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The occurrence of liver steatosis in patients with chronic hepatitis C – the experience of the Clinical Center of Vojvodina, Serbia

Pojava steatoze jetre kod bolesnika sa hroničnim hepatitisom C – iskustvo Kliničkog centra Vojvodine

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Abstract

Background/Aim. Hepatic steatosis in patients with chronic hepatitis C occurs in about half of the cases. Its occurrence is influenced by factors of the host and viral factors and its importance lies in the fact that it reduces the success of antiviral therapy based on interferon in the treatment of chronic hepatitis C and that, associated with other factors, exacerbates liver disease. The aim of this study was to determine the prevalence and severity of steatosis in patients with chronic hepatitis C and to determine the factors that affect its occurrence. **Methods.** The study included 123 patients with chronic hepatitis C with diagnosis of liver steatosis made by liver biopsy and histopathological examination according to which ≥ 5% of hepatocytes was affected by fatty change. Based on the presence of steatosis, the patients were divided into two groups: 43 patients with steatosis and 80 patients without steatosis. The influence of certain factors on the occurrence of steatosis was examined using standard statistical methods. **Results.** Liver steatosis was found in 34.96% of patients with chronic hepatitis C, and a majority of patients (76.74%) had mild steatosis. Of the examined predictive factors for the occurrence of steatosis, statistical significance in its occurrence was connected to elevated body mass index (BMI), genotype 3 hepatitis C virus (HCV) and HCV viremia. **Conclusion.** Hepatic steatosis often occurs in people with chronic hepatitis C, and most often it is mild. The occurrence of hepatic steatosis in our sample was most often affected by genotype 3 HCV and HCV viremia level. Hepatic steatosis can reduce the success of antiviral therapy based on interferon and negatively affect chronic liver disease course. Therefore, we need to recognize it, treat it and make it withdraw.

Key words:
fatty liver; hepatitis c; risk factors; genotype; hepacivirus; body mass index.

Apstrakt

Uvod/Cilj. Steatoza jetre se javlja kod oko polovine bolesnika sa hroničnim hepatitisom C. Na njenu pojavu utiču faktori domaćina i faktori virusa, a njen značaj je u tome što smanjuje uspeh antivirusne terapije za lečenje hroničnog hepatitisa C zasnovane na interferonu i što, udružena sa drugim faktorima, pogoršava bolest jetre. Cilj ovog rada bio je da se utvrdi prevalenca i težina steatoze kod obolelih od hroničnog hepatitisa C i da se utvrde faktori koji utiču na njenu pojavu. **Metode.** Istraživanjem su obuhvaćena 123 bolesnika sa hroničnim hepatitisom C, kod kojih je dijagnoza steatoze jetre postavljena biopsijom jetre i patohistološkim (PH) pregledom. Uslov za pozitivnu PH dijagnozu steatoze jetre bio je da ≥ 5% hepatocita bude zahvaćeno masnom promenom. Na osnovu prisustva steatoze bolesnici su bili podeljeni u dve grupe: 43 ispitanika sa steatozom i 80 bez steatoze. Ispitivan je uticaj pojedinih faktora na nastanak steatoze, uz korišćenje standardnih statističkih metoda. **Rezultati.** Steatoza jetre nađena je kod 34,96% ispitanika sa hroničnim hepatitisom C, a najveći broj ispitanika (76,74%) imao je blagu steatozu. Od ispitivanih prediktivnih faktora za pojavu steatoze, statističku značajnost u njenoj pojavi imali su povišen indeks telesne mase [*body mass index* (BMI)], genotip 3 hepatitis C virusa (HCV) i HCV viremija. **Zaključak.** Steatoza jetre se često javlja kod bolesnika sa hroničnim hepatitisom C i najčešće je blaga. Na pojavu steatoze jetre u našem uzorku najviše su uticali genotip 3 HCV i visina HCV viremije. Steatoza jetre može umanjiti uspeh antivirusne terapije zasnovane na interferonu i može pogoršati tok hronične bolesti jetre. Zbog toga je treba prepoznati, lečiti i ukloniti.

Ključne reči:
jetra, masna infiltracija; hepatitis c; faktori rizika; genotip; hepatitis c, virus; telesna masa, indeks.

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Introduction

Interconnection and association of chronic hepatitis C (CHC) and liver steatosis were observed before detecting hepatitis C virus (HCV) when the occurrence of steatosis in the histopathological liver examinations of the patients with hepatitis non-A non-B with characteristic changes of chronic hepatitis was found [1]. Hepatic steatosis and CHC are more often found associated than separated, and the prevalence of hepatic steatosis in the patients with CHC is around 55% [2, 3]. With the prevalence of hepatitis C in general population from 1.6% to 2.8% worldwide and non-alcoholic fatty liver disease (NAFLD) from 20% to 30% of adults in Western countries, a significant number of patients in the world is affected with these two diseases [4–7].

Hepatitis C is a liver inflammation caused by HCV which in 75%–85% of cases has a chronic course with persistent liver inflammation. In case of the presence of risk factors, such as excessive alcohol consumption, age greater than 40 years at the time of acquiring infection, male gender, coinfection with hepatitis B virus (HBV), human immunodeficiency virus (HIV), the simultaneous presence of steatohepatitis, insulin resistance, etc., it could result in further progression of the disease and development of liver cirrhosis in approximately 10%–20% of patients during 20–30 years after acquiring HCV infection [8, 9]. HCV has 6 genotypes, of which the most often genotypes in humans are genotype 1 and 3 which have a proven direct steatogenic effect on liver [10, 11]. Hepatic steatosis may be mild and stable disease, but, if accompanied with necroinflammatory changes in hepatocytes (steatohepatitis), it receives a progressive form of the disease which induces the development of fibrosis, the formation of liver cirrhosis and even hepatocellular carcinoma [12, 13]. Hepatic steatosis occurs in people with excessive alcohol consumption and it is also common in obese patients, in patients with diabetes mellitus, dyslipidemia, as a side effect of certain drugs (corticosteroids) and states (parenteral nutrition, starvation) [7, 14].

In case of liver steatosis occurrence in patients with CHC, the 'viral factors' such as HCV genotype and HCV viremia, and the 'host factors' such as obesity, diabetes mellitus, dyslipidemia, alcohol consumption and others, are concerned when it comes to the development of steatosis [15]. If host factors are dominating, we talk about metabolic steatosis which is based on insulin resistance and which carries the risk of developing diabetes and cardiovascular diseases [16, 17]. With the infection with genotype 3 HCV, structural proteins of the virus act directly with a steatogenesis on hepatocytes causing the accumulation of fatty particles in hepatocytes. Therefore, liver steatosis with genotype 3 HCV infection is significantly more common (70%–80% of cases), and among them, the degree of steatosis correlates with HCV viremia and withdraws after successful eradication of viruses with antiviral therapy [18, 19]. The infection with other HCV genotypes involves the interference of metabolism of lipids which the virus uses for its life cycle in hepatocytes causing the formation of insulin resistance by a joint action of viral and metabolic factors of the host [20, 21]. In these patients, it is necessary to eliminate metabolic factors causing the development of liver steatosis and that involves dietary measures, treatment of insulin resistance, diabetes, hyperlipidemia, the application of hepatoprotectives, antioxidants, and lifestyle changes [22, 23]. Clinical significance of liver steatosis in patients with CHC reflects in a rapid progression towards liver fibrosis, reduces the success of the standard double antiviral therapy with pegylated interferon and ribavirin and increases a risk of cardiovascular diseases and diabetes [24, 25]. In case of unsuccessful treatment and the existence of other adverse factors, through the development of liver cirrhosis, steatosis can lead to the development of hepatocellular carcinoma [26, 27]. CHC and NAFLD are among most often indications for liver transplantation in developed countries [28, 29].

The aim of the study was to determine the existence, frequency and degree of liver steatosis in patients with CHC, and to examine the influence of individual factors of the host and viruses on the emergence appearance of liver steatosis.

Methods

The research included 123 patients with CHC at the Clinic for Infectious Diseases of the Clinical Center of Vojvodina (CCV) in Novi Sad, Serbia. All respondents gave their consent to participate in the research by signing an informed consent and the Ethical Committee of CCV approved the examination. Based on the presence of liver steatosis, the respondents were divided into two groups: there were 43 patients with hepatic steatosis and CHC in the first one and 80 people with CHC without steatosis in the other one. The CHC diagnosis was based on the presence of elevated activity of alanine aminotransferase (ALT) and anti-CHC antibodies in blood, lasting longer than six months, a positive Polymerase chain reaction (PCR) test and histopathological examination of a liver tissue sample obtained by blind biopsy. Qualitative and quantitative PCR test was done at the Virology Laboratory of the Institute for Infectious and Tropical Diseases at the Clinical Center of Serbia in Belgrade using Cobas Amplicor HCV Test version 2.0 (Roche Diagnostics, Menheim), sensitivity: 50 IU/mL. HCV genotyping was done using the Linear Array HCV genotyping test (Roche Diagnostics). Histopathological liver biopsy examination was done at the Centre for Pathology and Histology of CCV. Determination of necroinflammatory activity and the degree of fibrosis was expressed according to Knodell modified numerical score. The presence of steatosis was stated on the basis of the percentage of hepatocytes affected by fatty changes of ≥ 5%. The degree of steatosis was expressed by Brunt system modified by Kleiner, by which mild steatosis has 5%–33% of hepatocytes affected by the fatty change, moderate (> 33%–66%) and severe (> 66%). Data about taking medications that can lead to liver steatosis (amiodarone, nifedipine, diltiazem, tamoxifen, glucocorticoids, synthetic estrogens, methotrexate), contact with hepatotoxic substances (organic solvents, phosphorus, fungi toxins) and excessive alcohol consumption six months prior to the examination (daily alcohol intake of more than 20 g/day for women and more than 30 g/day for men) were

collected from the respondents, and such respondents were not included in the study. People with HBsAg and anti-HIV seropositivity were also not included in the study. All respondents did anthropometric measurements of body height and weight to calculate the body mass index (BMI) representing the ratio of body weight and body height square expressed in meters (kg/m^2) as follows: BMI > 30.0 kg/m^2 – obese people, BMI 25–29.9 kg/m^2 – overweight, i.e., pre-obese people and BMI 18.5–24.9 kg/m^2 – normal weight individuals.

Statistical data processing was carried out by using the statistical package SPSS version 13.0. Testing statistical significance was determined for parametric data by analysis of variance test (ANOVA) and for non-parametric tests by χ^2 test, Fisher's or Mann Whitney's test. For all tests, the level of of statistical significance was established at 0.05.

Results

Demographic and clinical characteristics of patients are shown in Table 1. Of 123 patients with CHC, liver steatosis was found in 43 (34.96%) respondents. Thirty-three patients (76.74%) had mild degree steatosis, six of them (13.95%) had moderate steatosis, while only four (9.3%) patients had signs of severe hepatic steatosis. As for the host factors which can influence the occurrence of steatosis, measuring BMI determined that respondents with steatosis had a statistically significant higher BMI compared to the group without steatosis (t = -4.129, p < 0.05). The mean BMI in respondents with hepatic steatosis amounted to 25.53 kg/m^2, whereas in respondents without liver steatosis the mean BMI was 23.53 kg/m^2. According to the BMI, respondents with hepatic steatosis fell within the range of pre-obese people, while those without steatosis fell within normal weight people range. The mean value of triglycerides in the group of subjects with hepatic steatosis was 1.503 mmol/L, which was statistically significantly higher than in the group without steatosis where this value was 1.228 mmol/L (t = -2.286, p < 0.05). The mean value of the total cholesterol in the serum of the respondents with liver steatosis amounted to 5.00 mmol/L, which was within the limits of the normal range and it was no significantly different when compared to the respondents without steatosis, where this value was 4.74 mmol/L (t = -1.445, p > 0.05). The analysis of HCV genotypes in the respondents with CHC and liver steatosis showed the greater share of genotype 3 compared to other genotypes in the respondents with hepatic steatosis and those without steatosis, 21/43 (48.84%) vs. 20/80 (25%), which was statistically significant (Fisher test, p < 0.05). The share of certain HCV genotypes in the group of patients with and without liver steatosisis is shown in Figure 1. As to the correlation of share of certain HCV genotypes and the degree of liver steatosis, we found that the share of genotype 3 HCV increased with the degree of steatosis which was statistically significant (c^2 = 7.882, p < 0.05). Measuring the level of HCV RNA in serum of the respondents in the group with hepatic steatosis, we found the mean value of 6,728.968 IU/mL which was statistically significantly higher than the mean value of HCV RNA level of the respondents without liver steatosis which was 2,397.232 IU/mL (t = -2.978, p < 0.05). Analysis of the mean values of the level of HCV RNA viremia in the respondents without steatosis, with first-degree steatosis and those with second and third-degree steatosis together, showed statistically significant difference among the observed groups. The mean value of HCV RNA viremia (Kruskal-Wallis test, X^2 = 9.492, p <0.05) increased with the degree of steatosis. The ratio of HCV RNA viremia and the degree of steatosisis is shown in Figure 2. The mean value of genotype 3 HCV RNA viremia in the group of subjects with hepatic steatosis was 10,833.357 IU/mL, which was significantly higher than the average viremia of HCV genotype 3 in the group of respondents without steatosis, 3,091.118 IU/mL (t = 2.207, p < 0.05). It was not the case with non-3 genotype HCV RNA viremia where a small difference in the mean viremia was measured (2,811.141 IU/mL in the group with steatosis, 2,165.936 IU/mL in the group without steatosis) which did not prove itself to be statistically significant. The ratio of the number of viral particles in serum of the patients with genotype 3 HCV infection and the degree of steatosis showed that the level of viremia increased with the degree of steatosis. The correlation was statistically significant (ANOVA, F = 3.36, p < 0.05). The ratio of HCV RNA viremia and the degree of steatosisis is shown in Figure 2.

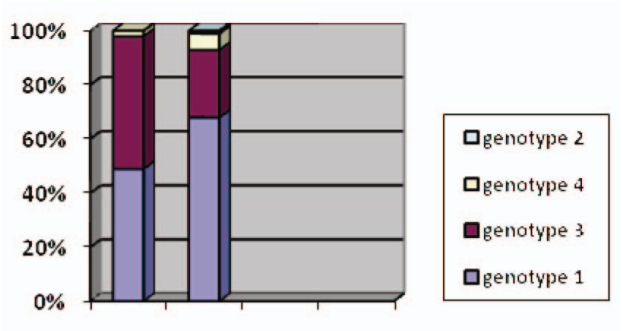

Fig. 1 – Hepatitis C virus (HCV) genotypes in patientes with without liver steatosis.
left – Steatosis; right – No steatosis

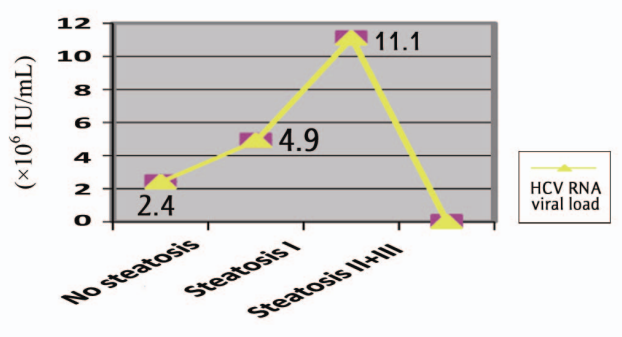

Fig. 2 – Hepatitis C virus ribonucleic acid (HCV RNA) viral load and the degree of liver steatosis.

Table 1

Demographic and clinical characteristics of patients

Characteristics	Steatosis (n = 43)	No steatosis (n = 80)	*p*
Gender, n (%)			
male	33 (76.7)	89 (72.4)	> 0.05
female	10 (23.3)	34 (27.6)	> 0.05
Age (mean ± SD; years)	35.8 ± 10.1	36.14 ± 11.6	> 0.05
BMI (mean ± SD; kg/m^2)	25.53	23.53	> 0.05
Glucosae (mean ± SD; mmol/L)	5.38 ± 1.42	5.03 ± 1.07	< 0.05
Triglycerides (mean ± SD; mmol/L)	1.503 ± 0.79	1.228 ± 0.527	> 0.05
Cholesterol (mean ± SD; mmol/L)	5.00 ± 1.16	4.74 ± 0.837	> 0.05
ALT (mean ± SD; IU/L)	116.26 ± 73.52	101.71 ± 74.38	> 0.05
AST (mean ± SD; IU/L)	59.67 ± 34.24	56.74 ± 38.13	> 0.05
GGT (mean ± SD; IU/L)	73.49 ± 53.12	70.21 ± 48.38	> 0.05
HCV genotype, n (%)			
1	21 (48.84)	54 (67.50)	> 0.05
2	1 (2.32)	1 (1.25)	> 0.05
3	21 (48.84)	20 (25.00)	< 0.05
4	0	5 (6.25)	> 0.05
HCV RNA viral load (×10^6 IU/mL), n (%)			
all genotypes	6.72	2.39	< 0.05
genotype 3	10.83	3.09	< 0.05
genotypes non-3	2.81	2.16	> 0.05

BMI – body mass index; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma-glutamyl transferase; HCV – hepatitis C virus; RNA – ribonucleic acid; SD – standard deviation.

Table 2

Results of multivariate logistic regression predictive factors for the development of hepatic steatosis

Variable	Regression coefficient	OR	95% CI	*p*
BMI	0.364	1.439	1.175–1.761	0.000
HCV load	0.000	1.0	1.0–1.0	0.025
HCV genotip 3	0.043	1.113	1.053–1.100	0.010

BMI – body mass index; HCV – hepatitis C virus; OR – odds ratio; CI – confidence interval.

A summary of all the examined predictive factors for hepatic steatosis showed a statistical significance for elevated BMI, elevated triglycerides, genotype 3 HCV and HCV viremia. When all of the above factors were taken into account when calculating multivariate logistic regression, we found that elevated BMI, genotype 3 HCV and HCV viremia statistically significantly contribute to liver steatosis. Histology activity index (HAI) score in the respondents with hepatic steatosis was not significantly different compared to the respondents without liver steatosis (Mann-Whitney U = 1,687, $p > 0.05$). A statistically significant difference regarding the degree of liver fibrosis between the observed groups (Fisher test, $p > 0.05$) was not found (Table 2).

Discussion

The prevalence of steatosis in patients with CHC occurs in about half of the cases [2, 3]. In hepatitis C viral infection caused by genotype 3 HCV, steatosis prevalence is higher and more pronounced than in other genotypes. Liver steatosis with infection with other HCV genotypes (non-3 genotype) is associated with the metabolic factors of the host and the occurrence of insulin resistance. Accordingly, if the sample has more people infected with genotype 3 HCV, or if the sample has more people with pronounced metabolic factors such as obesity, hypertriglyceridemia, diabetes mellitus and hypertension, steatosis percentage is higher. Liver steatosis is concerned when more than 5% of hepatocytes is affected by fatty changes, which can be seen in the histopathological examination of liver biopsy, and radiological examinations when the accumulation of fatty particles in the liver is even more pronounced [30]. The overall prevalence of steatosis is largely affected by histopathological criterion (what the lowest percentage of hepatocytes affected by fatty change is required for the diagnosis of hepatic steatosis. For some, it is more than 0%, according to others it is more than 1%, somewhere it is more than 3%, but usually it is more than 5% of hepatocytes affected by the fatty change.

In people with CHC, our research determined the prevalence of steatosis of 34.96% (43/123). The resulting prevalence of steatosis was lower compared with the data of most authors, due to heterogeneous criteria, different demographic characteristics of the sample and different share of genotype 3 HCV. The closest prevalence of steatosis was obtained in the research of Greek authors (31.74%) and the research of Pakistani authors (39%) where there was a group of patients with very similar demographic and clinical characteristics and the same histological criteria for the diagnosis of steatosis [31, 32]. An interesting research was conducted by Pais et al. [33] who used steatotest as a noninvasive marker of steatosis

instead of liver biopsy and found that 43% of respondents with CHC had signs of steatosis, which was also similar to our result. In our neighborhood, a group of Hungarian authors [34], found steatosis in 64% of the respondents infected by genotype 1 HCV, but their sample also included the respondents with significant alcohol consumption, patients with diabetes and a significant number of obese patients with BMI > 30 kg/m^2, and these are all diseases and conditions which facilitate the development and incidence of liver steatosis; therefore, they obtained a significantly higher percentage of people with liver steatosis. A group of Romanian researchers [35] found liver steatosis in 76.59% of the respondents with CHC, which was significantly larger percentage than that of the respondents with other viral hepatitides. However, their work did not state histopathological diagnostic criteria for steatosis, did not include the share of genotype 3 HCV which is steatogenic and also did not include the demographic characteristics of the respondents such as obesity, patients habits (such as excessive alcohol consumption), or comorbidities that may cause steatosis. Our results showed that most respondents, 33 (76.74%), had signs of mild steatosis, 6 (13.95%) had signs of moderate steatosis while 4 (9.31%) of respondents had signs of severe steatosis. According to the literature data, steatosis in patients with CHC is usually mild, when fatty changes affect up to 33% of hepatocytes. Using the same histopathological criteria for determining the degree of steatosis, Irimia et al. [36] also found a major presence of mild steatosis in patients with CHC while they had more people with severe steatosis. This can be explained by the greater age of the respondents in their study, lack of data on BMI of their subjects, habits of patients regarding alcohol and drugs use that can lead to steatosis and the existence of comorbidity that facilitate the emergence of liver steatosis.

As for the factors that may affect the occurrence of steatosis in our research, it was found that elevated BMI, elevated triglycerides, the presence of genotype 3 HCV and the level of HCV RNA viremia were statistically significant. When all of the above factors are taken into account together when calculating the multivariate logistic regression, elevated BMI, presence of HCV genotype 3 and the level of HCV RNA viremia remained as statistically significant predictors of steatosis. Such a result was also obtained in earlier investigations of other authors [37–39]. All of these factors (dietary measures, lifestyle changes and habits which can lead to the reduction of overweight and lowering of the BMI to the value of normal weight as well as effective antiviral therapy that can lead to the eradication of HCV) could be eliminated, and if eliminated, signs of hepatic steatosis withdraw. It is primarily provided by a new antiviral therapy for the treatment of CHC based on direct acting antivirals, which unlike standard antiviral therapy based on a combination of pegylated interferon and ribavirin, have high efficiency and leads to the eradication of the HCV in 95% of infected individuals [40].

Conclusion

In our study, hepatic steatosis occurred in 34%–96% of patients with CHC and it was usually mild. The occurrence of hepatic steatosis was mostly affected by elevated BMI, genotype 3 HCV and the level of HCV RNA viremia. In patients with CHC and hepatic steatosis, genotype 3 HCV was present in half (48.84%) of the respondents, and its presence was growing with the increase of the degree of steatosis. In our sample, respondents with hepatic steatosis had a statistically significant higher HCV RNA viremia compared to those without steatosis and this viremia grew along with the degree of steatosis. Hepatic steatosis can reduce the success of antiviral therapy based on interferon and ribavirin, but with the emergence of more efficiently new antivirals, the impact of steatosis on treatment efficacy needs to be examined. Steatosis caused primarily by viral factors would be eliminated after a successful antiviral treatment, but the one primarily caused by host's factors, i.e., metabolic factors may adversely affect the future course of the liver disease.

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