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ORIGINAL ARTICLE

Prospective Study

Fatty liver in hepatitis C patients post-sustained virological response with direct-acting antivirals

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Abstract

AIM

To determine steatosis and fibrosis prevalence in hepatitis C patients after a sustained virological response achieved with direct-acting antivirals.

METHODS

Transient elastography with controlled attenuation parameter (CAP) was used to assess hepatic steatosis post-sustained virological response (SVR); the CAP technology was not available in the United States at study initiation. Liver stiffness/fibrosis was measured before and 47 wk after treatment completion. Patients with genotype 3 and patients with cirrhosis were excluded.

RESULTS

One hundred and one patients were included in the study. Post-SVR there were decreases from baseline in alanine aminotransferase (ALT) (63.1 to 17.8 U/L), aspartate aminotransferase (51.8 to 21.5 U/L) and fibrosis score (7.4 to 6.1 kPa) ($P < 0.05$). Post-SVR, 48 patients (47.5%) had steatosis on CAP; of these, 6.25% had advanced fibrosis. Patients with steatosis had higher body mass index (29.0 *vs* 26.1 kg/m^2), glucose (107.8 *vs* 96.6 mg/dL), ALT (20.4 *vs* 15.3 mg/dL), CAP score (296.3 *vs* 212.4 dB/m) and fibrosis score (7.0 *vs* 5.3 kPa); $P < 0.05$. Interestingly, compared to baseline, both patients with and without steatosis had change in fibrosis score post-SVR (7.7 kPa *vs* 7.0 kPa and 7.0 kPa *vs* 5.3 kPa); alternatively, ($P < 0.05$) and therefore patients with steatosis continued to have clinically significant stiffness ($\geqslant$ 7 kPa).

CONCLUSION

Fatty liver is very common in hepatitis C virus (HCV) patients post-SVR. These patients continue to have elevated mean fibrosis score ($\geqslant$ 7 kPa) compared to those without fatty liver; some have advanced fibrosis. Long term follow up is needed to assess steatosis and fibrosis in HCV patients post-SVR.

Key words: Nonalcoholic fatty liver disease; Hepatitis C; Fibrosis; Steatosis; Sustained virological response; Direct-acting antivirals

Core tip: This is the first prospective study to assess the prevalence of fatty liver in hepatitis C patients who have achieved a sustained virological response with direct-acting antivirals. The study's findings that fatty liver is present in 47.5% of these patients and that some steatotic patients have clinically significant fibrosis despite normal liver enzymes should raise awareness of the post-sustained virological response (SVR) prevalence of fatty liver and the importance of post-SVR assessment of steatosis and fibrosis and long-term follow up with these patients.

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INTRODUCTION

With the growing epidemic of obesity and type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD) currently has a worldwide prevalence of 25.24% (approximately 1.8 billion people)[1], making it the most common cause of chronic liver disease (CLD), followed by chronic hepatitis B (CHB, 257 million people), and chronic hepatitis C (CHC, 71 million people)[2]. In the United States, NAFLD and CHC are the two most common CLD causes[3], and nonalcoholic steatohepatitis (NASH)-associated cirrhosis is the second leading indication for liver transplant (LT) after hepatitis C virus (HCV)-associated end-stage liver disease[4]. With the recent study that showed that between 2004 and 2013 the number of adult patients with NASH awaiting LTs almost tripled[4], combined with the rapidly expanding population of CHC patients achieving sustained virological responses (SVRs) with direct-acting antivirals (DAAs), it is thought that NASH may soon become the leading indication for LT. NAFLD prevalence is now estimated to be approximately 30% in the United States[5].

NAFLD is usually diagnosed by detecting steatosis after excluding other causes of liver disease. However, hepatic steatosis may occur in patients with other liver diseases, often in those with obesity and other metabolic factors typical of NAFLD, potentially creating an additive or synergistic combination of steatosis, oxidative damage, cellular impairment and other factors that may worsen liver injury[6]. Steatosis is known to escalate liver necroinflammatory activity and accelerate fibrosis in CHC patients[7]. The hepatic steatosis prevalence in

CHC patients has been reported to be approximately 50% (range 30%-70%)[8]. The mechanisms leading to steatosis in CHC have not been fully elucidated but may include host factors leading to insulin resistance and interactions between lipid metabolism pathways and the HCV core protein[9,10]. It has been proposed that HCV's effects on hepatic lipid metabolism may inhibit the export proteins needed for the assembly and secretion of very low density lipoproteins (VLDL), resulting in triglyceride accumulation in the liver[8]. Therefore, hepatic steatosis in HCV patients may result from some combination of viral and metabolic factors, other than in genotype 3 (GNT3) patients in which the steatosis may be due to direct effects of genotype 3 viral proteins[11].

Historically, an SVR with interferon was not associated with steatosis resolution except in GNT3 patients which has a different steatosis etiology[10]. In patients with an SVR achieved with DAAs steatosis prevalence is unknown. In this prospective, cross-sectional study, we assessed steatosis prevalence and degree of fibrosis in CHC patients who achieved an SVR through treatment with DAAs.

MATERIALS AND METHODS

Study design

This is a prospective, cross-sectional study of patients with CHC who achieved an SVR after treatment with DAAs. The patients in this cohort had been treated with a variety of direct-acting antiviral regimens: ledipasvir/sofosbuvir (Harvoni), 75 patients; elbasvir/grazoprevir (Zepatier), 1 patient; dasabuvir/ombitasvir/paritaprevir/ritonavir (Viekira), 7 patients; dasabuvir/ombitasvir/paritaprevir/ritonavir with ribavirin, 2 patients; sofosbuvir (Sovaldi) with ribavirin, 9 patients; sofosbuvir with daclatasvir (Daklinza), 1 patient; sofosbuvir with simeprevir (Olysio), 2 patients; sofosbuvir/velpatasvir (Epclusa), 4 patients. Between January 2016 and March 2017, 101 adult patients were enrolled, excluding patients with other liver diseases, secondary causes of steatosis (*e.g.*, medications, excessive alcohol), and GNT3 which has a different steatosis etiology. After achieving an SVR, patients were invited to undergo standardized history and anthropometric examination, laboratory testing, and transient elastography (TE) at the California Liver Research Institute in Los Angeles. This study received approval and was done under IRB protocol CLRI-01. Ethical guidelines for human research were followed. All patients signed informed consent.

Transient elastography

TE was performed using the FibroScan 502 Touch model (M Probe, XL Probe; Echosens, Paris, France) by an experienced TE-certified technician blinded to clinical data. Patients were asked to fast for at least 4 h prior to the examination. The procedure was performed in the supine position with the right arm adducted while holding the breath for 10 s. All patients were first scanned with the M probe (3.5 MHz) over the right liver lobe. If indicated by the machine, patients were re-evaluated using the XL probe (2.5 MHz). Ten measurements were made and the interquartile range was less than 30%. We defined test failure when no stiffness measurement was obtained or there were unreliable measurements (success rate < 60% or interquartile range/median > 30%)[12-14].

Liver stiffness/fibrosis scores were measured before and within one year after completion of HCV treatment with DAAs; the median time interval between treatment completion and post-SVR TE was 47 wk, with no significant difference between patients with and without steatosis. Simultaneous liver steatosis measurements were obtained using controlled attenuation parameter (CAP) values in dB/m only after SVR achievement as the technology was not available in the United States at the study's initiation. Based on the recent large patient data meta-analysis of studies containing histology-verified CAP data for grading of steatosis that determined optimal cut-offs for CAP[15], steatosis was defined as ≥ 248 dB/M. Clinically significant stiffness was defined as ≥ 7 kilopascal (kPa)[16,17].

Patients' specifications

We included patients if they were 18 years or older, were treated for CHC using DAAs and were able to provide informed consent. We excluded patients if they (1) had a history of significant alcohol intake within 2 years of recruitment (14 drinks/wk for men or 7 drinks/wk for women) as assessed by the hepatologist as well as the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire; (2) had secondary causes of fatty liver such as medications (for example, methotrexate) or other infectious causes (for example, human immunodeficiency virus); (3) had evidence of liver diseases other than hepatitis C; (4) were HCV GNT3 as it is thought to have a different underlying etiology of steatosis related to the virus (viral steatosis) and we sought to investigate this genotype separately; or (5) had cirrhosis based on imaging or FibroScan. All the following information was collected: medical history, age, sex, height, weight, body mass index (BMI), ethnic background, and vital signs.

Laboratory measurements

The biochemical tests that were measured included aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin, albumin, fasting glucose, hemoglobin A1c, triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein. Other measurements included platelets, prothrombin time, and international normalized ratio.

Statistical analysis

The chi-square test was used to compare between categorical variables, and a paired t test to compare

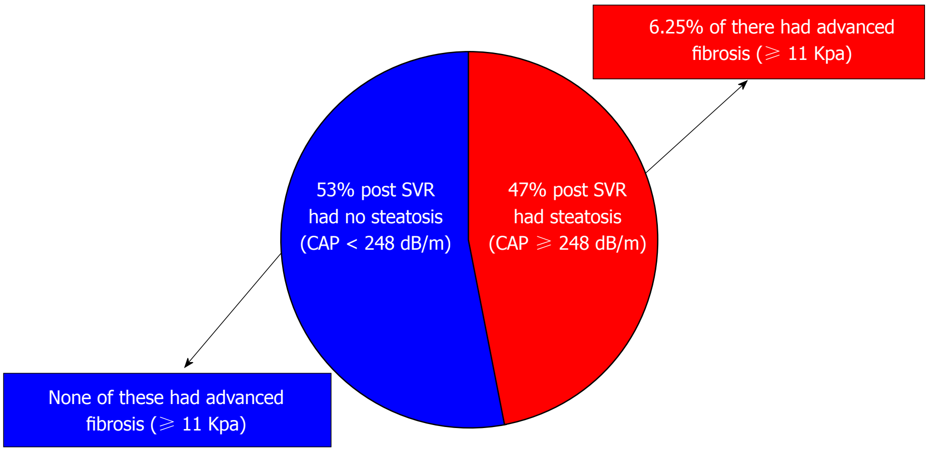

Figure 1 Post-sustained virological response steatosis prevalence in hepatitis C virus patients and advanced fibrosis prevalence in those with and without steatosis. SVR: Sustained virological response; CAP: Controlled attenuation parameter.

mean differences between continuous variables. Primary and secondary comparisons within groups were calculated with paired *t* tests, two-tailed, independent-sample *t* tests, or nonparametric tests including Wilcoxon signed-rank test as applicable. A two-tailed $P < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS 21.

RESULTS

Patient characteristics

Between January 2016 and March 2017, 101 adult CHC patients who achieved SVR were enrolled. At baseline the average age for the entire cohort was 60.3 ± 10.7 years and BMI was 27.6 ± 6.9 kg/m^2; 37% were Caucasian and 26% were Hispanic. The average fibrosis score was 7.4 ± 1.9 kPa. HCV genotypes were: GNT1 (85%), GNT2 (14%), and GNT4 (1%) (Table 1).

Changes post-SVR

Changes in the Entire Cohort: As expected, post-SVR HCV viral load was undetectable compared to prior baseline (prior to starting treatment) (0.0 ± 0.0 IU/m *vs* 6.2 ± 0.9 IU/m, $P < 0.0001$). ALT and AST decreased to normal levels post-SVR compared to baseline (17.8 ± 12.3 U/L *vs* 63.1 ± 62.6 U/L for ALT, $P < 0.0001$ and 21.5 ± 8.0 U/L *vs* 51.8 ± 41.1 U/L for AST, $P < 0.0001$). There was no change in BMI post-SVR compared to baseline (27.5 ± 6.9 kg/m^2 *vs* 27.6 ± 6.9 kg/m^2). In the overall cohort, post-SVR there was a significant decrease in fibrosis score on TE (7.4 ± 1.9 kPa to 6.1 ± 3.6 kPa; $P = 0.013$), a decline that is considered clinically significant.

Changes in patients with and without steatosis post-SVR: Post-SVR, 48 patients (47.5%) had steatosis with mean CAP score 296.3 ± 37.4 compared to a mean CAP score 212.4 ± 29.4 dB/m in patients without steatosis ($P < 0.0001$) (Figure 1). Patients with steatosis were more likely than patients without steatosis to have type 2 diabetes (18.7% *vs* 7.5%, $P = 0.04$), dyslipidemia (10.4% *vs* 5.7%, $P = 0.048$), higher body mass index (28.9 ± 6.6 kg/m^2 *vs* 26.1 ± 6.9 kg/m^2, $P = 0.049$), ALT (20.4 ± 16.5 U/L *vs* 15.3 ± 5.5 U/L, $P = 0.048$), fasting glucose (107.8 ± 30.5 mg/dL *vs* 96.5 ± 11.1 mg/dL, $P = 0.023$) and triglycerides (138.8 ± 77.9 mg/dL *vs* 109.7 ± 63.9 mg/dL, $P = 0.05$) (Table 2). None of the patients without steatosis had abnormal liver enzymes; only 6.25% of patients with steatosis had abnormal liver enzymes.

Changes in patients with and without steatosis between baseline and post-SVR: Interestingly, patients with steatosis continued to have clinically significant liver stiffness (mean baseline 7.7 ± 1.7 kPa; post-SVR 7.0 ± 4.8 kPa; $P = 0.037$) while patients without steatosis did not (mean baseline 7.1 ± 2.1; post-SVR 5.3 ± 1.5 kPa; $P < 0.0001$) (Table 3). Among patients with post-SVR steatosis, 6.25% had advanced fibrosis defined as ⩾ 11 kPa. No patients without steatosis had advanced fibrosis (Table 3).

Post-SVR, neither weight nor BMI changed while levels of transaminases and other liver enzymes dropped in patients both with and without steatosis, including ALT (55.6 ± 60.9 U/L to 15.3 ± 5.5 U/L in patients with steatosis, $P < 0.0001$, and 68.78 ± 52.8 U/L to 20.4 ± 16.5 U/L in patients without steatosis; $P < 0.0001$, respectively); AST (43.3 ± 35.6 U/L to 20.2 ± 5.4 U/L; $P < 0.0001$ and 61.3 ± 44.7 U/L to 22.9 ± 9.8 U/L; $P < 0.0001$, respectively); and alkaline phosphatase (78.5 ± 43.1 U/L to 70.8 ± 28.8 U/L; $P = 0.01$ and 75.5 ± 21.8 U/L to 71.3 ± 19.4 U/L; $P = 0.04$ (Table 3).

DISCUSSION

Since hepatic steatosis prevalence in CHC patients has previously been reported to be approximately 50%[8] our findings of a 47.5% prevalence post-SVR achieved with DAAs should perhaps not be surprising. However, this very high prevalence with continuing

Table 1 Demographic and clinical characteristics of the chronic hepatitis C patients prior to direct-acting antivirals treatment and after achieving sustained virological response 12 *n* (%)

	Prior to DAA treatment (baseline)	Post-SVR 12	*P*[1] value
Demographics			
Male	49 (48)	49 (48)	NS
Age (yr, mean ± SD)	60.3 ± 10.7	60.3 ± 10.7	NS
White	37 (37)	37 (37)	NS
Hispanic	26 (26)	26 (26)	NS
African American	13 (13)	13 (13)	NS
Asian	7 (7)	7 (7)	NS
Other	2 (2)	2 (2)	NS
Declined	16 (15)	16 (15)	NS
Clinical			
Hypertension	45 (43)	45 (43)	NS
Type 2 diabetes	13 (12.3)	13 (12.3)	NS
Dyslipidemia	8 (7.5)	8 (7.5)	NS
Anthropometric (mean ± SD)			
Body mass index (kg/m^2)	27.6 ± 6.9	27.5 ± 6.9	NS
Weight (Lbs.)	174.9 ± 46.9	172.7 ± 44.5	NS
Laboratory panel (mean ± SD)			
HCV vial load log_{10} IU/mL	6.2 ± 0.9	0.0 ± 0.0	< 0.0001
HCV genotype			
Genotype 1	86 (85)		
Genotype 2	15 (14)		
Genotype 4	1 (1)		
AST (U/L)	51.8 ± 41.1	21.5 ± 8.0	< 0.0001
ALT (U/L)	63.1 ± 62.6	17.8 ± 12.3	< 0.0001
Alkaline phosphatase (U/L)	77.5 ± 34.0	71.0 ± 24.3	0.004
Albumin (g/dL)	4.3 ± 0.4	4.4 ± 0.4	NS
Bilirubin, total (mg/dL)	0.6 ± 0.2	0.6 ± 0.3	NS
Fasting glucose (mg/dL)	99.1 ± 30.1	102.1 ± 23.5	NS
FibroScan (mean ± SD)			
Fibrosis Score (kPa)	7.4 ± 1.9	6.1 ± 3.6	0.013
IQR (%)	12.6 ± 4.9	12.3 ± 5.5	NS

[1]*P* values (2-sided) determined from either a Fisher's exact test for categorical variables or *t*-test for continuous variables. DAA: Direct-acting antivirals; SVR: Sustained virological response; HCV: Hepatitis C virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; IQR: Interquartile range.

clinically significant fibrosis in the steatotic patients despite normal liver enzymes should be of concern to clinicians. The current European guidelines recommend assessing ALT and HCV RNA 48 wk post-treatment in non-cirrhotic patients with SVR, with no further follow up with normal ALT/undetectable HCV RNA[18]. The current United States guidelines for patients post-SVR recommend follow up only for those with advanced fibrosis; assessing other liver disease causes is only recommended in cases of persistently abnormal transaminases[19]. Importantly, we show that fatty liver may be present despite normal liver enzymes, confirming previous studies that have shown this[20]. Therefore, we recommend post-SVR assessment of steatosis and fibrosis in those with abnormal BMI or other risk factors typical of NAFLD. In patients found to have hepatic steatosis long-term follow up is warranted.

To our knowledge this is the first prospective study to assess the prevalence of fatty liver in HCV patients who achieved an SVR with DAAs. We hope that our study will raise awareness of the post-SVR prevalence of fatty liver and the need for screening and long-term follow up. Our study's strengths include the community-based hepatology setting, which likely accurately represents real life experience. In addition, we used TE, which is highly sensitive and specific, and is widely used and easy to perform. Although liver biopsy is still the gold standard to assess fatty liver and staging with MRI proton density fat fraction may be more accurate[21], biopsy is invasive and costly and many patients are reluctant to undergo the procedure because of concerns about pain and, although limited, possible complications. With biopsy there is also the possibility of inter-and intra-observer variability and sampling error[22]. MRI techniques are quite expensive. Neither of these is likely to be performed in post-SVR patients with normal liver enzymes. Thus, the use of TE with CAP is realistic in a real-world setting.

There is substantial data showing good sensitivity and specificity for the use of TE in determining either presence of advanced fibrosis or no fibrosis. In eight studies that compared the usefulness of TE and liver biopsy for assessment of liver fibrosis in NAFLD patients it was shown that TE is very good for diagnosis of F ⩾ 3, with 84%-100% sensitivity and 83%-97% specificity[23-30]. Similar findings were reported in a recent large systematic review and meta-analysis that confirmed that TE was excellent for diagnosis of F ⩾ 3 in NAFLD patients[31]. Although there is reduced accuracy using TE for distinguishing early fibrosis

Table 2 Characteristics of chronic hepatitis C patients after achieving sustained virological response 12 comparing those with and without steatosis *n* (%)

	Patients without steatosis (CAP < 248 dB/m) (*n* = 53)	Patients with steatosis (CAP ⩾ 248 dB/m) (*n* = 48)	P^1 value
Demographics			
Male	25 (47)	27 (56)	NS
Age (yr, mean ± SD)	59.4 ± 11.6	60.9 ± 9.4	NS
White	18 (34)	18 (38)	NS
Hispanic	14 (26)	12 (25)	NS
Clinical			
Hypertension	25 (47.2)	20 (41.7)	NS
Dyslipidemia	3 (5.7)	5 (10.4)	0.048
Type 2 diabetes	4 (7.5)	9 (18.7)	0.04
Anthropometric (mean ± SD)			
Body mass index (kg/m^2)	26.1 ± 6.9	28.9 ± 6.6	0.049
Weight (Lbs.)	161.0 ± 33.4	172.7 ± 44.5	0.005
Hepatology and viral hepatitis panel (mean ± SD)			
AST (U/L)	20.2 ± 5.4	22.9 ± 9.8	NS
ALT (U/L)	15.3 ± 5.5	20.4 ± 16.5	0.048
Alkaline phosphatase (U/L)	70.7 ± 28.2	71.3 ± 19.4	NS
Albumin (g/dL)	4.3 ± 0.2	4.5 ± 0.6	NS
Bilirubin, total (mg/dL)	0.6 ± 0.3	0.6 ± 0.2	NS
Other laboratory studies (mean ± SD)			
Total cholesterol (mg/dL)	184.8 ± 35.1	179 ± 37.2	NS
HDL cholesterol (mg/dL)	57.6 ± 18.6	50.8 ± 17.0	NS
LDL cholesterol (mg/dL)	102.6 ± 33.2	100.7 ± 31.5	NS
Triglycerides (mg/dL)	109.7 ± 63.9	138.9 ± 77.9	0.05
HbA1c (%)	5.7 ± 0.6	6.0 ± 0.9	NS
Fasting serum glucose (mg/dL)	96.5 ± 11.1	107.8 ± 30.5	0.023
FibroScan (mean ±SD)			
Fibrosis Score (kPa)	5.3 ± 1.6	7.0 ± 4.8	0.0013
CAP (dB/m)	212.4 ± 29.0	296.3 ± 37.4	< 0.0001
% of patient with fibrosis score of (⩾ 7 kPa)	0%	6.25%	0.066

[1]*P* values (2-sided) determined from either a Fisher's exact test for categorical variables or *t*-test for continuous variables. CAP: Controlled attenuation parameter; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HDL: High density lipoprotein; LDL: Low density lipoprotein; CAP: Controlled attenuation parameter.

stages (F1-F2), in our study we were mainly comparing results in patients with and without advanced fibrosis. There is also substantial data showing good sensitivity and specificity of TE with CAP for assessing hepatic steatosis[32]. Although cutoff values for defining steatosis with CAP have not been fully formalized, we chose the value that defined steatosis (⩾ 248 dB/M) based on a very recent large (2735 patients) meta-analysis of studies containing histology-verified CAP data for grading of steatosis that determined optimal cut-offs for CAP[15].

Although until relatively recently, obesity (BMI > 30 kg/m^2) was associated with a reduced ability of TE to accurately determine fibrosis and steatosis, this problem has been largely addressed with the development of the obese-specific XL probe which we used in our study, confirmed in multiple studies to obtain reliable liver stiffness measurement in obese patients[33-35]. Another strength of our study is our inclusion of a detailed metabolic profile and alcohol questionnaire, with other causes carefully ruled out. It has been suggested that post-SVR some patients might feel free to indulge in alcohol consumption, with a resulting increase in liver stiffness measurements. Importantly, we ruled out increased alcohol intake through both medical records and use of the AUDIT-C at the time of the TE CAP assessment post-SVR.

Although our exclusion of HCV GNT3 patients means that our findings cannot be applied to the approximately 30.1% of HCV patients with this genotype[36], the exclusion is a strength of the study in other ways. Steatosis has been shown to correlate with intrahepatic viral replication in GNT3, with resolution of steatosis seen after effective antiviral treatment, suggesting a direct steatogenic effect of GNT3 virus[8]. In a study of patients treated with interferon, steatosis improvement post-SVR was seen in 91% of GNT3 patients *vs* 43% of patients with other genotypes (*P* < 0.04)[37]. In a study that compared the effects of interferon treatment in GNT1 and GNT3 patients, hepatic steatosis did not change in GNT1 patients, regardless of the treatment response, while steatosis was significantly reduced in GNT3 patients who achieved an SVR (*P* < 0.001) but not in patients who did not[38], again suggesting a direct steatogenic effect of GNT3 HCV. Thus, GNT3 patients represent a unique population in terms of steatosis that should be studied separately. Inclusion of these patients in our study could have substantially altered our findings regarding post-SVR steatosis, likely substantially reducing the prevalence due to steatosis reduction

Table 3 Comparison of pre-treatment *vs* post-sustained virological response characteristics in patients with and without post-sustained virological response steatosis

	Patients without steatosis n = 53			Patients with steatosis n = 48		
	Pretreatment	Post SVR	P value	Pretreatment	Post SVR	P value
Body mass index (kg/m^2)	25.5 ± 4.0	26.1 ± 6.9	NS	30.0 ± 8.5	29.0 ± 6.6	NS
Weight (Lbs.)	161.9 ± 32.6	161.0 ± 33.4	NS	187.3 ± 55.8	186.1 ± 51.3	NS
Laboratory panel (mean ± SD)						
HCV vial load $\log_{10}$ IU/mL	6.1 ± 1.0	0.0 ± 0.0	< 0.0001	6.3 ± 0.8	0.0 ± 0.0	< 0.0001
AST (U/L)	43.3 ± 35.6	20.2 ± 5.4	< 0.0001	61.3 ± 44.7	22.9 ± 9.8	< 0.0001
ALT (U/L)	55.6 ± 60.9	15.3 ± 5.5	< 0.0001	68.78 ± 52.8	20.4 ± 16.5	< 0.0001
Alkaline phosphatase (U/L)	78.5 ± 43.1	70.8 ± 28.8	0.01	75.5 ± 21.8	71.3 ± 19.4	0.04
Albumin (g/dL)	4.2 ± 0.5	4.4 ± 0.3	0.006	4.3 ± 0.2	4.5 ± 0.6	0.006
Bilirubin total (mg/dL)	0.6 ± 0.2	0.6 ± 0.3	NS	0.6 ± 0.3	0.6 ± 0.2	NS
Fasting glucose (mg/dL)	95.6 ± 31.9	96.6 ± 11.1	NS	103.0 ± 27.5	107.8 ± 30.5	NS
FibroScan (mean ± SD)						
Fibrosis score (kPa)	7.1 ± 2.1	5.3 ± 1.5	< 0.0001	7.7 ± 1.7	7.0 ± 4.8	0.0037

SVR: Sustained virological response; HCV: Hepatitis C virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

in GNT3 patients, resulting in an overall steatosis prevalence which would not be representative of the almost 70% of HCV patients with other genotypes[36].

A limitation of our study is that, because the CAP technology was not available in the United States at the time of study initiation, we were unable to estimate steatosis prevalence with CAP prior to the initiation of DAAs in order to determine treatment effect. However, regardless of baseline steatosis prevalence, there is real clinical value in assessing post-SVR prevalence so that appropriate long-term follow up can be recommended. Another limitation is the length of follow-up as the median time interval in our study is 47 wk between treatment completion and the post-SVR TE. Lengthier studies are definitely needed to assess NAFLD progression and steatosis and fibrosis changes over time in this population. However, by assessing patients at almost a year post-SVR we have at least provided a foundation upon which lengthier studies could expand. The sample size could be considered as a limitation; however, this is a proof of concept study that this is first of its kind and warrants larger studies. Finally, we excluded patients with cirrhosis. However, these patients are usually followed up closely post-SVR and steatosis has been found to be low when patients have advanced fibrosis[39].

In conclusion, our findings that 47.5% of HCV patients had steatosis post-SVR and that some steatotic patients had clinically significant fibrosis, despite normal liver enzymes, highlight the importance of post-SVR assessment of steatosis and fibrosis in these patients. We believe these patients should be followed longitudinally, both to provide appropriate patient care and to advance our understanding of the long-term consequences of hepatic steatosis in post-SVR patients. In addition, we note that despite SVR these steatotic CHC patients are excluded from most NAFLD clinical trials, predominantly because of the current guidelines' definition of NAFLD as a diagnosis of exclusion[40,41]. We propose revisiting this and implementing new definitions of those with concomitant liver diseases, including those with HCV SVRs, that might allow patients' participation in trials, an unmet need in the rising epidemic of NAFLD.

ARTICLE HIGHLIGHTS

Research background

It is known that the hepatic steatosis prevalence in hepatitis C patients who have achieved a sustained virological response with interferon is approximately 50%. However, the prevalence of fatty liver in hepatitis C patients who have achieved a sustained virological response with direct-acting antivirals has not previously been studied. Knowledge of this is important in order to direct appropriate long-term follow up for patients.

Research motivation

Post-sustained virological response (SVR), hepatitis C patients, many of whom have normal liver enzymes, are too often being discharged from their hepatologists' care with no further plans for follow up. The current European and United States guidelines only recommend long-term follow up in patients with elevated enzymes. In addition, many hepatitis C patients who have achieved an SVR are excluded from nonalcoholic fatty liver disease (NAFLD) clinical trials. We think it is important to determine the prevalence of NAFLD post-SVR and assess the severity of liver disease in these patients. Determining these things can provide a basis for future research aimed at determining the long-term natural history of the disease in these patients, and may prompt changes in both liver society guidelines for follow up and in clinical trial exclusion criteria.

Research objectives

The main objective, to determine the prevalence of fatty liver in hepatitis C patients who have achieved a sustained virological response with direct-acting antivirals, was achieved. This knowledge provides a basis for future research aimed at determining the long-term natural history of the disease in these patients.

Research methods

In this study we used transient elastography with controlled attenuation parameter to measure steatosis and fibrosis in hepatitis C patients post-SVR. This was the first study to measure both fibrosis and steatosis in hepatitis C patients using the FibroScan technology.

Research results

Our findings have added knowledge previously unknown in this field that may help to guide the need for long-term monitoring of hepatitis C patients post-SVR, with a particular focus on the possible occurrence of NAFLD in these patients, whether or not there are elevated liver enzymes. The most important future research will be to carry out long-term follow up on hepatitis C patients post-SVR to determine the prevalence of fatty liver over time.

Research conclusions

This is the first prospective study to assess the prevalence of fatty liver in hepatitis C patients who have achieved a sustained virological response with direct-acting antivirals. The study's findings that fatty liver is present in 47.5% of these patients and that some steatotic patients have clinically significant fibrosis despite normal liver enzymes should raise awareness of the high post-SVR prevalence of fatty liver and the importance of post-SVR assessment of steatosis and fibrosis and long-term follow up with these patients. The study's findings raise concern that the recommendations found in the current U.S. and European guidelines for follow up of patients post-SVR could result in a lack of adequate long-term monitoring of these patients. In particular, the very high prevalence of fatty liver (47.5%) with continuing clinically significant fibrosis in the steatotic patients despite normal liver enzymes should be of concern to clinicians. Therefore, we recommend post-SVR assessment of steatosis and fibrosis in those with abnormal BMI or other risk factors typical of NAFLD. In patients found to have hepatic steatosis long-term follow up is clearly warranted.

Research perspectives

Our study's assessment of steatosis and fibrosis in hepatitis C patients at almost a year post-SVR has shown that long-term monitoring of these patients to assess the possibility of fatty liver and fibrosis is important. With this study, we have provided a foundation upon which lengthier and larger studies should expand, using regularly scheduled transient elastography with controlled attenuation parameter assessments in order to determine whether this high level of steatosis is still present multiple years post-SVR and the clinical ramifications for patients.

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