European Journal of Radiology 81 (2012) e325–e331

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

# Acoustic radiation force impulse-imaging and transient elastography for non-invasive assessment of liver fibrosis and steatosis in NAFLD

Mireen Friedrich-Rust[a,*], Daniela Romen[a], Johannes Vermehren[a], Susanne Kriener[b], Dilek Sadet[a], Eva Herrmann[c], Stefan Zeuzem[a], Joerg Bojunga[a,1]

[a] Department of Internal Medicine, J.W. Goethe-University Hospital, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany
[b] Institute of Pathology, J.W. Goethe-University Hospital, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany
[c] Institute of Biostatistics and Mathematical Modelling, Faculty of Medicine, J.W. Goethe-University, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany

ARTICLE INFO

*Article history:*
Received 23 July 2011
Received in revised form 29 October 2011
Accepted 31 October 2011

*Keywords:*
Ultrasound
ARFI
CAP
FibroScan
Steatohepatitis
Liver biopsy

ABSTRACT

*Background:* Transient elastography (TE) and acoustic radiation force impulse (ARFI)-imaging have shown promising results for the staging of liver fibrosis.
*Aim:* The aim of the present study was to compare ARFI of the left and right liver lobe with TE using the standard and obese probes for the diagnosis of liver fibrosis in NAFL/NASH. In addition, liver steatosis is evaluated using the novel controlled attenuation parameter (CAP).
*Methods:* Sixty-one patients with NAFLD/NASH were included in the study. All patients received TE with both probes, ARFI of both liver lobes and CAP. The results were compared with liver histology.
*Results:* 57 patients were included in the final analysis. The diagnostic accuracy for TE measurements with the M-and XL-probe and for ARFI of the right and left liver lobe was 0.73, 0.84, 0.71 and 0.60 for the diagnosis of severe fibrosis, and 0.93, 0.93, 0.74 and 0.90 for the diagnosis of cirrhosis, respectively. No significant difference of results was observed between TE and ARFI in the subgroup of patients with reliable TE-measurement when taking into account the best results of both methods. However, while a significant correlation could be found for TE with histological liver fibrosis, the correlation of ARFI with liver fibrosis was not statistically significant. A significant correlation was found for CAP with histological steatosis ($r = 0.49$, $p < 0.001$).
*Conclusions:* No significant difference in diagnostic accuracy for the non-invasive assessment of liver fibrosis was found for transient elastography and ARFI. Nevertheless TE significantly correlated with liver fibrosis while ARFI did not. CAP enables the non-invasive assessment of steatosis.


## 1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming a major health concern due to the increasing obesity epidemic and its potential to progress to liver fibrosis, cirrhosis and hepatocellular carcinoma [1]. At present, the prevalence of NAFLD in the United States is estimated to be as high as 30–50% [2]. Non-alcoholic steatohepatitis (NASH) represents a clinically important subset of NAFLD with increased risk for fibrosis progression and mortality [3]. Early detection of NASH-associated fibrosis is crucial for the prognosis of disease progression. However, identification of patients with fibrosis has been difficult because liver biopsy was traditionally required for diagnosis. Liver biopsy is associated with substantial patient discomfort and carries a risk for complications [4]. In addition, liver biopsy is prone to sampling errors and intra- and inter-observer variability [5]. Recently, advances have been made in the development of non-invasive methods for assessment and follow-up of patients with liver fibrosis.

Transient elastography (TE; FibroScan®; Echosens, Paris, France) has shown excellent diagnostic value in the detection of advanced fibrosis and cirrhosis in patients with NAFLD/NASH [6]. However, obesity, a major risk factor for NAFLD/NASH, was associated with TE failure in up to 25% of patients [6]. This limitation was recently overcome by the introduction of a new XL-probe with improved diagnostic utility in obese patients [7].

Acoustic radiation force impulse (ARFI) imaging (ACUSON S2000™; Siemens Medical Solutions, Mountain View, CA, USA) represents another promising ultrasound-based method for the

* Corresponding author. Tel.: +49 069 6301 5297; fax: +49 069 6301 6247.
*E-mail addresses:* Mireen.Friedrich-Rust@kgu.de (M. Friedrich-Rust), Joerg.Bojunga@kgu.de (J. Bojunga).
[1] Tel.: +49 069 6301 87686; fax: +49 069 6301 6448.

0720-048X/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejrad.2011.10.029

assessment of liver stiffness. ARFI is integrated into a conventional ultrasound system and preliminary results have shown that even severe obesity is not a limitation for this technique [8]. However, it remains unclear how ARFI imaging compares to TE, including TE with the new XL-probe, in patients with NAFLD/NASH.

The aim of the present study was to assess the diagnostic accuracy of ARFI imaging of the left and right liver lobe in comparison to TE with both standard (M) and obese (XL) probes for the diagnosis of fibrosis and cirrhosis in patients with NAFLD/NASH. Liver histology was used as the reference method. In addition, non-invasive measurement of liver steatosis was evaluated with a novel controlled attenuation parameter (CAP) that uses the same radio-frequency data as acquired by TE.

## 2. Materials and methods

### 2.1. Patients

Sixty-one patients with NAFLD or NASH were enrolled consecutively between May 2009 and December 2010. All patients received acoustic radiation force impulse (ARFI)-imaging of the right and left liver lobe (Siemens, Mountain View, CA), as well as transient elastography (FibroScan®) with the standard probe (M-probe) and the obese probe (XL-probe) (Echosens, Paris, France) on the same day of presentation. The distance between skin and liver capsule at the site of ARFI and TE measurement was measured using conventional ultrasound. Diagnosis of NAFLD or NASH was made histologically by liver biopsy. As the mean progression rate of liver fibrosis is low, a time interval between liver biopsy and study inclusion of up to 18 months was accepted for enrolment in the present study. The time interval between liver biopsy and study inclusion ranged from 0 to 17 months (median 3.0 months, mean 4.3 ± 4.0 months). Men with alcohol consumption of more than 30 g of alcohol per week and women with more than 20 g of alcohol per week were excluded from the study. In addition, patients with other causes of liver disease (positive hepatitis B surface antigen or anti-hepatitis C virus antibody, positive autoantibodies) or histological evidence of other concomitant chronic liver diseases were excluded.

Patient characteristics and biochemical values are shown in Table 1.

The present study was performed in accordance with the ethical guidelines of the Helsinki Declaration and was approved by the local ethics committee. Written informed consent was obtained from all patients.

**Table 1**
Patients' characteristics.

| Characteristics | Patients ($n = 57$) |
|---|---|
| Sex | 30 male/27 female patients |
| Age | Mean ± SD: 45 ± 14 years; median: 45 years; range: 21–71 years |
| Waist circumference | Mean ± SD: 98 ± 14 mm; median: 97 mm; range: 65–140 mm |
| Hip circumference | Mean ± SD: 104 ± 11 mm; median: 102 mm; range: 80–140 mm |
| Skin capsule distance | Mean ± SD: 25 ± 7 mm; median: 24 mm; range: 15–45 mm |
| BMI | Mean ± SD: 28 ± 5.5 kg/m$^2$; median: 27.8 kg/m$^2$; range 18–43 kg/m$^2$ |
| AST | Mean ± SD: 50 ± 27 IU/L; median: 43 IU/L; range: 18–136 IU/L |
| ALT | Mean ± SD: 72 ± 53 IU/L; median: 58 IU/L; range: 13–275 IU/L |
| GGT | Mean ± SD: 161 ± 27 IU/L; median: 58 IU/L; range: 14–2580 IU/L |
| Total bilirubin | Mean ± SD: 0.75 ± 0.38 mg/dL; median: 0.6 mg/dL; range: 0.3–2.0 mg/dL |
| Platelet count | Mean ± SD: 235 ± 53 × 10$^3$/mm$^3$; median: 242 × 10$^3$/mm$^3$; range: 70–353 × 10$^3$/mm$^3$ |
| Total cholesterol | Mean ± SD: 206 ± 52 mg/dL; median: 205 mg/dL; range: 94–363 mg/dL |
| Triglycerides | Mean ± SD: 185 ± 154 mg/dL; median: 131 mg/dL; range: 22–972 mg/dL |
| Fasting glucose | Mean ± SD: 102 ± 33 mg/dL; median: 91 mg/dL; range: 69–266 mg/dL |
| Histological fibrosis stage | |
| F0 | 21 patients |
| F1 | 20 patients |
| F2 | 5 patients |
| F3 | 9 patients |
| F4 | 2 patients |
| NAS score | |
| NAS ≤ 4 | 20 patients |
| NAS > 4 | 37 patients |
| Histological steatosis grade | |
| S0 | 1 patients |
| S1 | 14 patients |
| S2 | 18 patients |
| S3 | 24 patients |

SD, standard deviation; pat., patients; BMI, body mass index; AST, aspartate aminotransaminase; ALT, alanine aminotransaminase; GGT, gamma-glutamyl transpeptidase.

### 2.2. Liver histology

Liver biopsy specimens were fixed in 4%-buffered formalin and embedded in paraffin. Two-micrometer-thick sections were stained with haematoxylin-eosin, Perls iron stain, dPAS (periodic acid Schiff after digestion with diastase) and Masson Trichrome. All biopsy specimens were analysed by an experienced pathologist who was blinded to the clinical results of the patients. Histological scoring was performed according to Kleiner et al. [9]. Steatosis was assessed according the number of hepatocytes with fatty degeneration: S0 = <5%, S1 = 5–33%, S2 = >33–66%, S3 = >66% of hepatocytes. Liver fibrosis was staged on a F0–F4 scale according to Kleiner: F0, no fibrosis; F1, perisinusoidal or periportal fibrosis; F2, perisinusoidal and portal or periportal fibrosis; F3, bridging fibrosis and F4, cirrhosis. The NAFLD Activity Score (NAS) was calculated according to Kleiner from the unweighted sum of the scores of steatosis (0–3), lobular inflammation (0–3) and ballooning (0–2). Using the NAS, the diagnosis of steatohepatitis is present if NAS is greater than 4. Biopsies were judged to be adequate if the length of liver biopsy at least 1 cm or if the number of portal tracts was at least 6. The mean length of the included liver biopsies was 22.9 ± 9.5 mm (median 22 mm, range 10–60 mm).

### 2.3. Acoustic radiation force impulse (ARFI)-imaging

All patients received ARFI-imaging and TE by physicians blinded to the results of liver biopsy. Before ARFI-measurement the distance between the skin and the liver capsule at the site of the planned TE measurement and ARFI-measurement of the right lobe was measured using a 4.0-MHz curved ultrasound transducer.

ARFI imaging (Virtual Touch$^{TM}$ Tissue Quantification, Siemens ACUSON S2000) involves targeting of an anatomic region to be interrogated for elastic properties with a region-of-interest (ROI) cursor while performing real time B-mode imaging. Tissue at the ROI is mechanically excited using short-duration acoustic pulses with a fixed transmit frequency of 2.67 MHz to generate localized tissue displacements in tissue. The displacements result in shear-wave propagation away from the region of excitation and are tracked using ultrasonic, correlation-based method. The maximum displacement is estimated for many ultrasound tracking beams laterally adjacent to the single push-beam, which are transmitted