ORIGINAL ARTICLE

UDC: 616.36-08
DOI: 10.2298/VSP150826190P

# The influence of hepatic steatosis on the success of antiviral therapy for chronic hepatitis C

## Uticaj steatoze jetre na uspeh antivirusne terapije hroničnog hepatitisa C

**Tomislav Preveden*†, Maja Ružić*†, Maria Pete***

***Clinic for Infectious Disease, Clinical Center of Vojvodina, Novi Sad, Serbia;**
**†Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia**

**Abstract**

**Background/Aim.** Chronic hepatitis C and liver steatosis often appear simultaneously in the same person, and steatosis can lead to worsening of liver disease and reducing the success of the treatment of chronic hepatitis C. Treatment of one disease can influence and cause favorable impact on treatment of other diseases. The aim of this study was to determine the incidence of liver steatosis in patients with chronic hepatitis C and to examine the impact of steatosis of the liver and other predictors on the success of antiviral therapy for chronic hepatitis C. **Methods.** The study included 123 patients with chronic hepatitis C treated with pegylated interferon alfa 2a in combination with ribavirin. The patients were divided into two groups based on the presence of cirrhosis: the group I consisted of 43 (34.9%) patients with steatosis and the group II consisted of 80 (65.1%) patients without liver steatosis. The success of the treatment was evaluated on the basis of the stable virological response. **Results.** The presence of steatosis was determined in 34.96% of the patients. The overall success of antiviral therapy was found in 74.79% of the patients. The success of antiviral therapy was present in 62.79% of the patients with hepatic steatosis, and in 81.25% the patients without steatosis ($p < 0.05$). The success of antiviral treatments was seen in 80.95% of the patients with hepatic steatosis and the genotype of hepatitis C virus 3. The predictors of antiviral therapy success for chronic hepatitis C in our study were patient's age, duration of infection, genotype 3, steatosis and severe fibrosis or cirrhosis. **Conclusion.** Liver steatosis is often present in patients with chronic hepatitis C. It has negative impact on the efficacy of antiviral therapy in patients with infection with genotype non-3 hepatitis C virus. Therefore, hepatic steatosis in these patients must be eliminated or treated prior to application of antiviral therapy.

**Key words:**
**hepatitis c; fatty liver; genotype; age factors; interferon-alpha; ribavirin; treatment outcome.**

**Apstrakt**

**Uvod/Cilj.** Hronični hepatitis C i steatoza jetre se često javljaju udruženo kod iste osobe, a steatoza jetre može dovesti do pogoršanja bolesti jetre i može smanjiti uspeh lečenja hroničnog hepatitisa C. Lečenjem jedne bolesti povoljno se utiče na ishod lečenja druge bolesti. Cilj ovog rada bio je da se utvrdi učestalost steatoze jetre kod bolesnika sa hroničnim hepatitisom C i da se ispita uticaj steatoze jetre i drugih prediktora na uspeh antivirusne terapije hroničnog hepatitisa C. **Metode.** U studiju su bila uključena 123 bolesnika sa hroničnim hepatitisom C, koji su lečeni pegilovanim interferonom alfa 2a u kombinaciji sa ribavirinom. Bolesnici su na osnovu prisustva steatoze jetre podeljeni u dve grupe, grupu I sa 43 bolesnika i steatozom jetre i grupu II sa 80 bolesnika bez steatoze jetre. Uspeh lečenja ocenili smo na osnovu postignutog stabilnog virusološkog odgovora. **Rezultati.** Postojanje steatoze utvrđeno je kod 34,96% bolesnika. Ukupan uspeh antivirusne terapije postignut je kod 74,79% bolesnika. Uspeh antivirusne terapije zabeležen je kod 62,79% bolesnika sa steatozom jetre i kod 81,25% bolesnika bez steatoze ($p < 0,05$). Uspeh antivirusnog lečenja postignut je kod 80,95% bolesnika sa steatozom jetre i genotipom 3 virusa hepatitisa C. Prediktori uspešnosti antivirusne terapije hroničnog hepatitisa C u našem radu bili su starost bolesnika, dužina trajanja infekcije, genotip 3, steatoza i izražena fibroza jetre. **Zaključak.** Steatoza jetre često je prisutna kod bolesnika sa hroničnim hepatitisom C i ima negativan uticaj na efikasnost antivirusne terapije kod bolesnika sa infekcijom genotipom non-3 hepatitis C virusa. Zbog toga se steatoza jetre kod ovih bolesnika mora eliminisati ili lečiti pre primene antivirusne terapije.

**Ključne reči:**
**hepatitis c; jetra, masna infiltracija; genotip; životno doba, faktor; interferon-alfa; ribavirin; lečenje, ishod.**

**Correspondence to:** Tomislav Preveden, Clinic for Infectious Disease, Clinical Center of Vojvodina, Novi Sad, HajdukVeljkova 1-5, 21 000 Novi Sad, Serbia. Phone: +381 21 484 3305. E-mail: tomislav.preveden@mf.uns.ac.rs

## Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. The third of those who become chronically infected are predicted to develop liver cirrhosis or hepatocellular carcinoma. According to recent estimates, more than 185 million people around the world have been infected with HCV, of whom 350,000 die each year [1]. Despite of the high prevalence of this disease, most people infected with the virus are unaware of their infection. Furthermore, the HCV prevalence across Europe ranges between 0.4% and 3.5%, with a wide geographical variation and higher rates in the south and the east [2, 3].There are six genotypes of HCV having epidemiological and clinical significance. Genotype 1 dominates in European countries and also in Serbia, genotype 3 is more common among injecting drug users, and has a direct steatogenic effect on the liver [4, 5].

During the last decade, the standard of care (SOC) for chronic HCV patients consisted of pegylated interferon-alfa (PEGIFN) 2a or 2b combined with ribavirin (RBV). In patients with HCV genotype 3, the combination therapy with PEGIFN plus RBV is usually given during 24 weeks, achieving rates of stable virological response (SVR) of about 75–85%. In patients with HCV genotype 1 antiviral therapy is usually given for 48 weeks, resulting in SVR of 40–50% [6]. Recently approved boceprevir and telaprevir used in combination with PEGIFN plus RBV and polymerase inhibitors such as nucleos(t)ide inhibitors (NIs) and non-nucleoside inhibitors (NNIs) substantially improve the SVR rates in both treatment-naive and treatment experienced genotype 1 patients, but they are not available in our country. Due to the lack of efficacy and frequent side effects, the predictors of favorable virological response are studied in order to improve antiviral therapy for selected patients who are most likely to achieve SVR and healing. The predictors of favorable virological response are: white race, younger patients (< 40 years), female gender, body mass index (BMI) $\leq 25$ kg/m$^2$, the absence of cirrhosis and severe fibrosis (F 3–4), the absence of insulin resistance and diabetes, the absence of steatosis, the absence of comorbidities such as HIV or hepatitis B coinfection, excess alcohol intake, HCV genotype 2 and 3, low HCV baseline viremia (< 600,000–800,000 IU/mL) and host interleukin 28B gene polymorphisms [7, 8].

Chronic hepatitis C and liver steatosis often appear simultaneously in the same person, and the prevalence of steatosis in chronic hepatitis C is 2–3 times higher than the prevalence of steatosis in other chronic liver diseases, ranging 40–80%, depending on the research and applied criteria [9, 10]. It has been proven that genotype 3 has a direct steatogenic effect on hepatocytes, and in patients with chronic hepatitis caused by HCV genotype 3, the prevalence of steatosis is 70–80% [11, 12]. Steatosis represents the accumulation of fatty particles, mainly of triglycerides in hepatocytes, the limit is usually set at 5% of hepatocytes affected by fatty change, < 5% is considered to be the normal state, > 5% is considered as steatosis [13]. The clinical significance of liver steatosis is reflected on faster progression to fibrosis in patients with chronic HCV infection, less success of antiviral therapy and risk for developing hepatocellular carcinoma [14–16].

Our hypothesis was that liver steatosis often occurs in patients with hepatitis C and reduces the success of antiviral therapy. The aim of this study was to determine the incidence of liver steatosis in patients with chronic hepatitis C, and the impact of steatosis and other predictors on the success of antiviral therapy.

## Methods

The study included 123 patients with chronic hepatitis C, treated in the Clinic for Infectious Diseases, Clinical Center of Vojvodina in Novi Sad, Serbia, during the period from January 2010 to June 2012. All the subjects were "naive patients", not treated with antiviral therapy before. The patients were divided into two groups based on the presence of steatosis of the liver: the group I of 43 patients with hepatic steatosis and the group II of 80 patients without steatosis. The presence of steatosis was determined by histopathological examination of liver biopsy, on the basis of > 5% of hepatocytes affected by fatty changes. Histopathological examination of liver biopsy was performed in the Centre for Pathology and Histology, Clinical Center in Novi Sad, Serbia according to the Metavir score. From the research were excluded: obese patients (BMI $\geq$ 30 kg/m$^2$), patients who used drugs that could lead to cirrhosis and people with excessive use of alcohol (alcohol consumption of more than 40 mg *per* day for men and more than 20 mg *per* day for women six months before treatment).

All the patients were treated with combined therapy, PEGIFN alfa 2a or alfa 2b and ribavirin in standard doses. The duration of treatment depended on the genotype of hepatitis C virus, genotype 2 and 3 HCV treatment lasted 24 weeks, and for genotype 1 and 4 HCV 48 weeks. Antiviral therapy is considered successful when a sustained viral response, based on the absence of HCV RNA in serum of patients 6 months after completion of antiviral treatment, using the polymerase chain reaction (PCR) method was achived. PCR testing and genotyping was conducted at the Virology Laboratory of the Institute for Infectious and Tropical Diseases, Clinical Center of Serbia, Belgrade, with Cobas Amplicor HCV Test version 2.0 (Roche Diagnostics, Menheim), sensitivity of 50 U/mL, before treatment, during treatment and six months following the completion of treatment.

Statistical analysis was performed with the statistical package SPSS version 13.0. The descriptive statistical parameters are shown in standard statistical variables, arithmetic mean ($\bar{x}$), standard deviation (SD), interval values (maximum and minimum). Tests of statistical significance were determined by ANOVA parametric data (analysis of variance), and the non-parametric Fisher's or Mann Whitney's test. A statistically significant value was set at $p < 0.05$. In analyzing the impact of risk factors on the success of the therapy multivariate logistic regression analysis was used.

**Results**

From a total of 123 patients the majority (89) of the patients were male (72.36%), the average age of patients was 36.05 (SD ± 11.12) years. In the overall sample 92 (74.79%) patients were younger than 40 years. The average BMI for all the patients was 24.37 ± 2.44 kg/m$^2$. The most common route of transmission of HCV infection was through intravenous drug use, in 81 (65.9%) patients. The average duration of HCV infection was determined in 106 of the patients with the known route of HCV transmission, which was 11 (11.96 ± 9.36 years). Alanine aminotransferase (ALT) was elevated in 113 (91.86%) of the patients, with the average value of 106.80 ± 74.112 U/L [normal range (nr) 5–48 U/L]. Aspartate aminotransferase (AST) was elevated in 78 (63.41%) of the patients, with the average value of 57.76 ± 36.706 U/L (nr 5–37 U/L). Gamma glutamiltransferase (GGT) was elevated in 61 (50.45%) of the patients, with the average value of 71.36 ± 49.900 U/L (nr 1–64 U/L). The value of total bilirubin was normal in all the subjects and all the patients had normal albumin. They were mostly HCV genotype 1, found in 75 (60.98%) of the patients, 41 (33.33%) of the patients had genotype 3, genotype 4 was found in 5 (4.06%) of the patients and genotype 2 in two (1.63%) of the patients. There were no patients simultaneously infected with two or more genotypes of HCV. The average value of HCV RNA viral load before treatment was 3,911578,888 ± 7,869,037,777 U/mL. The vast majority of the patients,107 from 123 (86.99%), had a HCV viral load greater than 800,000 U/mL. Histopathological examination of liver biopsy found that 28 (22.76%) of the patients were without liver fibrosis (F0), with mild fibrosis (F1) were 45 (36.58%) of the patients, with moderate fibrosis (F2) were 34 (27.64%) of the patients, with severe fibrosis (F3) were 15 (12.19%) of the patients and with liver cirrhosis (F4) was one (0.81%) of the patient. In relation to the existence of mild/moderate (F0-F2) and severe fibrosis or cirrhosis (F3-F4), the majority of the patients, a total of 79 (64.22%) had no or mild to moderate fibrosis (F0-2). From a total of 123 patients included in the study it was found that 43 (34.96%) of the patients had hepatic steatosis, while 80 (65.04%) of the patients had no steatosis. Demographic, clinical and virological characteristics of the patients are shown in Table 1.

The success of antiviral therapy combination (PEGIFN+RBV) measured by the achievement of SVR was found in 92 (74.79%) of the patients. From the usual predictive factors for achieving SVR, gender of patients did not show statistically significant (Fisher test, $p = 0.292$). SVR was achieved in 69 (77.52%) of the men and 23 (64.70%) of the women. The patients who achieved SVR were significantly younger mean age 33.41 ± 10.48 years compared to those who did not achieve SVR mean 46.17 ± 12.20 years (*t*-test, $p = 0.001$). The patients who achieved SVR had a slightly lower BMI (mean 24.17 ± 2.48 kg/m$^2$), compared to BMI in those who did not achieve SVR (mean 25.16 ± 2.16 kg/m$^2$) but this difference was not statistically significant (*t*-test, $p = 0.092$). The average duration of HCV infection in the patients who achieved SVR was 9.9 ± 8.75 years, which was significantly shorter compared to the duration of infection in the patients who did not achieve SVR and it was 16.87 ± 12.79 years (*t*-test, $p = 0.004$). None of biochemical parameters monitored as potential predictors of achieving SVR, was statistically significant.

**Table 1**

**Baseline characteristics of the patients with chronic hepatitis**

| Characteristics | Patients (n = 123) |
|---|---|
| Gender (male/female), n (%) | 89/34 (72.36/27.64) |
| Age (years), $\bar{x}$ ± SD | 36.05 ± 11.12 |
| BMI( kg/m$^2$), $\bar{x}$ ± SD | 24.37 ± 2.44 |
| IVDUs, n (%) | 81 (65.9) |
| Duration of HCV infection (years), $\bar{x}$ ± SD | 11.96 ± 9.36 |
| Glucose (mmol/L), $\bar{x}$ ± SD | 5.05 ± 1.01 |
| Cholesterol (mmol/L), $\bar{x}$ ± SD | 4.82 ± 0.964 |
| Triglycerides (mmol/L), $\bar{x}$ ± SD | 1.32 ± 0.641 |
| ALT (U/L), $\bar{x}$ ± SD | 106.80 ± 74.112 |
| AST (U/L), $\bar{x}$ ± SD | 57.76 ± 36.706 |
| GGT (U/L), $\bar{x}$ ± SD | 71.36 ± 49.900 |
| Alpha-fetoprotein (U/L), $\bar{x}$ ± SD | 3.80 ± 4.932 |
| HCV genotype, n (%) | |
| 1 | 75 (60.98) |
| 2 | 2 (1.63) |
| 3 | 41 (33.33) |
| 4 | 5 (4.06) |
| Viral load (×10$^6$ U/mL), $\bar{x}$ ± SD | 3.9 ± 7.8 |
| Liver fibrosis, n (%) | |
| F0-2 | 79 (64.22) |
| F3-4 | 44 (35.78) |
| Steatosis, n (%) | 43 (34.96) |

**BMI – body mass index; IVDUs – intravenous drug users; HCV – hepatitis C virus; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma glutamyltransferase; $\bar{x}$ – mean value; SD – standard deviation.**

According to HCV genotype, all the patients were divided into two groups, the group I of the patients with genotype 3 and the group II of the patients with genotype non-3 (HCV genotype 1, 2 and 4). SVR in the genotype 3 group was achieved in 36 (87.80%) of the patients, and in the genotype non-3 group in 56 (68.29%) of the patients which was statistically significantly higher SVR in patients with HCV genotype 3 ($\chi^2$ test, $p$ = 0.049). The mean value of HCV viral load in the successfully treated patients was 2.330.839 U/mL, whereas in the patients treated unsuccessfully it was 2.735.340 U/mL, which was not statistically significantly different ($p$ = 0.608). According to liver fibrosis the patients without fibrosis or with mild/moderate fibrosis (F0-2) had SVR in 63 (79.74%) of the cases, the patients with severe fibrosis or cirrhosis (F3-4) in only 17 (38.63%) of the cases. This difference was statistically significant ($\chi^2$ test, $p$ = 0.004). The impact of demographic, biochemical, virological and histopathological factors on SVR are shown in Table 2.

Finally, in the patients with hepatic steatosis SVR was achieved in 27/43 (62.79%) of the patients, whereas in the patients without steatosis SVR was achieved in 65/80 (81.25%) of the patients. The difference in achieving SVR in the patients with steatosis and the group without steatosis was statistically significant (Fisher test, $p$ = 0.042). Analysis of all the predictive factors for achieving SVR (age, duration of infection, genotype 3, the presence of steatosis and fibrosis) observed in the multivariate logistic regression analysis, showed that two factors, namely age of the patients and the presence of fibrosis, significantly contributed to achieving SVR. Considering SVR in 21 patients with steatosis and HCV genotype 3, it was achieved in 17 (80.95%) of the patients, while in 22 patients with genotype non-3 and steatosis it was achieved in 11 (50.00%) of the patients. The SVR according to the presence of steatosis and HCV genotype is shown in Figure 1.

## Discussion

Several factors have influence on the prevalence of steatosis: the number of patients infected with HCV genotype 3, which gives a higher incidence of steatosis compared to ot-

**Table 2**

**Characteristics of patients with respect to stable virological response (SVR) rates**

| Characteristics | SVR (n = 92) | Without SVR (n = 31) | *p* |
|---|---|---|---|
| Gender (male/female), n | 69/23 | 20/11 | 0.292 |
| Age (years), $\bar{x}$ ± SD | 33.41 ± 10.48 | 46.17 ± 12.20 | **0.001** |
| BMI (kg/m$^2$), $\bar{x}$ ± SD | 24.17 ± 2.48 | 25.16 ± 2.16 | 0.092 |
| Duration of HCV infection (years), $\bar{x}$ ± SD | 9.9 ± 8.75 | 16.87 ± 12.79 | **0.004** |
| HCV genotype 3/non3, n (%) | 36/56 (87.80/68.29) | 5/26 (12.20/31.71) | **0.049** |
| HCV viral load (×10$^6$ U/mL) | 2.33 | 273 | 0.608 |
| Fibrosis (F0-2/F3-4), n (%) | 63/17 (79.74/38.63) | 16/27 (20.25/61.36) | **0.004** |
| Steatosis (yes/no), n (%) | 27/65 (62.79/81.25) | 16/15 (37.21/18.75) | **0.042** |

**BMI – body mass index; HCV – hepatitis C virus; $\bar{x}$ – mean value; SD – standard deviation.**

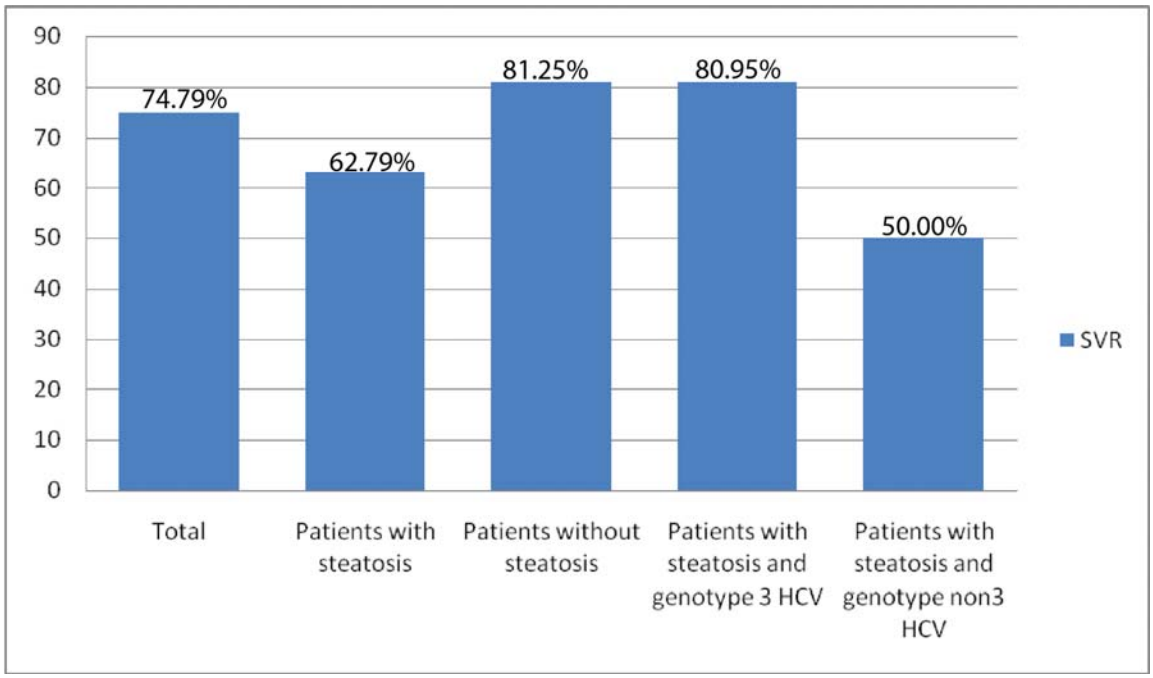


**Fig. 1 – Sustained viral response (SVR) according to the presence of steatosis and hepatitis C virus (HCV) genotype.**

her genotypes, the number of patients with a higher BMI, or a larger number of obese and overweight patients, patients with diabetes mellitus, patients with metabolic syndrome, and histopathological criteria for the diagnosis of steatosis (> 0% > 1%, or more than 5% of hepatocytes affected by fatty change). In our study, the prevalence of liver steatosis in the patients with chronic HCV infection was 34.96%. A similar prevalence of steatosis in patients with hepatitis C by 31.92% found Savooula et al. [17]). Fierbinteanu-Bratićevici et al. [18], found the prevalence of steatosis as 57%, but they applied lower histopathological criteria for the diagnosis of steatosis (≥ 1% of hepatocytes affected by fatty change) and they did not exclude patients with excessive alcohol consumption, which contributed to the greater prevalence of steatosis.

The overall success of antiviral therapy in the treatment of chronic hepatitis C by achieving SVR in our study was found in 74.79% of the patients. Results of studies with dual antiviral therapy (PEGIFN+RBV) show that treatment success is achieved in about 60% of cases, regardless of HCV genotype, in 50% of patients with HCV genotype 1 infection, and in 80% of patients with HCV genotypes 2 and 3 [19, 20]. This result is consistent with the results of studies in Serbia [21, 22], and better than studies from other countries [19, 23]. Better treatment success could be explained by choosing patients with predictors of good therapeutic response. In our study all the patients were "naive" patients not previously treated with antiviral therapy, the study excluded obese patients and active addicted to psychoactive substances. The predictive factors for achieving SVR in our study were age, duration of infection, HCV genotype 3, the presence of steatosis and the presence of marked fibrosis, as it was found by other authors who studied the predictive factors for successful treatment of patients with chronic hepatitis C [8, 24].

In most of previous studies steatosis is considered as a negative predictive factor of antiviral therapy [25–28]. In recent years, researchers have found that steatosis has a negative impact on the achievement of SVR only in patients with HCV genotype 1, but liver steatosis in patients with genotype 2 or 3 HCV does not have influence on the success of antiviral therapy [29–31], and achieving successful treatment of chronic HCV infection leads to the reduction in liver steatosis [15, 32]. In our study, the treatment success in the patients with hepatic steatosis was achieved in 62.79% of the patients, whereas in the patients without liver steatosis SVR was achieved in 81.25% of the patients, with statistically significant difference. Similar results were obtained Savvoula et al. [17], in patients with chronic hepatitis C and steatosis treatment success of 56.6% *vs* 76.8% in the patients without steatosis Werling et al. [33] applying the same methodology as in our study, also showed that hepatic steatosis has a negative impact on the effectiveness of antiviral therapy, e. g. 36% of patients with steatosis compared to 71% in patients without steatosis. In their study, not all patients were naive, and all had genotype 1 HCV, and this is the reason for the success of the treatment to be worse than in our study. Among the authors showing that steatosis has no negative impact on the success of antiviral therapy are Cross et al. [34], who found that only HCV genotype and obesity have negative influence on the success of antiviral treatment. Today, the prevailing opinion is that hepatic steatosis has a negative impact on the efficacy of antiviral therapy in patients with genotype 1 HCV, while in patients with hepatic steatosis and HCV infection with genotype 3 steatosis has no negative impact on the success of antiviral therapy [31, 35, 36] Negro [37], the author who studied much steatosis in patients with hepatitis C, concludes that viral steatosis induced by genotype 3 HCV does not reduce the success of antiviral therapy, whereas metabolic steatosis caused by other factors (obesity, insulin resistance, diabetes, etc), reduces the success of antiviral therapy for chronic hepatitis C. In our study, concerning the SVR in the patients with steatosis and HCV genotype 3, it was achieved in 80.95% of the patients, which is the same as in all the patients without steatosis (81.25% of the patients), which confirms the opinion that steatosis in patients with HCV genotype 3 has no influence on the success of antiviral therapy.

## Conclusion

Hepatic steatosis often occurs in patients with chronic hepatitis C, and has a negative impact on the success of antiviral therapy for chronic hepatitis C. Hepatic steatosis has the strongest negative impact on the success of antiviral therapy in patients with genotype non-3 HCV, whereas in those with genotype 3 steatosis does not have influence on the success of antiviral therapy. Therefore, hepatic steatosis in patients with genotype 1 HCV should be eliminated or treated before switching to antiviral therapy, while in patients with steatosis and genotype 3 HCV antiviral therapy should be applied regardless of the degree of steatosis, because successful antiviral therapy will eliminate or reduce steatosis. Today it is believed that hepatic steatosis has a negative impact on the efficacy of antiviral therapy in patients with genotype 1 HCV, while in patients with hepatic steatosis and HCV infection with genotype 3 steatosis does not have negative impact on the success of antiviral therapy.

## R E F E R E N C E S


1. *Mohd HK, Groeger J, Flaxman AD, Wiersma ST*. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013; 57(4): 1333−42.
2. *Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C*, et al. Asystematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int 2011; 31(Suppl 2): 30−60.
3. *Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F*. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013; 58(3): 593−608.
4. *Svirtlih N, Delic D, Simonovic J, Jevtovic D, Dokic L, Gvozdenovic E,* et al. Hepatitis C virus genotypes in Serbia and Montenegro: The prevalence and clinical significance. World J Gastroenterol 2007; 13(3): 355−60.

5. *Castera L, Chouteau P, Hezode C, Zafrani E, Dhumeaux D, Pawlotsky J.* Hepatitis C virus-induced hepatocellular steatosis. Am J Gastroenterol 2005; 100(3): 711−5.
6. *European Association for the Study of the Liver.* EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011; 55(2): 245−64.
7. *Asselah T, Estrabaud E, Bieche I, Lapalus M, De Muynck S, Vidaud M*, et al. Hepatitis C: Viral and host factors associated with non-response to pegylated interferon plus ribavirin. Liver Int 2010; 30(9): 1259−69.
8. *Zhu Y, Chen S.* Antiviral treatment of hepatitis C virus infection and factors affecting efficacy. World J Gastroenterol 2013; 19(47): 8963−73.
9. *Persico M, Iolascon A.* Steatosis as a co-factor in chronic liver diseases. World J Gastroenterol 2010; 16(10): 1171−6.
10. *Arrese M, Riquelme A, Soza A, Barrera FM, Soza A.* Insulin resistance, hepatic steatosis and hepatitis C: A complex relationship with relevant clinical implications. Ann Hepatol 2010; 9(Suppl 1): 112−8.
11. *Rubbia-Brandt L, Quadri R, Abid K, Giostra E, Malé PJ, Mentha G*, et al. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. J Hepatol 2000; 33(1): 106−15.
12. *Negro F.* Hepatitis C virus-induced steatosis: An overview. Dig Dis 2010; 28(1): 294−9.
13. *Kleiner DE, Brunt EM, Van NM, Behling C, Contos MJ, Cummings OW*, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005; 41(6): 1313−21.
14. *Younossi ZM, McCullough AJ.* Metabolic syndrome, nonalcoholic fatty liver disease and hepatitis C virus: Impact on disease progression and treatment response. Liver Int 2009; 29(2): 3−12.
15. *Negro F, Clément S.* Impact of obesity, steatosis and insulin resistance on progression and response to therapy of hepatitis C. J Viral Hepat 2009;6(10): 681−8.
16. *Koike K.* Steatosis, liver injury, and hepatocarcinogenesis in hepatitis C viral infection. J Gastroenterol 2009; 44(19): 82−8.
17. *Savvoula S, Dimitrios C, George P, Spilios M, Christos T, John G.* The impact of host metabolic factors on treatment outcome in chronic hepatitis C. Gastroenterol Res Pract 2012; 2012: 420156.
18. *Fierbinţeanu-Braticevici C, Mohora M, Tribus L, Petrişor A, Creţoiu SM, Creţoiu D,* et al. Hepatocyte steatosis in patients infected with genotype 1 hepatitis C virus. Rom J Morphol Embryol 2010; 51(2): 235−42.
19. *McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J,* et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009; 361(6): 580−93.
20. *Ferguson MC.* Current therapies for chronic hepatitis C. Pharmacotherapy 2011; 31(1): 92−111.
21. *Kuljić-Kapulica N, Jovanović D, Savić D, Ristanović E, Nožić D, Rajić R.* Therapy of chronic hepatitis C: Virologic response monitoring. Vojnosanit Pregl 2010; 67(11): 923−7. (Serbian)
22. *Jovanović M, Konstantinović L, Kostić V, Vrbić M, Popović L.* Efficiency of a combined peginterferon alpha-2a and ribavarin therapy in intravenous opiate substances abusers with chronic hepatitis C. Vojnosanit Pregl 2009; 66(10): 791−5.
23. *Deborah Friedman N, Green JH, Weber HM, Stephen S, Lane SE, Ting AY*, et al. Hepatitis C virus treatment in the 'real-world': How well do 'real' patients respond. J Clin Exp Hepatol 2014; 4(3): 214−20.
24. *Ansaldi F, Orsi A, Sticchi L, Bruzzone B, Icardi G.* Hepatitis C virus in the new era: Perspectives in epidemiology, prevention, dignostics and predictors of response to therapy. World J Gastroenterol 2014; 20(29): 9633−52.
25. *Szanto P, Grigorescu M, Dumitru I, Serban A.* Steatosis in hepatitis C virus infection. Response to anti-viral therapy. J Gastrointestin Liver Dis 2006; 15(2): 117−24.
26. *Soresi M, Tripi S, Franco V, Giannitrapani L, Alessandri A, Rappa F,* et al. Impact of liver steatosis on the antiviral response in the hepatitis C virus-associated chronic hepatitis. Liver Int 2006; 26(9): 1119−25.
27. *Thomopoulos KC, Theocharis GJ, Tsamantas AC, Siagris D, Dimitropoulou D, Gogos CA,* et al. Liver steatosis is an independent risk factor for treatment failure in patients with chronic hepatitis C. Eur J Gastroenterol Hepatol 2005; 17(2): 149−53.
28. *Abdel-Aziz M, Abdel-Aziz A, El-Arman M.* Non Alcoholic Fatty Liver Diseases in Chronic Hepatitis C: Impact on End Treatment Virologic Response. IJCRIMPH 2009; 1(9): 215−31.
29. *Rodriguez-Torres M, Govindarajan S, Diago M, Morgan T, Anand B, Barange K,* et al. Hepatic steatosis in patients with chronic hepatitis C virus genotype 2 or 3 does not affect viral response in patients treated with peginterferon alpha-2a (40KD) (PEGASYS) plus ribavirin (COPEGUS) for 16 or 24 weeks. Liver Int 2009; 29(2): 237−41.
30. *Westin J, Lagging M, Dhillon AP, Norkrans G, Romero AI, Pawlotsky JM,* et al. Impact of hepatic steatosis on viral kinetics and treatment outcome during antiviral treatment of chronic HCV infection. J Viral Hepatol 2007; 14(1): 29−35.
31. *Sanyal AJ.* Role of insulin resistance and hepatic steatosis in the progression of fibrosis and response to treatment in hepatitis C. Liver Int 2011; 31 Suppl 1: 23−8.
32. *Cross TJ, Rashid MM, Berry PA, Harrison PM.* The importance of steatosis in chronic hepatitis C infection and its management: A review. Hepatol Res 2010; 40(3): 237−47.
33. *Werling K, Schaff Z, Dinya E, Tulassay Z.* Effect of liver steatosis on therapeutic response in chronic hepatitis C virus genotype 1 infected patients in hungary. Pathol Oncol Res 2010; 16(2): 149−57.
34. *Cross TS, Quaglia A, Nolan J, Hughes S, Harrison PM.* Do steatosis and steatohepatitis impact on sustained virological response (SVR) rates in patients receiving pegylated interferon and ribavirin for chronic hepatitis C infection. J Med Virol 2010; 82(6): 958−64.
35. *Hwang SJ, Lee SD.* Hepatic steatosis and hepatitis C: Still unhappy bedfellows. J Gastroenterol Hepatol 2011; 26(Suppl 1): 96−101.
36. *Abenavoli L, Masarone M, Peta V, Milic N, Kobyliak N, Rouabhia S*, et al. Insulin resistance and liver steatosis in chronic hepatitis C infection genotype 3. World J Gastroenterol 2014; 20(41): 15233−40.
37. *Negro F.* Facts and fictions of HCV and comorbidities: Steatosis, diabetes mellitus, and cardiovascular diseases. J Hepatol 2014; 61(1 Suppl): S69−78.


Received on August 26, 2015.
Revised on October 28, 2015.
Accepted on November 10, 2015.
Online First July, 2016.