Noninvasive assessment of hepatic fibrosis regression in hepatitis C virus-infected patients treated with sofosbuvir-based therapy

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Background
Accurate evaluation of the degree of liver fibrosis in patients with chronic liver diseases is crucial to make therapeutic decisions and to determine the prognosis of liver disease and also the protocol of further follow-up. Multiple noninvasive methods have been used successfully in the prediction of fibrosis; however, early changes in noninvasive parameters of hepatic fibrosis after effective antiviral therapy are still not well unknown. The aim of the paper was to evaluate early changes in the hepatic fibrosis-related parameters in patients with chronic hepatitis C virus (HCV) infection using shear wave elastography (pSWE) and serum parameters [aspartate aminotransferase-platelet ratio index (APRI) and fibrosis-4 score (FIB4)] before and 24 weeks after sofosbuvir-based antiviral therapy.
Materials and methods
This is a prospective cohort study that included 109 Egyptian patients with chronic hepatitis C. pSWE values were recorded as well as APRI and FIB4 scores were calculated at baseline and at 12 and 24 weeks after treatment.
Results
A total of 109 HCV-infected patients were included, with mean age of 45.76±13.91 years. Overall, 25 (22.90%) patients had cirrhosis and were treated with sofosbuvir 400 mg/day, daclatasvir 60 mg/day, and weight-based ribavirin. Moreover, 84 (77.10%) were treated with sofosbuvir 400 mg/day and daclatasvir 60 mg/day. The overall sustained virological response-12 rate was 100%. There were significant improvements in APRI score (from 0.64±0.66 at baseline to 0.26±0.22 at 24 weeks after treatment) and FIB4 score (from 1.77±1.77 at baseline to 1.11±1.04 at 24 weeks after treatment), with P value of 0.0001 in both. In addition, there was a significant reduction in liver stiffness measurements by pSWE 24 weeks after treatment (from 1.72±0.55 m/s at baseline to 1.48±0.44 m/s at 24 weeks after treatment, with P=0.003).
Conclusion
Sofosbuvir-based treatment regimens for chronic HCV infection result in significant improvement of the fibrosis scores (FIB4 and APRI) 24 weeks after treatment. Moreover, there was a significant reduction in the liver stiffness measurements by pSWE.

Keywords:
directly acting antiviral drugs, hepatitis C virus and hepatic fibrosis regression, liver stiffness, sofosbuvir

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Introduction

In 2015, the global prevalence of hepatitis C virus (HCV) infection was 1.0%, with the highest prevalence in the Eastern Mediterranean region (2.3%) followed by the European one (1.5%). The annual mortality owing to HCV-related complications is estimated to be ~700 000 deaths [1]. The objective of chronic hepatitis C (CHC) treatment is to achieve a sustained virological response (SVR), defined as the absence of viral replication 12 or 24 weeks after treatment completion. A SVR which is stable over time reduces morbidity and mortality and is considered in most cases to be equivalent to cured HCV infection [2]. Liver fibrosis is the main determinant of HCV-related morbidity and mortality [3]. In addition, the stage of fibrosis is prognostic and provides information on the likelihood of disease progression and response to treatment [4]. A multitude of fibrosis scores calculated from laboratory values have been developed and validated over the recent years. The advantage of these scores is obvious, as they neither require

invasive or time-consuming procedures nor expensive equipment besides a routine laboratory. Fibrosis-4 score (FIB4) and aspartate aminotransferase-platelet ratio index (APRI) scores have been validated for CHC and show acceptable sensitivity and specificity, particularly in advanced fibrosis and cirrhosis [5]. They have been demonstrated to be accurate in staging chronic liver diseases before antiviral treatment and prediction of hepatic fibrosis in HCV-infected patients [6]. Moreover, they have been used to longitudinally follow up patients with chronic hepatitis and to assess the effect of antiviral treatment [7]. Elastography has recently been presented as a novel imaging modality technique for the evaluation of tissue stiffness [8]. The acoustic radiation force impulse elastography is a sonography-based noninvasive method for measuring liver stiffness (LS), and it can be applied for the diagnosis of liver fibrosis and cirrhosis in chronic viral hepatitis, such as hepatitis B virus or HCV-infected patients, and nonalcoholic fatty liver disease [9].

The aim of this study was to evaluate early changes of the hepatic fibrosis-related parameters in patients with chronic HCV infection using serum parameters (APRI and FIB4) and liver stiffness measurement (LSM) using shear wave elastography (Siemens-Acuson S2000) before and 24 weeks after sofosbuvir-based antiviral therapy.

Materials and methods

This is a prospective cohort study that recruited 109 Egyptian patients with chronic hepatitis C who were recruited and followed up in the period between July 2017 and September 2018. All patients were candidates for antiviral therapy according to the guidelines of the National Committee for Control of Viral Hepatitis (NCCVH). The patients were recruited from viral hepatitis treatment unit in Sohag Cardiology and Hepatogastroentrology Center. All candidate patients received sofosbuvir (SOF) 400 mg once daily, daclatasvir (DAC) 60 mg once daily with or without weight-based ribavirin (RBV) [1000 mg (<75 kg) to 1200 mg (>75 mg)] with dose adjustment of RBV according to hemoglobin level for 12 weeks and were followed up regularly at 4, 8, and 12 weeks. The study was approved by the Ethical Committee for the National Control of Viral Hepatitis of the Ministry of Health. A written informed consent was obtained from all patients. The study was performed in compliance with the ethics principles of the 1975 Declaration of Helsinki and its later amendments with Good Clinical Practice (GCP) guidelines.

All patients were included according to the inclusion criteria approved by NCCVH: patients with chronic HCV infection proven by positive HCV PCR, both sexes, aged above 18 years old, treatment naive, different stages of hepatic fibrosis (F1–F4) having compensated liver disease (Child–Pugh class A), and having no contraindication for treatment. Exclusion criteria included other etiologies of chronic liver disease rather than HCV, being aged below 18 years, Child–Pugh classes B and C, any patient with hepatocellular carcinoma or extrahepatic malignancy, inadequately controlled diabetes mellitus (HbA1c>9%), being a recipient of liver transplantation, being pregnant or being unable to adopt contraceptive measures, having severe medical disease including severe hypertension, heart failure, significant coronary disease, or decompensated chronic obstructive pulmonary disease, or having untreated depressive illness.

All patients were subjected to the following: full history taking, thorough clinical examination, and laboratory investigations, including complete blood count, kidney function tests, liver function tests, liver enzymes, α-fetoprotein, HCV Ab, HBsAg, and PCR for HCV. Pregnancy test was requested from all female patients in the childbearing period. ECG and clinical cardiological assessment were done for patients aged over 65 years old or with controlled cardiological problems. Abdominal ultrasonography was done for the assessment of liver parenchymal echogenicity, focal lesions and the presence of ascites.

Calculation of the following serum markers of fibrosis:

(1) Aspartate aminotransferase-to-platelet ratio index (APRI): this was calculated using Wai's
Formula = (AST/upper limit of normal)/platelet count(expressed as platelets $\times 10^9/l$) $\times$ 100 [10].

(2) FIB4 score was calculated using Sterling's
Formula = [age (years) $\times$ AST (IU/l)]/ $\left[\text{platelet count } (10^9/l) \times \text{ALT (IU/l)}^{1/2}\right]$ [11].

Cutoff values for significant liver fibrosis and cirrhosis were adopted from the European Association for Study of Liver guidelines for noninvasive assessment of liver fibrosis where APRI scores greater than 0.77 were regarded as significant fibrosis and scores greater than 0.84 as indicating cirrhosis, whereas FIB4 scores greater than 1.45 indicated significant fibrosis and scores greater than 3.25 indicated cirrhosis [12].

Liver stiffness measurement using shear wave elastography

LSMs were recorded for all patients before treatment and at 12 and 24 weeks after the end of treatment with the shear wave elastography device (Siemens-Acuson S2000 VC25, Osaka, Japan) using a curved linear 6C1 transducer. Patients were fasting for a minimum of 6 h before examination. Although the patients were in a supine position with the right arm in abduction, they were asked to hold their breath for a moment at the end of expiration to minimize breathing motion during the examination. LSM were taken in the right lobe of the liver in between the 9th and 11th intercostal spaces, at a depth of 1–2 cm from the liver capsule avoiding large vessels and fissures in the liver. Results were considered valid when a number of 10 valid measurements are obtained. A success rate (the ratio of valid readings to the total number of readings) was above 60%. The median value of LSM is expressed in meters per second (m/s). Cutoff values for LSMs in m/s in relation to Metavir score used during this study were according to Lupsor *et al.* [13]:

$$F\geq 1 = 1.19,\ F\geq 2 = 1.34,\ F\geq 3 = 1.61,\ F4 = 2$$

Patients were followed up monthly during treatment by complete blood count, liver function tests and liver enzymes. Point shear wave elastography (pSWE) was performed at 12 and 24 weeks after the end of treatment. HCV-RNA PCR was done at 12 weeks after the end of treatment. If HCV-RNA was undetectable, the patient was considered to have SVR12.

Statistical analysis

The statistical analysis was conducted by using statistical SPSS package program version 24 for Windows (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean, SD and ranges when their distribution was found to be parametric. Moreover, qualitative data were presented as number and percentages. The comparison between two independent groups with qualitative data was done by using χ^2-test and/or Fisher's exact test only when expected count in any cell was found to be less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent *t*-test. The comparison between more than two independent groups with quantitative data and parametric distribution was done by using one-way analysis of variance (ANOVA). The comparison between more than two paired groups with quantitative data and parametric distribution was done by using repeated measures ANOVA. Comparison between the two groups with Quantitative data and parametric distribution of the tested variables was done by using post hoc multiple comparison tests. All statistical analyses were significant at 0.05 level of probability ($P\leq 0.05$).

Results

A total of 120 patients were recruited in the current study. After applying the inclusion and exclusion criteria for treatment, eight patients were excluded and 112 patients started therapy, with only three patients lost during follow-up, leaving a total of 109 patients who completed the treatment and follow-up period.

A total of 109 HCV-infected patients treated with sofosbuvir-based therapy for 12 weeks were identified; 84 (77.10%) were treated with sofosbuvir 400 mg/day and daclatasvir 60 mg/day and 25 (22.90%) were treated with sofosbuvir 400 mg/day and daclatasvir 60 mg/day with weight-based ribavirin [1000 mg (<75 kg) to 1200 mg (>75 mg)] (Table 1).

All biochemical tests were within normal, except elevation in liver enzymes. The mean values of FIB4 and APRI were 1.77±0.74 and 0.64±0.39, respectively (Tables 2–5).

There was a significant improvement regarding liver enzymes and total and direct bilirubin 12 and 24 weeks after treatment compared with baseline (Table 6).

There were significant changes in the distribution of patients among the fibrosis stages, with *P* value of 0.0001, except for liver fibrosis stage 4 (F4) (Table 7 and Fig. 1).

Table 1 Demographic data of studied patients

Age (*n*=109)	Sex (*n*=109)		Diabetes mellitus (*n*=109)		Hypertension (*n*=109)		Ischemic heart disease (*n*=109)		Treatment received (*n*=109)	
Mean ±SD	Male	Female	Yes	No	Yes	No	Yes	No	Sofosbuvir, daclatasvir	Sofosbuvir, daclatasvir, ribavirin
45.76 ±13.91	67 (61.50)	42 (38.50)	8 (7.30)	101 (92.70)	11 (10.10)	98 (89.90)	3 (2.80)	106 (97.20)	84 (77.10)	25 (22.90)

Continuous variables are expressed as mean±SD, and categorical variables are expressed in their absolute and relative frequencies (number and percentage).

Table 2 Baseline laboratory investigations and serum markers of fibrosis

	Baseline (*n*=109) (mean±SD)
AST	41.79±26.43
ALT	46.51±29.00
Total bilirubin	0.78±0.34
Direct bilirubin	0.35±0.14
Serum albumin	4.42±0.47
INR	1.11±0.15
WBC	5.71±1.85
Hb	13.44±1.43
Platelets	203.95±68.75
Serum creatinine	0.87±0.26
AFP	9.33±5.16
FIB4	1.77±0.74
Aspartate aminotransferase-to-platelet ratio index	0.64±0.39

AFP, α-feto protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB4, fibrosis-4 score; Hb, hemoglobin; INR, international normalized ratio; WBC, white blood cell.

Table 3 Baseline liver stiffness stages by shear wave elastography

Liver stiffness	Baseline (*n*=109)
F0	0
F1	23 (21.10)
F2	45 (41.30)
F3	21 (19.30)
F4	20 (18.30)

Categorical variables are expressed in their absolute and relative frequencies (number and percentage).

Table 4 Laboratory investigation and serum markers of fibrosis at 12 and 24 weeks after treatment

	After treatment	
	12 weeks (*n*=109)	24 weeks (*n*=109)
AST	20.04±8.60	17.78±9.20
ALT	20.50±7.73	18.15±6.60
Total bilirubin	0.64±0.26	0.60±0.24
Direct bilirubin	0.25±0.13	0.27±0.13
Serum albumin	4.34±0.44	4.37±0.48
INR	1.11±0.16	1.09±0.14
WBC	5.88±1.95	5.48±1.29
Hb	12.78±1.54	12.57±1.29
Platelets	213.87±63.03	216.62±62.19
FIB4	1.12±0.84	1.11±1.04
Aspartate aminotransferase to platelet ratio index	0.27±0.17	0.26±0.22

Continuous variables are expressed as mean±SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB4, fibrosis-4 score; Hb, hemoglobin; INR, international normalized ratio; WBC, white blood cell.

Discussion

This prospective cohort study aims to evaluate early changes of hepatic fibrosis-related parameters in patients with chronic HCV infection using LSM using shear wave elastography (Siemens-Acuson S2000) and serum parameters such as APRI and FIB4 before and after 12 and 24 weeks of sofosbuvir-based antiviral therapy. The patients were recruited from viral hepatitis treatment unit in Sohag Cardiology and Hepatogastroentrology Center, one of the centers of NCCVH.

Table 5 Liver stiffness stages 12 and 24 weeks after treatment

Liver stiffness	12 weeks after treatment (*n*=109)	24 weeks after treatment (*n*=109)
F0	16 (14.70)	33 (30.30)
F1	21 (19.30)	27 (24.80)
F2	37(33.90)	20 (18.30)
F3	16 (14.70)	9 (8.30)
F4	19 (17.40)	20 (18.30)

Categorical variables are expressed in their absolute and relative frequencies (number and percentage).

This study showed that the mean age of the studied patients was 45.76±13.91 years, with male predominance (61.50%), which is in accordance with the study by Yosry *et al.* [6], which showed the mean age of the studied patients was 44.818±8.8745 years, with male predominance (61.4%).

Regarding treatment responses in the current study, the total SVR after 12 weeks was 100%, which comes in accordance with the study by Welzel *et al.* [14], which showed the use of SOF-DCV with or without RBV in patients with HCV and advanced liver disease; it included 19 HCV-G4 patients, and the SVR12 rate was 100%.

In this study, regarding the liver enzymes indices, both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels significantly declined after 12 weeks of treatment among all studied patients (from 46.51±29.00 to 20.51±7.73 U/l and from 41.79±26.43 to 20.04±8.60 U/l, respectively) with p value of 0.0001 for both, which is in accordance with Ahmed *et al.* [15] who reported significant reduction in AST and ALT level ($P<0.001$ for both) after 12 weeks of antiviral treatment.

Moreover, the decline was remarkable in both ALT and AST levels with follow-up at 24 weeks after the end of treatment (from 46.51±29.00 to 18.15±6.60 U/l and from 41.79±26.43 to 17.78 ±9.20 U/l, respectively) with P value less than or equal to 0.0001 for both.

Table 6 Comparison between baseline vs 12 weeks and baseline vs 24 weeks after treatment regarding liver function tests and liver enzymes

Liver function tests and liver enzymes	Groups		Mean±SD	*P* value	Significant
AST	Baseline vs. 12 weeks after treatment	Baseline (*n*=109)	41.79±26.43	0.0001	S
		After 3 months (*n*=109)	20.04±8.60		
	Baseline vs. 24 weeks after treatment	Baseline (*n*=109)	41.79±26.43	0.0001	S
		After 6 months (*n*=109)	17.78±9.20		
ALT	Baseline vs. 12 weeks after treatment	Baseline (*n*=109)	46.51±29.00	0.0001	S
		After 3 months (*n*=109)	20.51±7.73		
	Baseline vs. 24 weeks after treatment	Baseline (*n*=109)	46.51±29.00	0.0001	S
		After 6 months (*n*=109)	18.15±6.60		
Total bilirubin	Baseline vs. 12 weeks after treatment	Baseline (*n*=109)	0.78±0.34	0.0001	S
		After 3 months (*n*=109)	0.64±0.26		
	Baseline vs. 24 weeks after treatment	Baseline (*n*=109)	0.78±0.34	0.001	S
		After 6 months (*n*=109)	0.60±0.24		
Direct bilirubin	Baseline vs. 12 weeks after treatment	Baseline (*n*=109)	0.35±0.14	0.001	S
		After 3 months (*n*=109)	0.25±0.13		
	Baseline vs. 24 weeks after treatment	Baseline (*n*=109)	0.35±0.14	0.001	S
		After 6 months (*n*=109)	0.27±0.13		
Serum albumin	Baseline vs. 12 weeks after treatment	Baseline (*n*=109)	4.42±0.47	0.207	NS
		After 3 months (*n*=109)	4.34±0.44		
	Baseline vs. 24 weeks after treatment	Baseline (*n*=109)	4.42±0.47	0.444	NS
		After 6 months (*n*=109)	4.37±0.48		
INR	Baseline vs. 12 weeks after treatment	Baseline (*n*=109)	1.11±0.15	0.925	NS
		After 3 months (*n*=109)	1.11±0.16		
	Baseline vs. 24 weeks after treatment	Baseline (*n*=109)	1.11±0.15	0.445	NS
		After 6 months (*n*=109)	1.09±0.14		

Continuous variables are expressed as mean±SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; S, significant; WBC, white blood cell.

Table 7 Comparison of liver stiffness stages between baseline, 3 months after treatment, and 6 months after treatment

Liver stiffness	Groups			*P* value	Significant
	Baseline (*n*=109)	12 Weeks after treatment (*n*=109)	24 Weeks after treatment (*n*=109)		
F0	0	16 (14.70)	33 (30.30)	0.0001	S
F1	23 (21.10)	21 (19.30)	27 (24.80)	0.0001	S
F2	45 (41.30)	37 (33.90)	20 (18.30)	0.0001	S
F3	21 (19.30)	16 (14.70)	9 (8.30)	0.0001	S
F4	20 (18.30)	19 (17.40)	20 (18.30)	0.39	NS

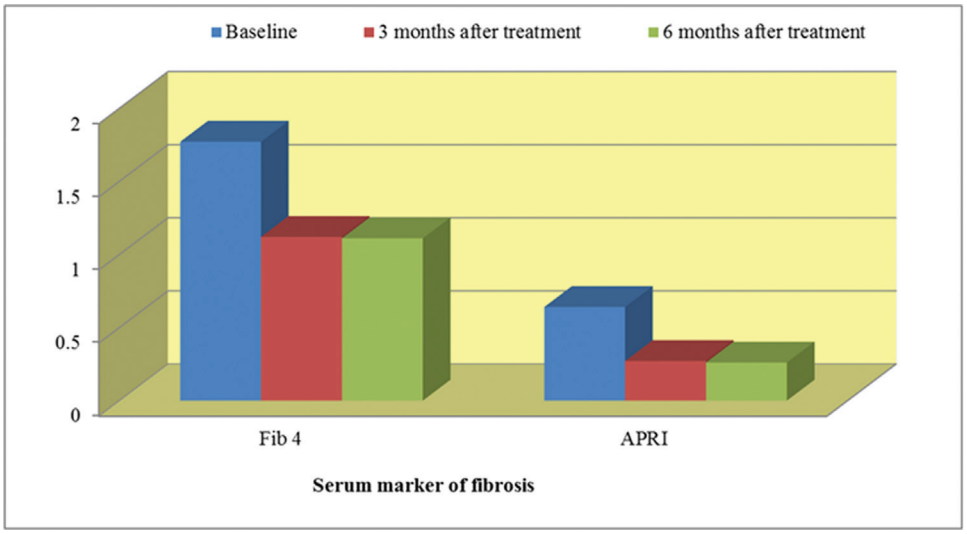
Categorical variables are expressed in their absolute and relative frequencies (number and percentage). S, significant.

Moreover, the total bilirubin level was significantly declined after 12 weeks of treatment among all studied patients (from 0.78±0.34 to 0.64±0.26 mg/dl), with *P* value of 0.0001. Our results were in agreement with the study performed by Bernuth *et al.* [16] who documented that total bilirubin, which was already in the normal range (0.91 mg/dl) before therapy, decreased to 0.74 mg/dl at SVR12, providing additional evidence for the improvement in liver function by highly effective antiviral therapy.

Similar to the study by Elsharkawy *et al.* [17] which discussed the effect of sofosbuvir-based treatment regimen on the biochemical profile of patients with chronic hepatitis C infection discussed and concluded that DAAs improve liver necroinflammatory markers in cirrhotic and noncirrhotic cases.

In this study showed that hemoglobin concentration was significantly declined after 12 weeks of treatment among all studied patients (13.44±1.42–12.78±1.54 g/dl; *P*=0.001), owing to RBV administration. This finding was previously reported by Wu *et al.* [18] who suggested that RBV is a triggering factor of hemolytic anemia, and RBV combination with SOF revealed a decrease in hemoglobin concentration. Thus, adverse effects of RBV were reduced in the current study owing to modulating the dose according to the patients' tolerability.

Figure 1



The serum markers of fibrosis (FIB4 and APRI scores) calculated at baseline and at 3 and 6 months after the end of treatment. APRI, aspartate aminotransferase-platelet ratio index; FIB4, fibrosis-4 score.

The current study showed a significant declination in FIB4 score after 12 weeks following the end of treatment (1.77±1.77–1.12±0.84; P=0.0001).

In addition, the study showed significant declination in APRI score after 12 weeks following the end of treatment (0.64±0.66–0.27±0.17; P=0.0001).

These results came in accordance with the study by Shousha *et al.* [19], which showed significant improvement in FIB4 and APRI scores 12 weeks following the end of sofosbuvir-based treatment, with P value of 0.005 and less than 0.001, respectively. This could be explained by the significant improvement in parameters of liver fibrosis such as ALT and AST levels after completing treatment regimens, which were reflected on FIB4 and APRI.

The current study showed significant reduction in the average LSMs by pSWE 12 weeks following the end of antiviral therapy (1.72±0.55–1.59±0.47 m/s), with P value 0.003, which is in accordance with Shousha *et al.* [19] who showed rapid significant reduction in LSMs as measured by transient elastography 12 weeks following the end of sofosbuvir-based treatment (10 ±8.06–9.27±8.51 kPa, with value 0.001).

Moreover, in this study showed a significant reduction in liver fibrosis stage 4 (F4) measurements by pSWE 24 weeks following the end of antiviral therapy (2.67 ±0.60–2.29±0.17 m/s), with P value of 0.032. The study by Knop *et al.* [20] also reported significant decrease in LS assessed by acoustic radiation force impulse between baseline [median (range), 2.7 (1.2–4.1) m/s] and follow-up at 24 weeks [median (range), 2.4 (1.2–3.9) m/s], with P value of 0.002.

In this study showed a significant change in the distribution of patients among the fibrosis stages except liver fibrosis stage 4 (F4), with P value of 0.0001, which in contrast with Shousha *et al.* [19] who showed nonsignificant changes in the distribution of patients among the fibrosis stages.

Conclusion

In conclusion, sofosbuvir-based treatment regimens for CHC result in significant reduction in LSMs by pSWE with significant changes in the distribution of patients among the fibrosis stages, except liver fibrosis stage 4 (F4), and significant improvement in fibrosis scores (FIB4 and APRI) 24 weeks after treatment.

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Conflicts of interest

All authers have no conflict of interest to disclose related to the research or data presented in this manuscript.

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