regal ME, et al. Nonalcoholic fatty liver disease: a comprehensive review of a growing epidemic. World J Gastroenterol 2014; 20: 12082-101;

16.Kim K.H., Hong S.P., Kim K., Park M.J. et al. HCV core protein induces hepatic lipid accumulation by activating SREBP1 and PPARgamma. BiochemBiophys Res Commun, 2007. - Vol.20. - No. 355. - P.883-888;

17.Kirpich IA, Marsano LS, McClain CJ. Gut-liver axis, nutrition, and non-alcoholic fatty liver disease. Clin Biochem 2015; 48 (13-14): 923-30;

18.Moriishi K., Mochizuki R., Moriya K., et al. Critical role of PA28gamma in hepatitis C, virus - associated steatogenesis and hepatocarcinogenesis. - AcadSci USA, 2007. - Vol. 30.- No. 5.- P. 1661-1666;

19.Negro F. Mechanisms and significance of liver steatosis in hepatitis C, virus infection. - World Journal Gastroenterology, 2006. - Vol.14 - No. 42. - P. 6756-6761;

20.Powell E.F., Jonsson J.R., Clouston A.D. Steatosis: co-factor in other liver diseases // Hepatology. - 2005. - Vol. 42. - P. 5-13;

21.Ratziu V, Bellentani S, Cortez-Pinto H, et al. A position statement on NAFLD / NASH based on the EASL 2009 special conference. J Hepatol 2010; 53: 372-84;

22.Szanto P., Grigorescu M., Dumitru I., Serban A. Steatosis hepatitis C, virus infection. Response to anti-viral therapy / Journal Gastrointestin Liver Dis. 2006. Vol.15 No. 2. P.

117-124;

23.Tsochatzis E, Papatheodoridis GV, Manesis EK, et al. Metabolic syndrome is associated with severe fibrosis in chronic viral hepatitis and non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2008; 27: 80-9;

24.Walsh M. J., Jonsson J. R., Richardson M. M., et al. Non-response to antiviral therapy is associated with obesity and increased hepatic expression of suppressor of cytokine signaling 3 (SOCS-3) in patients with chronic hepatitis C, viral genotype 1.- Gut., 2006.- Vol 55.- No. 4. - P. 529-535;

25.Waris G., Felmlee D.J., Negro F., Siddiqui A. Hepatitis C virus induces proteolytic cleavage of sterol regulatory element binding proteins and stimulates their phosphorylation via oxidative stress. Journal Virology, 2007. - Vol. 81.- No. 15.- P.8122-8130;

26.Wong V. W., Chan H. L. Transient elastography // J Gastroenterol Hepatol. - 2010. - Nov. - T. 25, No. 11. - p. 1726-1731;

27.Zhang D., Li P., Chen M., Liu L., Liu Y., Zhao Y., Wang R. Non-invasive assessment of liver fibrosis in patients with alcoholic liver disease using acoustic radiation force impulse elastography // Abdom Imaging. - 2015. - Apr. - T. 40, No. 4. - P. 723-729.