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ULTRASONOGRAPHY

Shear wave elastography and transient elastography in HCV patients after direct-acting antivirals

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Abstract

Purpose To compare the ultrasound (US) and pulse shear wave elastography (pSWE, Elast PQ®) methods with transient elastography (TE), clinical scores and laboratory tests, during the follow-up of HCV patients receiving direct-acting antiviral drugs (DAA).

Methods Our prospective study from June 2016 to December 2017 included 22 consecutively enrolled HCV-positive patients (59.7 ± 12.3 years, 11 male) which were subjected to antiviral therapy. All patients underwent B-mode ultrasound, color-Doppler, pSWE and TE five times: before therapy (T0), at the end of therapy (post-Tx), and at 12, 24, 48 weeks post-therapy. The liver stiffness (LS) values obtained with pSWE and TE and the data coming from US assessment and clinical evaluation were compared.

Results We obtained a statistically significant reduction of LS values (kPa) measured by pSWE, between T0 (14.3 ± 9.3), post-Tx (11.8 ± 10.5), 12 weeks (7.5 ± 3.3), 24 weeks (8 ± 3.8) and 48 weeks (8.5 ± 4.6) ($p = 0.02$). The reduction of kPa measured by TE was not significant between T0 (14.7 ± 9.3), post-Tx (12 ± 9.5), 12 weeks (11.6 ± 7.7), 24 weeks (10.3 ± 6) and 48 weeks (10.8 ± 7.5) ($p > 0.05$). Multivariate baseline analysis showed significant independent association among measurement of TE stiffness with cirrhosis, type of vein hepatic flow and showed significant independent association between delta-pSWE measurement (difference between stiffness measurements at the baseline and 12 months after treatment) with staging of fibrosis ($p = 0.006$) and sustained virologic response after 12 weeks of treatment (SVR12, $p = 0.017$).

Conclusion The pSWE method has shown better ability than TE to identify a reduction in LS. Therefore, pSWE allow to evaluate stiffness reduction in HCV patient during DAA treatment follow-up, which is related to SVR12.

Keywords Transient elastosonography · Pulse shear wave elastography · Liver stiffness · Sustained virological response · Direct antiviral acting drugs

Introduction

Hepatitis C virus (HCV) is one of the major causes of liver cirrhosis and hepatocellular carcinoma (HCC) in the Western countries [1]. Evaluation of liver parenchymal fibrosis by noninvasive methods has been available for over 10 years. The main techniques include Transient Elastography (TE), elastography techniques integrated in ultrasound (US) machines, as point shear wave elastography (pSWE) or acoustic radiation force impulse (ARFI), magnetic resonance imaging (MRI) Elastography and serum markers [2]. Moreover, acoustic structure quantification (ASQ) ultrasound software is a software programme that was used in order to estimate the degree of hepatic fibrosis [3].

TE is the most validated and widespread used technique in HCV patients, and has been validated by numerous studies that have correlated this method with the gold standard, that is the liver biopsy (LB) [4]. Consequently, most literature data about fibrosis evaluation of HCV patients refer to TE [5, 6]. The use of pSWE is more recent and has a less consolidated literature [7].

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TE, LB and pSWE present substantial differences, and each is subjected to a series of disadvantages. TE presents itself as a technique of easy and fast use and is able to detect liver stiffness (LS) by measuring the velocity of elastic shear waves in parenchyma generated by a mechanical push on the cutaneous surface of the right flank in standardized intercostal positions generating values in kPa [8]. This technique does not allow to carefully choose the sampled hepatic portion and unreliable results could be obtained in high BMI patients and in presence of ascites [9].

LB is the current gold standard, but it is an invasive, painful and not free from complications maneuver, with 1–3% of hospitalizations, without considering the not negligible inter-observer variability and sampling error [10].

Recent studies have shown good reproducibility of pSWE (Elast PQ ®) [11], which seems to be not influenced by sex, ascites and patient age [12]. It could be performed after an US 2D liver examination, allowing an exploration of liver parenchyma and a better region of interest (ROI) placement in order to ensure optimal pSWE data acquisition [13, 14].

US examination allows to assess other parameters that integrate liver stiffness evaluation, such as splenic diameter and hepatic hemodynamics by measuring portal vein diameter, hepatic veins flow phases, and portal vein average velocity [2, 15, 16].

Liver stiffness changes during and after antiviral therapy could be useful in order to evaluate necroinflammation and/or fibrosis reduction and this hepatic parameter could correlate with laboratory tests in predicting therapeutic efficacy.

Materials and methods

From June 2016 to December 2017, 22 patients with HCV infection and a pathological diagnosis of chronic liver disease were prospectively enrolled in our hospital. Each patient was evaluated five times: before therapy (T0), at the end of therapy (post-Tx), and at 12 weeks, 24 weeks, 48 weeks after the end of therapy. Each time fibrosis stage was evaluated by TE (Fibroscan Echosense® 402) and pSWE (ElastPQ® Philips healthcare Affinity® 70) [4, 14, 17].

As regards TE and pSWE, mean values were calculated on the basis of 10 measurement performed on the right lobe using an intercostal evaluation [18, 19]. Fibroscan was performed on the right lobe of the liver by trained clinicians at our hospital. pSWE measurements were performed with patients in the supine position with their right upper extremity lifted, at least 1.5–2 cm beneath the right liver capsule in order to avoid reverberation artifact and away from the intrahepatic vessels and the gallbladder [13]. When the elasticity imaging mode was selected, the patient held his or her breath for 3–5 s. When the target area was located, the operator initiated the SWE sequence measurements. A rectangular quantitative sampling frame with a diameter of 10 mm was used to evaluate the region of interest. The software automatically calculated the median elastic modulus (Young's modulus) in kPa within the region of interest. Afterward, fibrosis staging was calculated [12]. For this purpose we used the reference values proposed by Fraquelli et al. [12], which means that we evaluated as F1 < 7.6 kPa, F2 between 7.6 and 8.7 kPa, F3 between 8.8 and 10.3 kPa and F4 ≥ 10.4 kPa.

Conventional US parameters measurements were performed on the right lobe using an intercostal evaluation (portal vein average velocity, hepatic vein flow, portal vein diameter. Splenic diameter and the presence of ascites and steatosis were also evaluated using US machine. Laboratory data (ALT, AST, ALKP, GGT, total bilirubin) were acquired before and after HCV treatment. MELD and APRI score were subsequently calculated [20, 21].

The inclusion criteria were as follows: (1) informed consent prior to enrollment; (2) presence of the serum anti-hepatitis C virus antibody for > 6 months and detectable HCV-RNA; (3) treatment with Direct-Acting-Agents until evaluation of sustained viral response; (4) reliable liver stiffness measurement (median of 10 valid measurements, successful detection rate > 60% and interquartile range < 30%).

The exclusion criteria were as follows: (1) refusal to provide informed consent; (2) patients under 18; (3) presence of liver disease caused by other etiologies; (4) decompensated liver disease.

The study was approved by the institutional review board and ethics committee of our institution. Informed consent was obtained from all individual participants included in the study.

As regards statistical analysis, continuous parametric variables were expressed as mean ± standard deviation, indicating where appropriate, the minimum and maximum values observed. Continuous variables with nonparametric distribution were expressed as medians. Categorical variables were expressed as frequency and percentage of the cases. The differences were calculated using the "Student's t" and the "Mann–Whitney" tests for continuous variables and the "chi-square" test for categorical ones. To evaluate differences of the stiffness values at multiple measurement times, we performed ANOVA statistical and Kruskal–Wallis test of variance for nonparametric variables.

To investigate univariate associations between stiffness by TE and pSWE with any variables, we performed a multiple correlation matrix analysis. Thus, any variables resulted significant associated with the target variables were analyzed in a multivariate fashion by linear logistic regression. Statistical analysis was performed with SPSS software 15.0®, Graph-Pad Prism 8.0® and Excel 2016®.

Results

Baseline and demographics characteristics of the patient cohort are shown in Table 1. The mean age was 59.7 (± 12.3) years, and 11 (50%) of them were men. Only one patient needed to interrupt the therapy after two weeks because of a cerebrovascular accident.

In Table 2 are shown the laboratory data at the baseline while in Table 3 are shown the pSWE and US data at the baseline. The mean Kpa value measured with pSWE was 14.3 (SD 9.3) and 68.2% of patients had a F4 fibrosis stage.

Table 1 Patients' demographics and baseline characteristics

Characteristics	*n* (%) or mean (SD)
Age (years)	59.7 (± 12.3)
Sex, M/F (% male)	11/11 (50%)
Height (cm)	171.7 (± 7.3)
Weight (kg)	73.8 (± 13.5)
BMI (kg/m^2)	24.9 (± 4.14)
Alcohol intake	8 (36.4%)
Liver cirrhosis	5 (22.7%)
OLT	5 (22.7%)
HCC	1 (4.5%)
NAFLD/NASH	1 (4.5%)
*Fibrosis stage**	
F1 (< 7.6 kPa)	4 (18.2%)
F2 (7.6–10.9 kPa)	6 (27.3%)
F3 (10.9–15.3 kPa)	5 (22.7%)
F4 (> 15.3 kPa)	7 (31.8%)
Kpa*	14.7 (± 9.3)
IQR*	2.3 (± 2)
Type of treatment	
Sofosbuvir	5 (22.7%)
Ledipasvir/sofosbuvir	8 (36.4%)
Sofosbuvir/daclatasvir	7 (31.8%)
Elbasvir/grazoprevir	1 (4.5%)
Sofosbuvir/velpatasvir	1 (4.5%)
Treatment duration (weeks)	
12	17 (77.27%)
24	5 (22.72%)
HCV genotype	
1	12 (54.5%)
2	5 (22.7%)
3	5 (22.7%)
SVR 24	22 (100%)
DAA failure	1 (4.7%)
Experienced	5 (22.7%)

BMI, body mass Index; *OLT*, orthotopic liver transplantation; *HCC*, hepatocellular carcinoma; *NAFLD*, non-alcoholic fatty liver disease; *NASH*, non-alcoholic steatohepatitis; *SVR*, sustained virological response; *DAA*, direct antiviral agent

*Liver stiffness measurement using transient elastosonography (TE)

Table 2 Laboratory data at the baseline

Status (*n* = 22)	Mean (SD)
AST (U/l)	53.3 (± 34.7)
ALT (U/l)	63.3 (± 52.2)
ALKP (U/l)	89.7 (± 30.9)
GGT (U/l)	61.7 (± 46%)
Total bilirubin (mg/dl)	0.8 (± 0.4)
MELD	6.9 (± 2)
APRI	1.2 (± 1.1)

AST, aspartate aminotransferase (normal range < 40 U/l); *ALT*, alanine aminotransferase (normal range < 40 U/l); *ALKP*, alkaline phosphatase (normal range < 135 U/l); *MELD*, model for end-stage liver disease; *APRI*, AST/platelet ratio index

The Kpa values measured by pSWE showed statistically significant modification from the baseline (T0) and after HCV treatment (precisely at the end of treatment and 12, 24 and 48 weeks later) with the same p value ($p = 0{,}02$) (Fig. 1). On the other hand, Kpa values measured by Fibroscan did not show statistically significant modification during time [Fig. 2].

At multivariate analyses performed at the baseline, BMI emerged as the only variable independently associated to pSWE-stiffness ($p = 0.08$; 95%CI 0.79–3.73) after adjustment of statistical confounding analyzing the following variables: weight, AST, bilirubin, MELD, staging of fibrosis, flow in the hepatic veins, steatosis and bipolar diameter of the spleen.

As regards the Fibroscan-stiffness at the baseline, the only two variables that emerged independently associated were liver

Table 3 pSWE and US data at the baseline

Status (*n* = 22)	*n* (%) o mean (SD)
Kpa	14.3 (± 9.3)
Fibrosis stage	
F1	5 (22.7%)
F2	0
F3	2 (9.1%)
F4	15 (68.2%)
Portal vein average velocity (cm/s)	19.4 (± 7.4)
Hepatic vein flow	2.6 (± 0.7)
Portal vein diameter (cm)	1.2 (± 0.3)
Splenic diameter (cm)	12.9 (± 3.1)
Ascites	1 (4.5%)
Steatosis	
No	8 (36.2%)
Mild	7 (31.6%)
Moderate	4 (18.1%)
Severe	3 (14.2%)

pSWE, point shear wave elastography; *US*, ultrasound; *IQR*, interquartile range

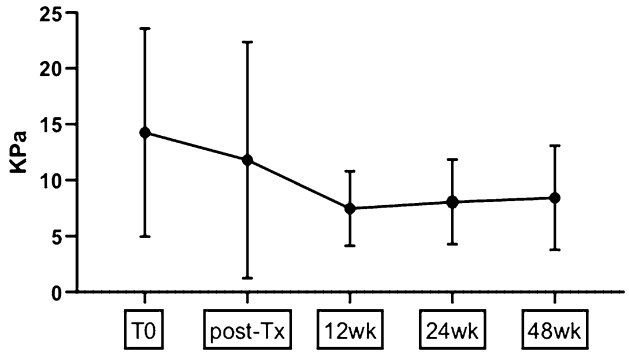

Fig. 1 Liver stiffness measurement using pSWE ($p = 0.02$)

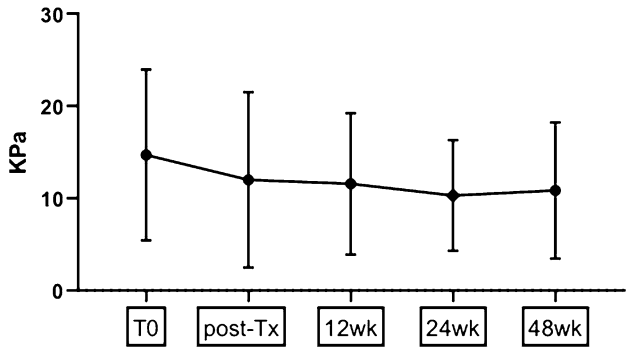

Fig. 2 Liver stiffness measurement using Fibroscan ($p = \text{NS}$)

cirrhosis and the hepatic vein flow. The adjustment was performed by univariate analysis of: SVR 12, MELD, cirrhosis, staging of fibrosis, portal vein diameter, spleen diameter, AST, ALP, bilirubin, steatosis and IQR.

We also analyzed the associations with any variables and delta changes of stiffness, i.e., differences between stiffness measurements at the baseline and twelve months after treatment. The variables that emerged to be independently associated with delta pSWE-stiffness were staging of fibrosis ($p = 0.006$; 95%CI 1.30–5.37) and SVR12 ($p = 0.017$; 95%CI −18.54 to 2.53). Statistical adjusted by: experienced treatments, failure of the treatment, BMI, veins flow, bilirubin and MELD.

Finally, the regression analysis for delta Fibroscan-stiffness resulted that MELD score was the only variable associated ($p = 0.02$; 95%CI 0.24–2.33) after computation with SVR 12, BMI, bilirubin, HCC, staging of fibrosis, spleen diameter and weight.

Discussion

Monitoring disease progression in chronic hepatitis C is a determinant of patient risk stratification and clinical management. Such a crucial role has not changed after the introduction of DAA therapy, since HCV eradication is supposed to halt the inflammatory injury of the liver and disease progression. However, no information is yet available to predict disease course after DAA therapy, nor which is the best method to be applied in the clinical setting.

The gold standard for assessing liver disease stage in HCV patients has been historically considered to be liver biopsy. Nevertheless, liver biopsy has limitations, given mostly by correct sampling, invasiveness/risk factors and costs. As such, its key role has been has hampered in the last decade by the advent of non invasive tests of liver injury, such as those based on biochemical tests (APRI, Fibrotest) or instrumental, such as transient elastography. The latter, in particular, has found a large consensus in the clinical setting, given its reproducibility and noninvasivity. In Italy, the reliability and operator-independent results, together with a quite robust scientific literature in support of, convinced regulators (AIFA, Italian Medicine Agency) to consider transient elastography as the surrogate indicator of the liver disease stage to access DAA therapy.

A limit of all the indirect tests of liver injury, transient elastography included, is that their predictive accuracy has been tested in the setting of a progressive disease. Whether they do maintain or not their accuracy in a condition of possible reduction of liver injury has yet to be verified. Such an aspect is crucial nowadays, when the vast majority of patients subjected to DAA therapy eliminate HCV infection. How to appropriately manage those patients will depend on what will happen to the liver, whether the injury remains stable or, presumably, might decrease.

Our study has investigated prospectively a cohort of HCV patients subjected to DAA therapy, before and after treatment. We observed that if before treatment transient elastography (TE) and pSWE show overlapping measurements of liver stiffness, they do indicate different degree of changes up to 48 weeks after therapy, with pSWE depicting a more rapid and prominent reduction of liver stiffness. Liver stiffness measured by pSWE showed indeed a statistically significant reduction during and after HCV treatment, whereas TE did not. At baseline the variables that showed to be independently associated with TE were hepatic vein flow and liver cirrhosis. At twelve month after treatment the variables that showed to be independently associated with pSWE-stiffness variation during time were staging of fibrosis and SVR12. The only variable that demonstrated to be associated with Fibroscan-stiffness change during time was MELD score.

As regards the significant variation of pSWE during time and not of TE, it is possible due to the different physical principles of the two techniques. In fact, pSWE evaluates the average speed of propagation and the time of arrival of the shear wave within the tissue from the focal point positioned on one lateral boundary of a measurement ROI to another on the opposite lateral boundary of the ROI, and ultrasound imaging is used to guide placement of the ROI [14]. Instead, TE works through a mechanically induced axial shear wave pulse at tissue surface.

The different technical characteristics of these two methods may also be the cause of the different variables independently associated with the delta stiffness assessed with the pSWE (staging of fibrosis and SVR 12) and TE (MELD score).

A previous study that used ARFI showed that pSWE was superior to transient elastography to detect liver fibrosis in HBV patients [22]. However, in this study elastography measurements were performed only 5 times, and this could be a limitation, as a reduction in the number of acquisitions from 10 to 5 can led to a significant reduction of intra-operator agreement [11].

To our knowledge is not analyzed in recent literature that MELD represents an evaluation that correlates with the delta TE measures yet.

Previously published studies reported a reduction in kPa values measured with pSWE from baseline to 24 weeks after end of treatment and this reduction is reported to be particularly pronounced in patients with progressive liver fibrosis [23, 24]. Only one previous published article evaluated only not co-infected HCV patients, but the data were evaluated until 36 weeks after end of treatment [25]. In this study in which ElastPQ was used, the authors concluded that SWE is a feasible, easily applicable noninvasive relatively inexpensive assessment method of liver fibrosis [25].

In fact, as regards clinical implications of the present study, the authors think that pSWE allow to evaluate stiffness reduction in HCV patient during DAA treatment follow-up, and this stiffness reduction is related to SVR12.

The current study has some limitations, such as the small sample size, the single-center analysis and the fact that pSWE inter-observer variability was not evaluated. Moreover, liver biopsy was not performed. However, only two studies evaluated prospectively pSWE and LS before and after HCV treatment. Moreover, the study population of one of them included patients with and without HIV co-infection, as well as patients with and without concomitant HCC. In the other study pSWE was evaluated until 36 weeks after treatment. Therefore, our study is the only one prospective that evaluated only not co-infected HCV patients treated with interferon-free DAAs until 48 weeks post-therapy.

In conclusion, pSWE allow to easily and noninvasively evaluate stiffness reduction in HCV patient during DAA treatment follow-up, which is related to SVR12. However, larger, multicenter studies are needed to confirm these results.

Compliance with ethical standards

Conflict of interest The authors declared no potential conflicts of interests associated with this study.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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