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Analysis of hepatic stiffness after viral eradication in a population with chronic hepatitis C treated with DAAs

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ABSTRACT

Introduction and objectives: Despite chronic hepatitis C (CHC) is still a global burden as the high morbidity and mortality, the recently approved direct-acting antivirals (DAAs) permit a very high rate of sustained virologic response (SVR) in these patients. The clinical improvement due to viral eradication is being documented, however it is not clear why a subset of patients does not benefit in terms of fibrosis regression or hepatocellular carcinoma (HCC) development. Aim of the study was to assess the hepatic stiffness regression at SVR24 and detect factors impacting stiffness course.
Patients and methods: Hepatic stiffness assessed by *acoustic radiation force impulse* (ARFI) and anthropometric- and biochemical parameters were retrospectively collected by 166 CHC patients treated with DAAs, form baseline and SVR24.
Results: Viral eradication significantly improved overall hepatic stiffness and other related hepatitis hallmarks such as ALT, AST, γGT, platelets count, *AST to Platelets ratio Index* (APRI), total- and LDL cholesterol. The multiple regression analysis showed that patients with baseline glucose > 110 mg/dl presented a stiffness regression significantly lower when compared to low glucose patients (<110 mg/dl), moreover baseline HbA1c strongly correlated with DeltaStiffness. 7 patients (4.2%) developed HCC and importantly, presented hyperglycaemia and no stiffness regression nor platelets count recover.
Conclusions: Although viral eradication with DAAs entails overall benefits, glycaemic decompensation negatively affects fibrosis regression and probably facilitates HCC development.

Análisis de la rigidez hepática después de la erradicación viral en una población con hepatitis C crónica tratada con AAD

Palabras clave:
Hepatitis
Antiviral de acción directa
Fibrosis
Glucosa
Metabolismo
Carcinoma hepatocelular

RESUMEN

Introducción y objetivos: Aunque la hepatitis C crónica (CHC) sigue siendo una carga global debida a la alta morbilidad y mortalidad, los antivirales de acción directa (AAD) recientemente aprobados, permiten un índice muy alto de respuesta virológica sostenida (RVS) en estos pacientes. La mejoría clínica debida a la erradicación viral está siendo documentada, pero no está claro por qué un subconjunto de pacientes no se beneficia en términos de regresión de fibrosis o desarrollo de carcinoma hepatocelular (HCC). El objetivo de este estudio fue evaluar la regresión de la rigidez hepática en SVR24 y detectar los factores que afectan el curso de la rigidez.
Pacientes y métodos: La rigidez hepática evaluada por la radiación acústica de la fuerza de impulso (ARFI) y los parámetros antropométricos y bioquímicos fueron recolectados retrospectivamente por 166 pacientes con CHC tratados con ADD, desde el punto de partida y SVR24.

Abbreviations: CHC, chronic hepatitis C; DAAs, direct-acting antivirals; SVR, sustained virologic response; HCC, hepatocellular carcinoma; SVR24, 24 weeks of sustained virologic response; ARFI, acoustic radiation force impulse; APRI, AST to Platelets Ratio Index; IFN, interferon; RBV, ribavirin; ΔStiffness, Delta Stiffness; INR, international normalized ratio; BMI, body mass index.

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Resultados: La erradicación viral mejoró significativamente la rigidez hepática general y otros signos relacionados con la hepatitis, como ALT, AST, γGT, conteo de plaquetas, *índice da razão AST/plaquetas* (APRI), colesterol total y LDL. El análisis de regresión múltiple mostró que los pacientes con glucosa basal >110 mg/dL tuvieron una regresión de rigidez significativamente inferior en comparación con los pacientes con glucosa baja (<110 mg/dL), además la HbA1c de referencia se correlacionó fuertemente con DeltaStiffness. Siete pacientes (4,2%) desarrollaron CHC y, lo que es más importante, presentaron hiperglucemia y no hubo regresión de rigidez ni recuperación del conteo de plaquetas.
Conclusiones: A pesar de que la erradicación viral con AAD conlleva diversos beneficios, la descompensación glucémica afecta negativamente la regresión de la fibrosis y probablemente facilita el desarrollo de CHC.

Introduction

The WHO estimated 71 million people with HCV infection, worldwide.[1] A considerable number of chronic infections develop cirrhosis or liver cancer. In fact, in 2016 it is estimated that approximately 399 000 people died from HCV-related cirrhosis or hepatocellular carcinoma.[1] The therapeutic regimens based on interferon and ribavirin were often unsuccessfully used for many years. In the last years the therapy of HCV infection has been revolutionized by the *direct-acting antivirals* (DAAs) which guarantee a rate of sustained virologic response (SVR; defined as HCV RNA negativity for 12-24 weeks after treatment ending) over 95%.[2,3] The high rate of viral eradication allowed clinicians to appreciate different clinical outcomes, since either hepatic and extrahepatic manifestations improve or disappear with recent IFN-free therapies.[4] Interestingly, studies were conducted also in patients with decompensated cirrhosis demonstrating a slight lower response rate (about 80%) but with significant overall improvement of liver function and scores such as MELD and CTP.[5,6] Furthermore, several reports documented a regression of fibrosis and cirrhosis during and after IFN/RBV based regimens,[7,8] while for DAAs-based therapy new evidence is accumulating describing the improvement of non-invasive liver stiffness assessment and fibrosis surrogate scores (FIB-4, APRI, Fibrotest).[4,9,10] On the other hand, the observation of a small rate of patients with persisting fibrosis, despite achieving SVR, fuels the research of negative predictors of fibrosis regression. Therefore, we decided to retrospectively analyse a population of patients affected by Chronic Hepatitis C (CHC) and responders to DAAs regimens, in order to find putative factor impacting stiffness course after 24 weeks of SVR (SVR24).

Patients and methods

The study included 166 patients with CHC who achieved SVR24 after treatment with different DAAs regimens from July 2015 to March 2019. A retrospective data collection was performed from baseline and SVR24, including anthropometric, serological and instrumental data. HCV-related chronic hepatitis was defined by positivity for anti-HCV antibodies and serum HCV-RNA. Serum HCV-RNA was detected by qualitative polymerase chain reaction (PCR) (CAP-TaqMan HCV Qualitative Test Version 2.0, Roche; sensitivity of 15 IU/mL) and quantitative real time kinetic PCR (VERSANT HCV RNA 1.0 Assay, sensitivity of 15 IU/mL). The abdomen ultrasonography was carried out and the hepatic stiffness was evaluated by *acoustic radiation force impulse* (ARFI), scoring patients as follows: F0-1 (KPa<7.1); F2 (KPa≥7.1); F3 (KPa≥9.5); F4 (KPa≥14.5). These values were based on metanalysis and systematic reviews, that associated transient elastography cut-offs with fibrosis METAVIR classification in HCV patients.[11,12] Steatosis grade (absent; mild; moderate; severe) was evaluated by echogenicity comparison of hepatic and renal parenchyma. Baseline (T0) characteristics are shown in Table 1. Subjects with decompensated cirrhosis, autoimmune disease, HIV co-infection, previous liver transplantation and other causes of liver disease (e.g. alcohol, hepatitis B virus) were excluded from analysis. The numerosity of the sample will be indicated when missing values are present. The analysis was performed in accordance with the law and in absence of a written informed consent. All the data were entered in a computerized database and they were anonymized and de-identified prior to analysis. Therefore, the "Comitato Etico Azienda Ospedaliero Universitaria Policlinico di Bari" was informed and provided the approval.

Table 1
Population baseline characteristics.

Variables		*N* (%)
Population		166
M		84 (50.6%)
F		86 (49.4%)
Fibrosis Stage		
F0-F1 (< 7.1 KPa)		52 (31.3%)
F2 (≥ 7.1 KPa)		18 (10.8%)
F3 (≥ 9.5 KPa)		41 (24.7%)
F4 (≥ 14.5 KPa)		55 (33.1%)
Steatosis Grade		
Absent		49 (29.52%)
Mild		77 (46.39%)
Moderate		36 (21.69%)
Severe		4 (2.41%)
Continuous Variables	n	Mean ± SEM
Age, years	166	67.1 ± 0.8
BMI, Kg/m^2	162	26.8 ± 0.3
Waist circumference, cm	115	100 ± 1
HCV RNA, IU/ml	146	2x10^6 ± 3.2x10^5
Total bilirubin, mg/dl	157	0.9 ± 4.3
INR	134	1.1 ± 0
Albumin, g/dl	130	3.9 ± 4.3
Platelets, u/μl	161	168.9 ± 5.7
AST, ULN	163	1.7 ± 9.8
ALT, ULN	161	1.5 ± 0.1
GGT, ULN	158	1.1 ± 0.1
Fasting glucose, mg/dl	150	107.7 ± 2.3
Total Cholesterol, mg/dl	95	156.7 ± 3.6
HDL, mg/dl	95	53.8 ± 1.7
LDL, mg/dl	95	84.7 ± 3.6
Triglycerides, mg/dl	95	97.1 ± 4.6
Uric acid, mg/dl	102	4.9 ± 0.1
APRI	161	1.5 ± 0.1

Statistical analysis

Data are shown as mean ± standard error (SEM). Differences between two groups were analysed by using Student's T test, while the paired sample T test was used when time dependent change (T0 vs SVR24) of a continuous variable was analysed. In order to compare the time dependent change of stiffness (ΔStiffness) between two groups, a multiple regression was used, including potential

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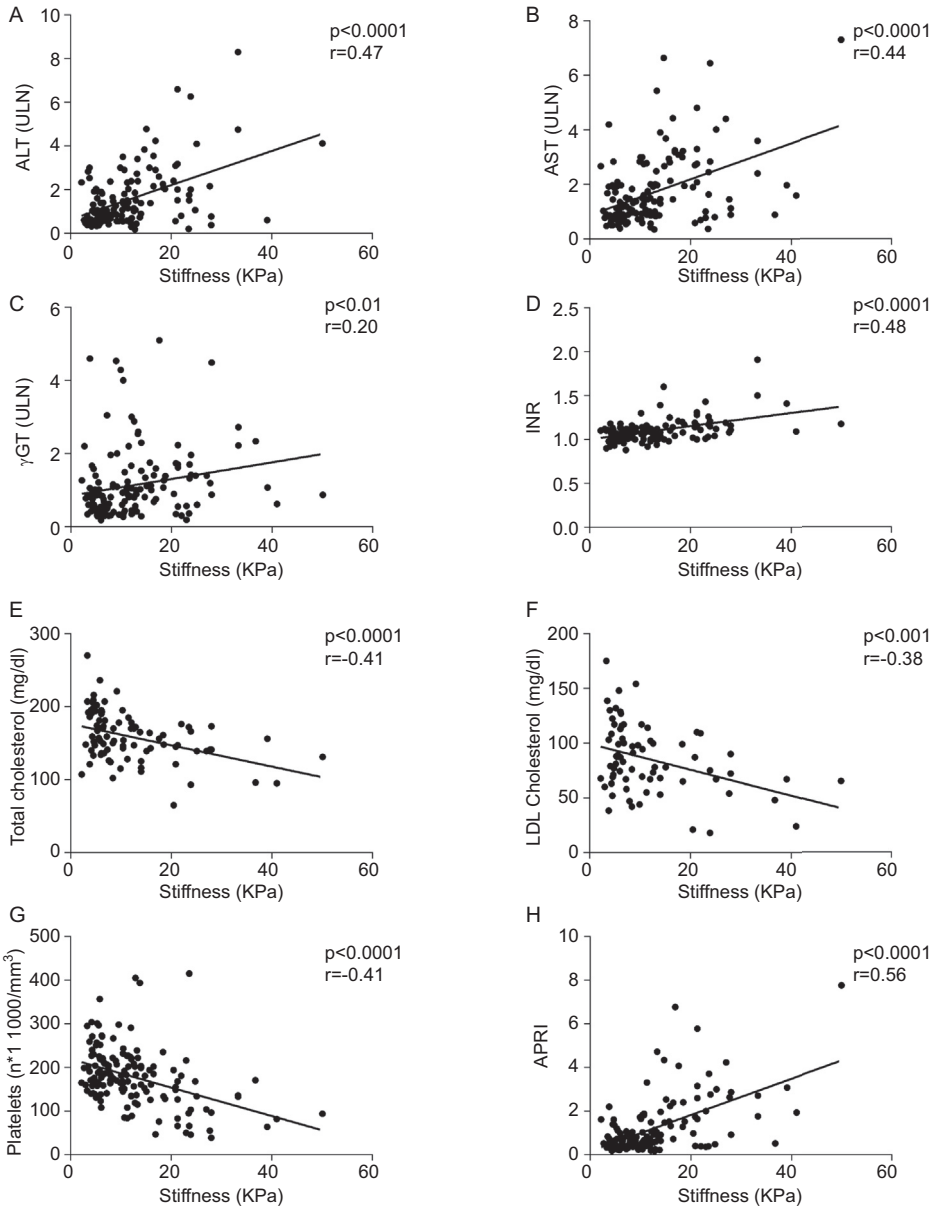

Figure 1. Hepatic stiffness correlations. Baseline hepatic stiffness expressed in KPa significantly correlates with ALT (A; n=136), AST (B; n=146), γGT (C; n=141); INR (D; n=118); total cholesterol (E; n=88); LDL cholesterol (F; n=73); Platelets (G; n=144); APRI (G; n=143). Correlations were evaluated with Person's test. *APRI*: AST to Platelet Ratio Index.

confounding factors in the analysis (i.e. age, gender, smoke, HCV RNA, BMI and steatosis grade). Pearson's correlation test was used to assess the strength of a correlation between two continuous variables.

Results

Baseline hepatic stiffness correlations

First, we investigated whether the entity of liver stiffness was related to other biochemical and anthropometric parameters at baseline. As expected, we found a significant correlation between liver stiffness (expressed in kPa) and hepatic enzymes (i.e. ALT, AST and γGT) (Figure 1A-C). INR strongly correlated with stiffness as well (Figure 1D). Interestingly, serum total cholesterol (TC) and LDL cholesterol inversely correlated with liver stiffness (Figure 1E, F), reflecting the incapacity of a damaged liver to export cholesterol into the bloodstream. The number of platelets also inversely correlated with stiffness (Figure 1G) and consequently the *AST to Platelets ratio index* (APRI) showed a strong positive correlation (Figure 1H). None significant correlation was found between hepatic stiffness and other biochemical and anthropometric parameters such as HCV-RNA levels, BMI, waist circumference and fasting glucose.

SVR outcomes

The second step of our analysis was to evaluate whether the viral eradication obtained with DAAs was effective to improve hepatic stiffness and all parameters related to it. As expected at SVR24 patients showed a significant improvement of liver stiffness (from 12.5 ± 0.7 kPa to 9.1 ± 0.5 kPa) (Figure 2A) and in fact, the reduction of METAVIR grade was reported in 36,6% of patients with F4 score, in 56,1% of F3 and 50% of F2 patients (Figure 2B).

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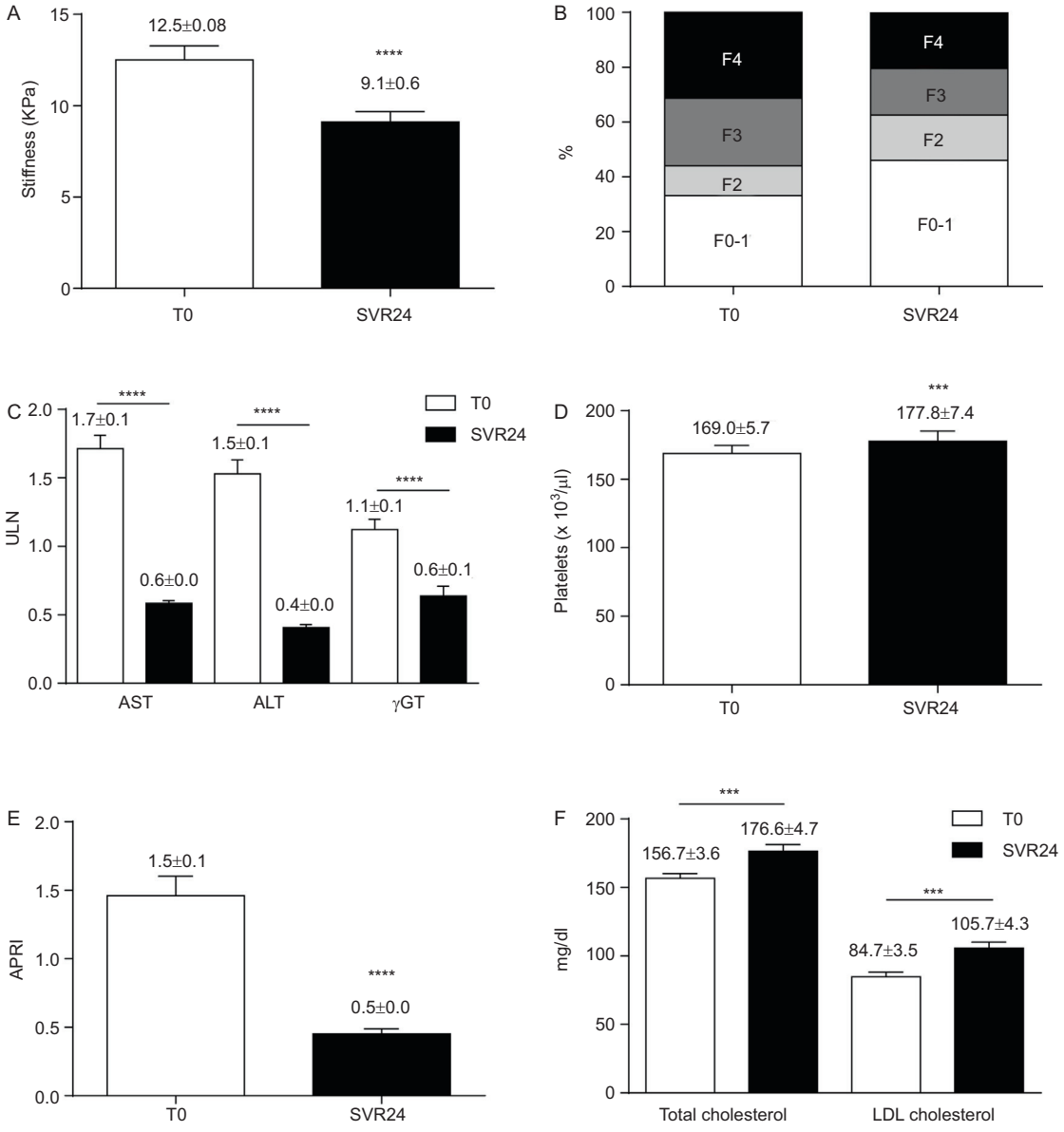

Figure 2. SVR24 outcomes. A. Change of hepatic stiffness from baseline to SVR24 (n=103); B. Prevalence of METAVIR stiffness stages at baseline and SVR 24; C-F. Modification of different parameters from baseline to SVR24: AST (n=111), ALT (n=109) and γGT (n=116) (C); Platelets (D; n=126); APRI (E; n=109); total (n=47) and LDL cholesterol (n=34) (F). Paired T test was performed to analyse time-dependent differences. *APRI*: AST to Platelet Ratio Index.

In parallel, the liver damage ameliorated as demonstrated by the significant reduction of AST, ALT and γGT (Figure 2C). The number of platelets significantly increased (Figure 2D) and the APRI drastically improved at SVR24 (Figure 2E). Interestingly, the viral eradication restored the hepatic lipoprotein synthesis and exportation as shown by the significant increase of total- and LDL cholesterol (Figure 2F).

Glucose metabolism impacts on fibrosis regression and HCC development

Despite the overall improvement of all hepatitis hallmarks, the clinical observation of cases with persisting or even worsened hepatic stiffness at SVR24 led us to investigate whether baseline characteristics could impact stiffness regression. Therefore, applying a multiple regression we found that fasting glucose at baseline influenced the entity of fibrotic regression (ΔStiffness expressed in ΔKPa) (Table 2). In particular, patients with high glycemia (fasting glucose > 110 mg/dl) showed a significantly lower regression when compared to patients with fasting glucose < 110 mg/dl (Figure 3A). Moreover, the baseline values of HbA1c of diabetic patients strongly correlated with ΔStiffness (expressed in ΔkPa or Δ%) (Figure 3B, C). Therefore, hyperglycaemia negatively affected liver fibrosis regression as high fasting glucose and high HbA1c were associated to

Table 2
Multiple regression analysis for stiffness regression (ΔStiffness). Steatosis grade considered as continuous variable (0 = no steatosis; 1=mild steatosis; 2=moderate steatosis; 3=severe steatosis).

Variables	Regression coefficient	p-value
Age (years)	- 0.09 ± 0.06	ns
Gender (male)	- 1.71 ± 1.15	ns
Smoke (Yes)	- 1.90 ± 1.54	ns
BMI (Kg/m^2)	- 0.04 ± 0.15	ns
HCV RNA (IU/ml)	0	ns
Fasting glucose > 110 mg/dl	3.31 ± 1.48	0.02
Steatosis grade	- 0.94 ± 0.71	ns

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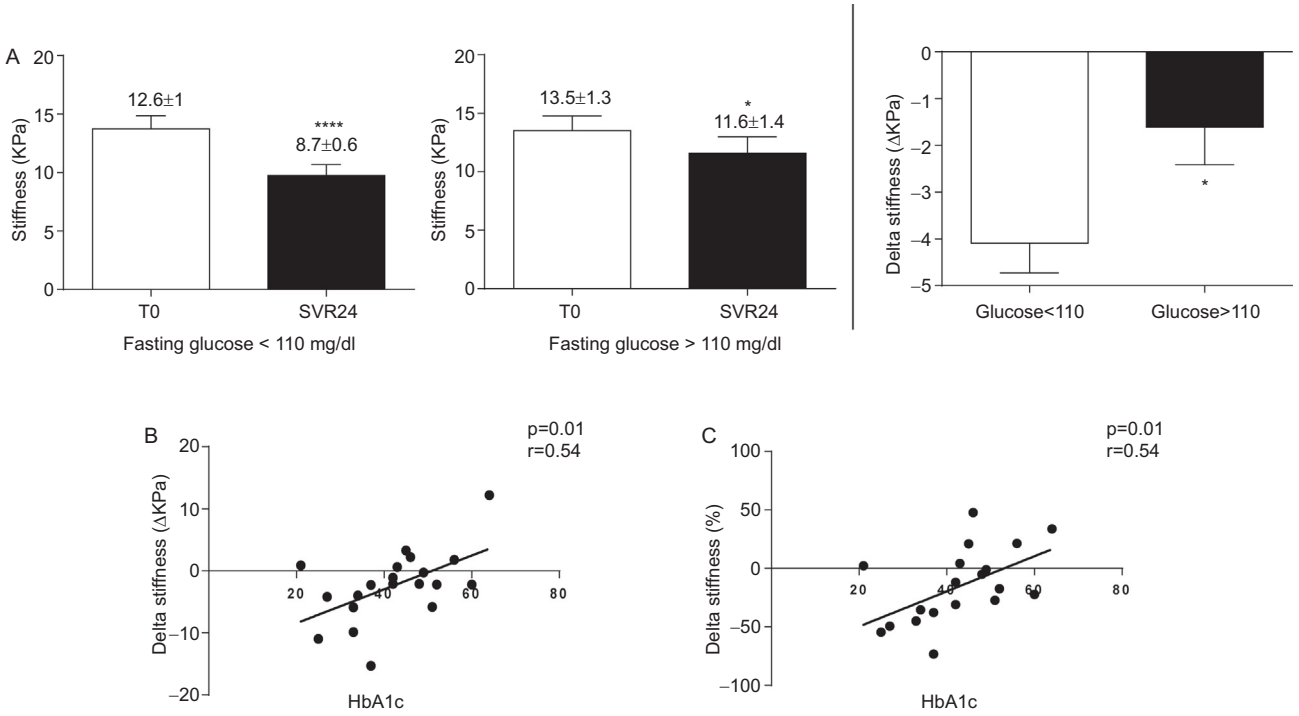

Figure 3. Impact of glucose on stiffness course. A. Different stiffness change after viral eradication between *low glucose* patients (<110 mg/dl; n=75) and *high glucose* patients (>110 mg/dl; n=31); B, C. Direct correlation of baseline HbA1c with ΔStiffness expressed in ΔKPa (B; n=20) and Δ% (C; n=20). Paired T test was performed to analyse time-dependent differences. The multiple regression was used to assess impact of *high-* and *low-glucose* category on ΔStiffness. Correlations were evaluated with Person's test.

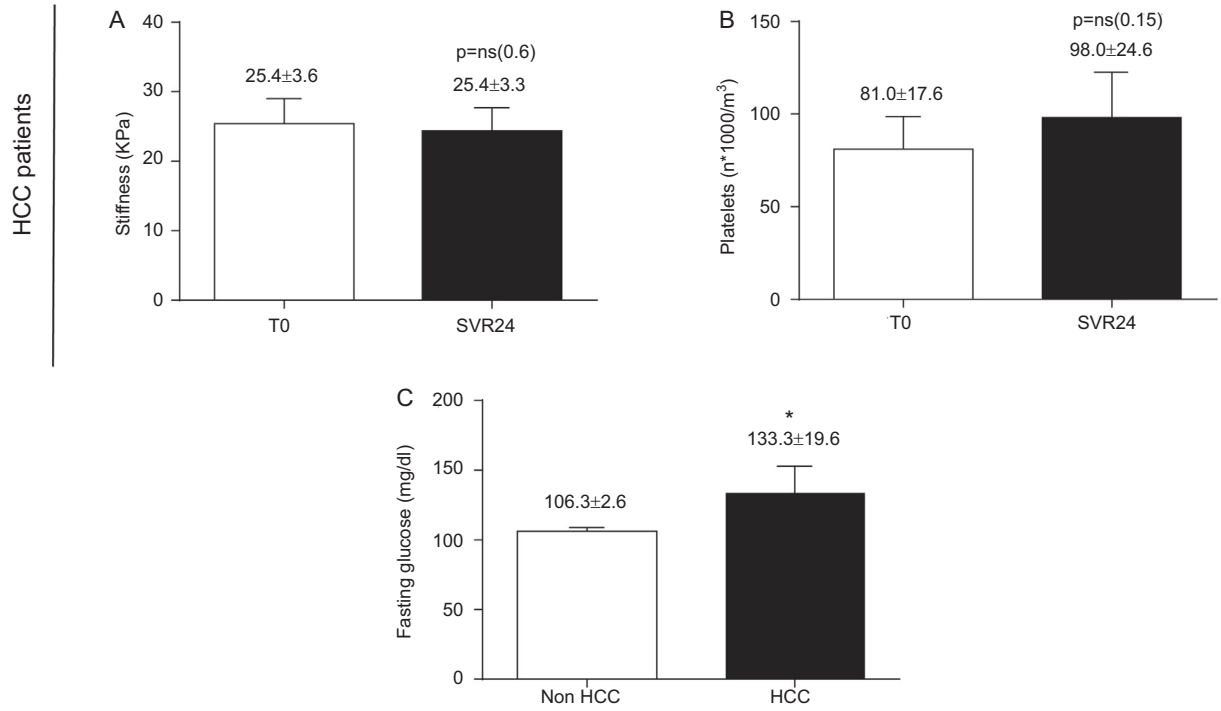

Figure 4. Features of patients who developed HCC. A. Change of hepatic stiffness from baseline to SVR24 (n= 7); B. Change of Platelets number from baseline to SVR24 (n=7); C. Baseline fasting glucose levels in patients with HCC occurrence (n=7) and patients with HCC-free follow-up (n=115). Paired T test was performed to analyse time-dependent differences, while Student's T test was used for differences between two groups.

poorer or absent stiffness improvement. Another important observation was that 7 (4.2%) patients developed HCC during post-SVR follow-up. None of these presented stiffness regression, so that 6 patients remained scored as F4 and one subject worsened form F3 to F4 (Figure 4A). In addition, the increase of platelets amount was not significant (Figure 4B). Very intriguingly, HCC developers showed significantly higher fasting glucose at baseline when compared to non-HCC developers (Figure 4C).

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Discussion

The rising of DAAs have drastically changed the history of HCV related hepatitis worldwide. The high rate of SVR (>95%) and the well documented improvement of hepatic and extrahepatic manifestations make treatment with DAAs feasible in all HCV infected patients. On the other hand, not all the patients benefit from the treatment (e.g. fibrosis regression) and since the high cost of these drugs, the decision to provide the therapy becomes a political issue. In this study, we retrospectively investigated the putative interactions of hepatic stiffness with other anthropometric and biochemical parameters, in order to predict liver fibrosis course after viral eradication. To do this, we used ARFI elastography, which has been demonstrated being a reliable technique for fibrosis evaluation and follow-up in CHC patients.[13–15] In line with previous studies, DAAs therapy was successful to improve hepatic stiffness and other correlated parameters such as liver enzymes, platelets count and APRI.[2,10–15] Intriguingly, also the TC and LDL cholesterol, which showed a direct correlation with baseline stiffness, significantly increased at SVR24. The high prevalence of hypocholesterolemia in CHC patients is known as well as the increase of TC and LDL after viral eradication,[16,17] although we did not find a previous description of a direct correlation with stiffness. The overall improvement of clinical status is clear and therefore the benefits of DAAs are incontrovertible, however a pool of patients did not show improvement of hepatic stiffness and a part of these even developed HCC. A recent study reported that hepatic steatosis affects stiffness regression,[18] while elevated BMI negatively impacts platelets count recover in subjects with advanced fibrosis.[19] Our analysis instead, showed that high fasting glucose (>110 mg/dl) is negatively associated with SVR24 stiffness regression. Moreover, values of HbA1c strongly correlated with ΔStiffness, underlining the negative impact of decompensated diabetes on liver fibrosis improvement. Type 2 diabetes is probably the most frequent extrahepatic manifestation in HCV infected people[20,21] and insulin resistance has been associated to SVR low rate in patients treated with IFN/ribavirin.[22] We acknowledge that diabetic patients might present hepatic steatosis with an overestimation of liver stiffness. However, we included steatosis ultrasound grade as confounding factor in the analysis, showing that only hyperglycaemia was significantly associated to poorer stiffness regression. In addition, ARFI has been demonstrated to be more reliable than Fibroscan in detection of advanced fibrosis in obese and steatotic patients.[23] Moreover, diabetes is a known risk factor for HCC development,[24] and a recent Italian study, which reported a higher HCC occurrence in DAAs ribavirin-free regimens, showed that diabetes remains a risk factor even post-SVR.[25] In fact, diabetes is a state of chronic inflammation where insulin resistance and hyperglycaemia fuel tumorigenesis.[26] Accordingly, in our cohort 7 patients (4.2%) developed HCC during post-SVR follow-up. They did not present stiffness regression nor platelets count recover and interestingly, baseline glucose was significantly higher than non-HCC developers, despite acknowledging the limit of sample numerosity. The role of DAAs in HCC incidence is still debated. We believe that patients with advanced fibrosis should be carefully screened, especially if they do not reach outcomes like liver fibrosis regression, although as shown by Pons M et al., a persisting stiffness ≥ 20 KPa at follow-up is not the lonely predictor factor of HCC.[27] Moreover, it is needed to pay attention to diabetic subjects as they are candidate for persisting hepatic inflammation and hence HCC. In 2011 a study revealed cirrhotic patients with diabetes presented a lower incidence rate of HCC if treated with metformin.[28] Other studies demonstrate benefits of metformin in HCC, but we do not know whether the effect is due to direct antitumorigenic properties or to insulin sensitization.[29,30]

Conclusions

In conclusion our analysis showed overall benefits of viral eradication with DAAs on hepatic stiffness and hepatitis hallmarks, but also a clear association of hyperglycaemia with persisting hepatic stiffness and probably cancer development. Further studies are needed to investigate whether a better anti-diabetic treatment might improve SVR outcomes.

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Declarations of interest

None.

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