

Original Article

PET/DW-MRI for evaluating treatment in chronic hepatitis C patients

Rikke J Petersen^{1*}, Nick S Nielsen^{2*}, Helle H Johannesen¹, Adam E Hansen¹, Sofie Jespersen², Caroline J Arnbjerg², Johan Löfgren¹, Mette S Kjær³, Mette R Clausen³, Andreas Kjær¹, Susanne D Nielsen², Barbara M Fischer^{1,4}

¹Department of Clinical Physiology, Nuclear Medicine and PET and Cluster for Molecular Imaging, Rigshospitalet and University of Copenhagen, Denmark; ²Infectious Diseases, ³Hepatology, Rigshospitalet, University of Copenhagen, Denmark; ⁴PET Centre, School of Biomedical Engineering and Imaging Sciences, Kings College London, St Thomas' Hospital, Westminster Bridge Road, London, UK. *Equal contributors.

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Abstract: This feasibility study set out to investigate the use of FDG-PET/DW-MRI in chronic hepatitis C patients to examine changes in local liver inflammation after treatment with direct-acting antivirals (DAA). Twelve patients with chronic hepatitis C were prospectively enrolled, performing FDG-PET/DW-MRI prior to and after DAA treatment. PET/DW-MRI included PET acquisition 60 and 90 min after FDG-injection, DIXON, for attenuation correction, T2- and DW-MRI with 10 b-values between 0-700 s/mm². The following parameters were measured from fusion of 3 volumes of interest (VOIs) placed in the liver parenchyma: Mean standard uptake value after 60 and 90 minutes (SUV_{mean60} and SUV_{mean90}), total Apparent Diffusion Coefficient (ADC), perfusion fraction (PF), pseudo-diffusion (D*) and perfusion-free diffusion (D). We found PET/DW-MRI of chronic hepatitis C patients to be feasible. Patients were cooperative, tolerated the scans well and the image quality was acceptable. A total of 10 patients were available for final analysis. All patients achieved sustained virologic response and normalized *alanine*-aminotransferase (ALAT) levels after treatment with DAA. Perfusion fraction measured by DW-MRI changed significantly after treatment, from mean 0.21 (± 0.04) to 0.26 (± 0.06), P=0.005 and D* from 0.50 (± 0.13) × 10⁻³ s/mm² to 0.62 (± 0.15) × 10⁻³ s/mm², P=0.028. All other parameters, including FDG-uptake, was unchanged. These results suggest that liver perfusion is changed shortly after DAA treatment, with no significant change in inflammation. The study concludes that PET/DW-MR is feasible in quantifying perfusion and possibly inflammation in chronic hepatitis C patients and may be used to follow treatment.

Keywords: PET/MRI, diffusion weighted MRI, FDG-PET, chronic hepatitis C, response evaluation, inflammation

Introduction

Globally, an estimated 71 million people have chronic hepatitis C virus infection (CHC) [1], which is associated with hepatic as well as systemic inflammation [2]. Hepatic inflammation contributes to the development of fibrosis, cirrhosis and hepatocellular carcinoma (HCC) [2], leading to approximately 400,000 deaths annually [1]. The degree of inflammation in the liver has prognostic value in the evaluation of progression of liver fibrosis [3], however, hepatic inflammation is difficult to assess non-invasively. Since 2014, direct-acting antiviral agents (DAA's) have been introduced for treatment of CHC, resulting in sustained virological response

(SVR) in the majority of patients (>90%) as well as fewer side effects compared to previous standard of care [4, 5].

Studies have shown though, that not all patients show regression in liver fibrosis level after successful treatment [6]. Traditionally, evaluation of liver fibrosis is done by analysis of liver biopsies. There are, however, several problems concerning this invasive procedure: discomfort for the patient, an overall complication rate of over 6%, bleeding risk of 1-2% and even a small mortality [3]. Furthermore, a biopsy only represents approximately 1/50,000 of total liver volume, sampling errors are frequent and intra- and inter-observer variations have been reported

[3]. Non-invasive methods for evaluating degree of fibrosis, such as transient elastography (Fibroscan), exist, but at present there are no non-invasive methods in clinical use to score liver inflammation. A tool to non-invasively measure the level of inflammation in the liver to guide timing of treatment, as well as monitoring local response in the liver after treatment, could therefore be a valuable tool in the clinic. Recently a number of magnetic resonance imaging (MRI) sequences, including MR elastography (MRE) and diffusion weighted MRI (DW-MRI), have shown great potential for diagnosing and grading fibrosis and local changes in the liver [7], but much less is known about the usefulness of DW-MRI for evaluating inflammation. DW-MRI is a functional imaging technique that displays information about water mobility, tissue cellularity and the integrity of cellular membranes. It also permits the quantitative evaluation of the apparent diffusion coefficient (ADC) from images with different b-values. ADC values derived from DW-MRI reflects the diffusion of water molecules in tissues and are therefore influenced both by capillary blood flow as well as water diffusion in the extracellular space [8], both of which may be impacted by the presence of inflammation. By bi-exponential modeling of multiple b-value DWI, it is possible to better account for non-monoexponential behavior of the diffusion signal intensity at different b-values, as well as take into the account the influence of perfusion at low b-values. This allows us to separate the pure molecular diffusion and the perfusion-related diffusion effects on ADC values, into pure diffusion (D), pseudo-perfusion (D^*) and the perfusion fraction (PF). This makes it possible to examine the effects of hepatitis C on the liver in greater detail.

Use of Positron Emission Tomography/Computed Tomography (PET/CT) with the tracer ^{18}F -Fluorodeoxyglucose (^{18}F -FDG) is well described for diagnosing and evaluating inflammatory conditions such as inflammatory bowel disease, vasculitis and fever of unknown origin, and as so, it might be a useful tool to assess inflammation over time such as in CHC patients [9-11]. FDG-PET has not been systematically evaluated in CHC patients, but by comparing FDG uptake in individual patients, this method may have the potential to be utilized to assess inflammation over time in liver disease [12].

PET/DW-MRI is a newly developed medical imaging technology combining the non-invasive information of tissue at the molecular level of PET and the excellent soft tissue differentiation as well as the function parameters of MRI [13]. The object of this pilot study was to evaluate the feasibility of PET/DW-MRI as a clinical tool for non-invasive evaluation of liver inflammation in chronic hepatitis C patients as well as changes after DAA treatment. To our knowledge, this is the first study to examine local inflammation in the liver with PET/DW-MRI. *The working hypothesis is that local inflammation in the liver of patients with chronic infection with hepatitis C virus will decrease after successful treatment with DAA's.*

Methods

Background and patients

This pilot study is a sub-study originating from the study "Coagulation and inflammation in patients with chronic hepatitis C", which took place at Rigshospitalet, Copenhagen University Hospital, from September 2014 to July 2015. The study was approved by The Committee on Biomedical Research Ethics for the Capital Region in Denmark (H-1-2014-064) and the Danish Data Protection Agency and conducted in accordance with the Second Declaration of Helsinki. Written informed consent was obtained from all participants.

For this pilot study we planned an inclusion of a total of 12 patients. To be eligible, patients had to have previously untreated chronic hepatitis C with or without fibrosis or cirrhosis, as estimated by Fibroscan (≥ 7 kPa for fibrosis and ≥ 12 kPa for cirrhosis). Only Child Pugh class A patients were eligible. Exclusion criteria were Child Pugh class B-C, diabetes, claustrophobia, magnetic metal implants and pacemaker. All patients had to complete a scan before and after treatment with DAA's to be eligible. All patients were recruited from the Department of Infectious Diseases and the Department of Hepatology at Rigshospitalet, Copenhagen University Hospital, during the period of September 2014 to July 2015.

Blood sampling and treatment

All patients had one blood sample of 30 mL taken before and after treatment with DAA.

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Table 1. Details on the individual patients included in the analysis

Patient	Sex	Age	BMI ⁱ	Current smoker	Current alcohol consumes	CHC with fibrosis	Child-Pugh score ⁱⁱ	HCV genotype	HCV RNA load (IU/ml) ⁱⁱⁱ
1	M	63	19.2	No	No	Yes	A	3	0.72·10 ⁶
2	M	66	29.7	Yes	Yes	Yes	A	1	2.50·10 ⁶
3	M	54	24.6	Yes	No	No	A	1	3.20·10 ⁶
4	F	45	22.8	No	No	No	A	1	0.80·10 ⁶
5	M	42	28.4	Yes	No	Yes	A	3	0.79·10 ⁶
6	F	61	22.9	No	Yes	Yes	A	1	0.39·10 ⁶
7	M	30	22.6	Yes	No	No	A	2	2.70·10 ⁶
8	M	40	23.1	No	No	Yes	A	3	3.70·10 ⁶
9	M	30	24.3	No	Yes	No	A	4	0.85·10 ⁶
10	M	43	24.1	No	No	No	A	4	1.30·10 ⁶

ⁱBody Mass Index. ⁱⁱChild-Pugh Score (A-C) assess the prognosis of chronic liver disease based on total bilirubin, serum albumin, prothrombin time, ascites and hepatic encephalopathy, Group A being the best prognostic group. ⁱⁱⁱHCV RNA lod prior to treatment.

Blood levels of ALAT, CRP, leukocytes and hepatitis C viral load were recorded. Treatment dose and length of treatment varied between participants depending on hepatitis C genotype. All patients received between 8 and 12 weeks of DAA treatment.

PET/DW-MRI

The pre- and post-treatment scans were performed no more than 14 days prior to, respectively after DAA treatment. FDG-PET/DW-MRI (Siemens Biograph mMR) was performed over the upper abdomen (1-2 bed positions). All patients fasted for a minimum of 4 hours prior to FDG-injection. PET was acquired 60 and 90 min after FDG-injection (2 Mbq/kg, maximum 250 Mbq). The dose of FDG used is half of what is normally used with PET/CT, which is made possible by the longer PET-acquisition time (8 min/bed) compared with standard PET/CT (2-4 min/bed). PET was reconstructed using 3 iterations, 21 subsets and 4 mm post-filtering). 3 T MRI included: 3D VIBE-DIXON for PET attenuation correction [echo time (TE) 1.23/2.46 ms, repetition time (TR) 3.60 ms, voxel size: 4.1 × 2.6 × 3.1 mm³]; coronal T2 HASTE [TE 92 ms, TR 1400 ms, pixel size: 2.1 × 1.5 mm², slice thickness 5.0 mm]; transverse T2 BLADE with fat saturation [TE 95 ms, TR 2500 ms, pixel size: 1.5 × 1.5 mm², slice thickness 5.0 mm]; and DW imaging with a prototype single-shot spin-echo EPI pulse sequence [TE 64 ms, TR 2800 ms, pixel size: 3.1 × 3.1 mm², slice thick-

ness 5.0 mm and 10 b-values: 0, 10, 20, 50, 100, 180, 300, 420, 550 and 700 s/mm²].

Measurement of ADC and SUV

An experienced PET-MRI radiologist and a nuclear medicine physician placed three volumes of interest (VOI) of each 12-15 cm³ in the liver parenchyma, two in the right lobe and one in the left, avoiding larger vessels and artefacts. After fusion of the 3 VOIs the following PET/DW-MRI parameters were extracted: SUV mean after 60 minutes (SUV_{mean60}) and SUV mean after 90 minutes (SUV_{mean90}), as defined as:

$$SUV = \frac{r}{\left(\frac{\alpha'}{w}\right)}$$

Where r is the radioactivity activity concentration [kBq/ml] measured by the PET scanner within a volume of interest, α' is the decay-corrected amount of injected radiolabeled FDG [kBq], and w is the weight of the patient in grams [14].

Furthermore, median total ADC (Median AD-Ctotal) obtained from single-exponential modeling as well as median Perfusion Fraction (PF), D* (pseudo-diffusion) and D (perfusion-free diffusion) obtained from bi-exponential modeling of the multiple b-value DWI using the equation

$$S/S_0 = PF \cdot e^{-b(D+D^*)} + (1-PF) \cdot e^{-bD}$$

as implemented in a Siemens works-in-progress research package.

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Table 2. Blood test results before and after treatment with direct acting antivirals

	Mean HCV RNA load (IU/ml)	Mean ALAT (U/L)	CRP (mg/L)	Leukocytes (10 ⁹ /L)	Fibroscan (kPa)
Pre-treatment	1.7·10 ⁶ ±1.2·10 ⁶	103±92	0.53±0.46	7.60±2.48	11.22±7.78
Post-treatment	0	22±12	0.83±0.71	7.14±2.74	8.08±6.07
p-value	0.005	0.005	0.066	0.333	0.249

Fibroscan after treatment was only completed in 6 patients. Mean HCV RNA load and mean ALAT decreased significantly after treatment.

Table 3. Summary of PET/DW-MR imaging data before and after treatment with direct acting antivirals

	Median ADC _{total} (× 10 ⁻³ mm ² /s)	*Perfusion fraction	Diffusion, D (× 10 ⁻³ mm ² /s)	*Pseudo-diffusion, D* (× 10 ⁻³ mm ² /s)
Pre-treatment	1.02±0.06, 1.00, 0.98-1.06	0.21±0.04, 0.21, 0.18-0.24	0.91±0.04, 0.90, 0.89-0.94	0.50±0.13, 0.50, 0.41-0.60
Post-treatment	1.01±0.09, 1.04, 0.95-1.08	0.26±0.06, 0.25, 0.22-0.30	0.87±0.11, 0.87, 0.80-0.94	0.62±0.15, 0.60, 0.51-0.73
	SUV _{mean60}	SUV _{mean90}	SUV _{mean90} /SUV _{mean60}	
Pre-treatment	1.93±0.24, 2.00, 1.76-2.10	1.72±0.29, 1.85, 1.51-1.93	0.89±0.03, 0.90, 0.65-1.05	
Post-treatment	1.96±0.32, 1.85, 1.73-2.19	1.71±0.23, 1.75, 1.54-1.88	0.88±0.02, 0.88, 0.84-0.91	

Group data presented as mean ± standard deviation, median, 95 % confidence interval. *Perfusion fraction and D* changes significantly.

Statistical analysis

Statistical tests were performed using IBM SPSS Statistics 25. Data is expressed as mean ± standard deviation (SD). Comparison of PET/DW-MRI parameters in the patient group before and after treatment were calculated using a Wilcoxon signed-rank test. The conventional p-value of 0.05 was used as the cutoff for statistical significance.

Results

A total of 12 patients had PET/DW-MRI scans performed prior to initiation of DAA treatment. One patient was diagnosed with HCC after the first scan and was excluded from the study. The remaining 11 patients had a second PET/DW-MRI after 12 weeks of treatment. In 1 patient MRI failed, leaving 10 patients for the final analysis, 10 patients had PET/DW-MRI scans performed prior to initiation of DAA treatment and after treatment was completed (2 women and 8 men with a mean age of 48.3 years, further characteristics in **Table 1**).

Effect of DAA treatment on Fibroscan-scores, blood liver test and systemic inflammation

Fibrosis level of the liver was assessed by Fibroscan. 4 patients had Fibroscan-score over 12, indicating cirrhosis, 2 had significant fibrosis and 4 had no evidence of fibrosis. Average HCV load prior to treatment was 1.7 × 10⁶ IU/ml

(± 1.2 × 10⁶). All patients obtained sustained virological response (SVR), defined as undetectable serum HCV RNA 12 weeks after treatment. Average ALAT decreased from 103 (± 92) U/l to 22 (± 12) U/l, P=0.005. CRP was within the normal range and did not change significantly during treatment, nor did leukocytes or Fibroscan-score (**Table 2**) [6].

Effect of DAA treatment on local inflammation monitored by PET/DW-MRI

An overview of PET/DW-MRI measurements before and after treatment can be seen in **Table 3** and **Figure 1**. Examples of obtained imaging from a single patient can be seen in **Figure 2**.

The main positive findings were that the perfusion fraction increased from mean 0.21 (± 0.04) to 0.26 (± 0.06), P=0.005 and D* from 0.50 (± 0.13) × 10⁻³ s/mm² to 0.62 (± 0.15) × 10⁻³ s/mm², P=0.028.

Prior to and after DAA treatment, SUV_{mean60} was 1.93 (± 0.24) and 1.96 (± 0.32), respectively. Mean SUV_{mean90} changed from 1.72 (± 0.29) to 1.71 (± 0.23). The mean ratio of SUV_{mean90}/SUV_{mean60} before treatment was 0.89 (± 0.03), after treatment this was 0.88 (± 0.02). None of these changes were significant, nor were the changes in ADC_{total}: 1.02 (± 0.06) to 1.01 (± 0.09) × 10⁻³ s/mm² and D: 0.91 (± 0.04) to 0.87 (± 0.11) × 10⁻³ s/mm².

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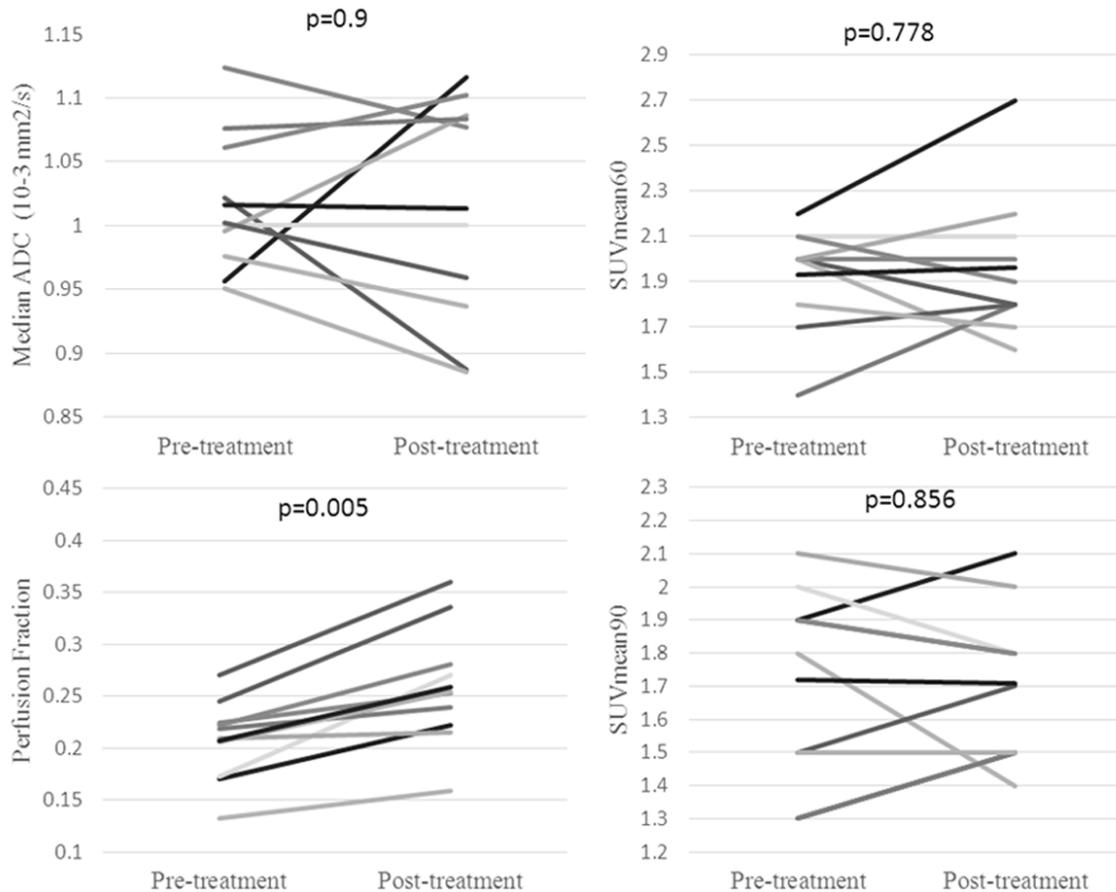


Figure 1. Selected PET/DW-MRI parameters before and after treatment. Only perfusion fraction is significantly improved after treatment, while the rest of the displayed parameters did not significantly change.

There was no significant correlation between Fibroscan-score and SUV or ADC values. Likewise, no correlation was found between Fibroscan-score and the changes in ADC or SUV before/after treatment (data not shown). **Figure 3** suggests a correlation between the difference in SUV ratio ($\frac{SUV_{mean90}}{SUV_{mean60}}$) before and after treatment and perfusion fraction, with increasing perfusion fraction correlated with larger difference in SUV-ratio before and after treatment.

Discussion

We found PET/DW-MRI of chronic hepatitis C patients to be feasible. Patients were cooperative and tolerated the scans well. The image quality was acceptable with no artefacts in 22 out of 23 images (The second scan in 1 patient failed and another patient was excluded after the first scan showed hepatocellular carcinoma).

Our pilot study found that perfusion fraction and D* measured by DW-MRI changed significantly after treatment with DAA's, both of which are dependent on perfusion. To determine whether this increase in perfusion of the liver is a direct result from treatment or an epiphenomenon requires further studies, as systematic Fibroscan of all patients after treatment were not completed. The incomplete data does however suggest a decrease in Fibroscan-score.

Despite all patients obtaining sustained virological response (SVR) with undetectable viral replication and normalized ALAT, our pilot study found that the DAA treatment did not significantly change the liver mean SUV or median ADC. With normalization of liver blood test results, we expected, as per our working hypothesis, that the reduction in liver inflammation post-treatment would be visible as changes in both SUV-uptake and total ADC.

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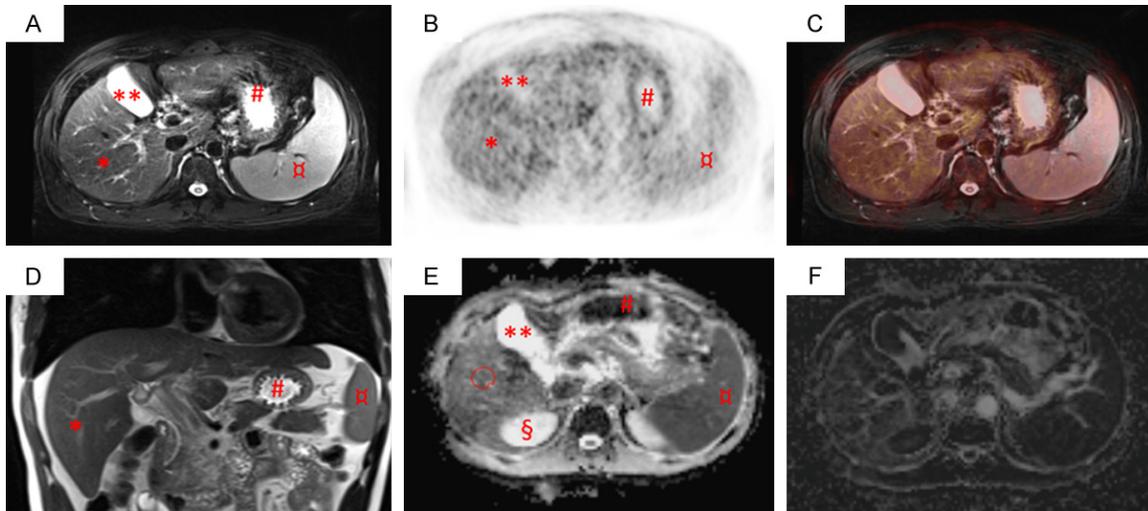


Figure 2. A-F: Examples of images obtained in a single patient prior to treatment. Main tissues marked as follows: *Right liver lobe, **Gall bladder, #Stomach, ♂Spleen and §Kidney. A: Transaxial T2 BLADE. B: Transaxial FDG PET. C: Transaxial combined FDG-PET/MRI (T2 BLADE). D: Coronal T2 Haste. E: Transaxial ADC map with volume of interest (VOI) placed in right liver lobe. F: Transaxial mapped Perfusion Fraction (PF).

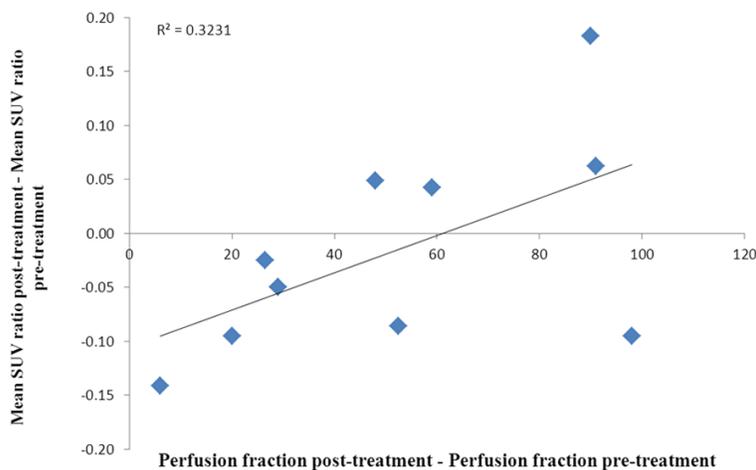


Figure 3. Post- and pre-treatment difference in mean SUV ratio ($\frac{SUV_{mean90}}{SUV_{mean60}}$) & difference in perfusion fraction. A correlation between SUV ratio and perfusion fraction, with increasing perfusion fraction correlated with larger difference in FDG-retention ratio before and after treatment.

SUV uptake in chronic hepatitis C patients does not differ from the liver SUV of healthy individuals. Paquet et al. found the mean SUV of 70 cancer-free patients to be 2.02 (± 0.39), which was stable over time [15], and Meyer et al. [16] found the mean liver SUV to be 2.16 from a total of 389 cases [16]. The SUV_{mean60} of this study was 1.93 (± 0.24). Although it is not possible to directly compare these results because of differences in e.g. study model, equipment and patients, it suggests that the liver SUV of healthy individuals and CHC patients might be comparable.

SUV is a quantitative measure of cellular glucose metabolism and has been shown to correlate with inflammation elsewhere in the body, such as inflammatory bowel disease and some types of vasculitis [10] as well as local lesions in the liver, for instance liver abscesses [11]. We therefore anticipated a decrease in mean SUV after the patients obtained SVR with normalized ALAT, but our findings show that its usefulness in diffuse liver diseases may be limited or at least require further examination. A possible explanation could be that mean liver

The mechanism of diffusion restriction measured with DW-MRI in CHC patients is not understood in detail yet, but is possibly in part caused by the extracellular matrix deposition of proton-poor macromolecules such as collagen, fibrous scar formation as well as decreased blood flow [17]. Studies have found that ADC values significantly differ between healthy subjects and CHC patients [18-20], but studies disagree on whether the presence of inflammation (assessed by liver biopsy) alter the diffusion properties of the tissue and therefore the ADC

values. Some studies found no significant correlation between inflammation score and ADC values [18, 21-24]. Other studies did find significant correlation between parameters, but it disappeared after using multiple regression [25], after adjusting for fibrosis [26] or when considering fibrosis and inflammation together [8]. The last group of studies, however, reported a significant correlation between ADC values and inflammation [20, 27-30], suggesting that the ADC values might reflect the intensity of inflammation, but different patient populations, varying methods of histological methods for scoring inflammation and technical parameters (e.g. manufacturer, field strength, b values) differ between studies and makes direct comparison difficult. Further effort should be made to standardize DW-MRI-protocols of the liver to make research using this image modality more easily comparable.

In this pilot study of 10 patients that all achieved SVR, we found no significant difference between ADC values before and after treatment. Due to low sample size, the power in our study was limited. If presence of inflammation has a direct effect on ADC values, it has not been substantial enough in our patient population to show a difference after reaching sustained virological response, where we would expect the inflammation to have subsided. In the same manner, Gúrcan N. et al. [31], found no difference in ADC values at follow-up 12 weeks after a 12-week treatment with Telaprevir-based treatment for hepatitis C. Several studies have highlighted the relationship between ADC and varying degrees of fibrosis and cirrhosis, with higher stages resulting in lower ADC values [17, 27, 28]. If the diffusion properties of the tissue reflected in ADC values are less dependent on inflammation, but more so on fibrosis, it might explain why there is no change this early after the treatment with DAA. Even though there is emerging evidence that fibrosis and cirrhosis might be at least partly reversible [32], it might be too early to see these changes reflected in the ADC value from the post-treatment scan done within 14 days of the last treatment. The correlation between ADC values and fibrosis found in several studies is however being challenged. A rat study from 2007 found that the correlation between ADC values and fibrosis may be the result of a decrease in perfusion, suggesting that changes in perfusion is the pri-

mary reason behind effects on ADC values [33]. Our study found a significant increase in perfusion fraction as well as in D^* , suggesting that treatment of the disease helps increase perfusion in the liver. Considering that an increase in perfusion in the liver after treatment might influence the FDG-uptake of the liver cells, changes in the ratio of $SUV_{mean90}/SUV_{mean60}$ were plotted against changes in PF. This plot proposes a connection between the two parameters as seen on **Figure 3**, suggesting that improvements in perfusion fraction is correlated with a bigger difference in FDG-retention from 60 to 90 minutes. This supports the notion that FDG-uptake is not only dependent on the presence of inflammatory cells, but also on perfusion, though not significant in our small study ($R^2 = 0.3231$). It is thus possible that the decrease in FDG-uptake we expected is hidden by the increased perfusion after treatment.

Whether or not PET/DW-MRI could be a useful tool to separate changes in FDG-uptake caused by changes in perfusion from changes in the number of inflammatory or malignant cells should be explored in future studies, as well as whether or not the changes in perfusion can be useful in predicting treatment response, for example identifying none-responders or those patients who do not experience regression in their liver fibrosis.

Our pilot study had several limitations. Only data from 10 patients were included in the final analysis and the patient group was diverse with all patients having varying stages of liver disease as determined by Fibroscan. The absence of histopathologic correlation during and after treatment to assess the parenchymal changes in the liver is one of the main limitations of this pilot study. Without this reference, it is difficult to assess the change in inflammatory activity before and after treatment, even though SVR and normalized ALAT suggests such a change.

Conclusion

This pilot study is, to our knowledge, the first to examine chronic hepatitis C patients with PET/DW-MRI and it was found feasible. All participants received SVR and ALAT decreased after treatment with DAA.

Perfusion fraction and D^* measured by DW-MRI changed significantly after treatment. It has been shown that liver total ADC values differ significantly between CHC patients and healthy individuals, but we did not see an effect on total ADC after treatment, possibly because the scan was done early after treatment. All other PET/DW-MRI parameters, including FDG-uptake were unchanged. This suggests that treatment with DAA may increase blood perfusion in the liver, but that the degree of inflammation in the liver of CHC patients may not differ enough from healthy individuals to be seen with FDG-PET. This should be explored further with a larger population and liver biopsy for histological comparison. The suggested correlation between SUV ratio and PF confirms that FDG-uptake is dependent on perfusion as well as inflammatory or malignant cell activity. The role of PET/DW-MRI in separating changes in FDG-uptake caused by changes in perfusion from changes in cellular activity is promising and should be explored in future studies, which may also help define a possible role for PET/DW-MRI in monitoring the liver of chronic hepatitis C patients after treatment with DAA's.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Barbara Malene Fischer, PET Centre, School of Biomedical Engineering and Imaging Sciences, Kings College London, St Thomas' Hospital, Westminster Bridge Road, London, UK. Tel: +45 35459824; +45 22266045; E-mail: malene.fischer@kcl.ac.uk

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