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● *Original Contribution*

THE B-MODE IMAGE-GUIDED ULTRASOUND ATTENUATION PARAMETER ACCURATELY DETECTS HEPATIC STEATOSIS IN CHRONIC LIVER DISEASE

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Abstract—The purpose of our study was to evaluate the diagnostic accuracy of the ultrasound-guided attenuation parameter (UGAP) for the detection of hepatic steatosis in comparison with the controlled attenuation parameter (CAP), using histopathology as the reference standard. We prospectively analyzed 163 consecutive chronic liver disease patients who underwent UGAP, CAP, computed tomography and a liver biopsy on the same day between April 2016 and July 2017. Radiofrequency signals corresponding to the images were compensated by the reference signal previously measured from the uniform phantom with known attenuation (0.44 dB/cm/MHz). The attenuation coefficient was calculated from the signals' decay slope. The median attenuation coefficient values in patients with S0 (n = 62), S1 (n = 63), S2 (n = 23) and S3 grade (n = 15) were 0.485, 0.560, 0.660 and 0.720, respectively. Significant correlations were found between attenuation coefficient and percentage steatosis, CAP values and liver-to-spleen computed tomography attenuation ratio ($p < 0.001$). The areas under the receiver operating characteristic curve of UGAP for identifying ≥S1, ≥S2 and ≥S3 were 0.900, 0.953 and 0.959, respectively, which were significantly better than the results obtained with CAP for identifying ≥S2 and ≥S3. In conclusion, UGAP had high diagnostic accuracy for detecting hepatic steatosis in patients with chronic liver disease, (E-mail: hikuro@iwate-med.ac.jp)

Key Words: **Controlled attenuation parameter, Liver steatosis, Diagnostic ultrasound, Non-alcoholic fatty liver disease, Chronic hepatitis C, Prospective studies.**

INTRODUCTION

The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing worldwide with the increased prevalence of obesity (Loomba and Sanyal 2013). Among such diseases, non-alcoholic steatohepatitis (NASH) has attracted attention, as it progresses to liver cirrhosis and hepatocellular carcinoma due to hepatocyte apoptosis, inflammation and fibrosis (Angulo 2002; Ekstedt et al. 2015; Kleiner et al. 2005; Musso et al. 2011). Therefore, for the screening and follow-up of NAFLD/NASH, it is important to establish a high-precision index of hepatic steatosis.

Currently, liver biopsy (LB) is the gold standard for the diagnosis and assessment of hepatic steatosis, but it has some problems, such as a bleeding risk, sampling error and inter-pathologist variability (Ratziu et al. 2005; Rockey et al. 2009). Therefore, a quantitative, non-invasive alternative to LB for the assessment of hepatic steatosis is desirable. Ultrasonography is a widely accessible imaging technique for the detection of hepatic steatosis and is also minimally invasive, inexpensive and repeatable (Joseph et al. 1979). However, it underestimates the prevalence of hepatic steatosis when there is <20% fat (Dasarathy et al. 2009). A novel non-invasive tool based on the evaluation of ultrasound attenuation using a

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FibroScan device (Echosens, Paris, France) was recently developed, using a novel proprietary algorithm called the controlled attenuation parameter (CAP) (Chan et al. 2014; de Ledinghen et al. 2016; Sandrin et al. 2003). The attenuation of ultrasound is caused by absorption, scatter and reflection. As the fat deposition increases, the attenuation of ultrasound increases (Fujii et al. 2002; Kanayama et al. 2013). CAP measures the degree of ultrasound attenuation caused by hepatic steatosis at the standardized frequency of 3.5 MHz, taking advantage of a technology called vibration-controlled elastography implemented on FibroScan. It is evaluated using the same radiofrequency data used for the measurement of liver stiffness; the results are measured in decibels per meter, over a range of 100−400 dB/m (Sasso et al. 2010). Karlas et al. reported favorable results in their meta-analysis, with an area under the receiver operating curve (AUROC) of CAP for steatosis grade ≥5% of 0.823, but they suggested issues, such as changes in the attenuation rates of CAP resulting from factors such as underlying disease, body mass index (BMI) and diabetes (Chan et al. 2014; de Ledinghen et al. 2016; Karlas et al. 2017). Furthermore, the main limitation of CAP is insufficient visual guidance, as it can only be performed in A-mode. For that reason, in the European Association for the Study of the Liver clinical guideline, it is carefully noted that further accumulation of data is required to assess the role of CAP in the diagnosis of steatosis (Karlas et al. 2017).

We investigated the attenuation coefficient (AC) (dB/cm/MHz) of B-mode ultrasonic signal with general ultrasonography, which we have named the ultrasound-guided attenuation parameter (UGAP). The aim of this study was to prospectively evaluate the diagnostic accuracy of UGAP for the diagnosis of steatosis in patients with chronic liver disease (CLD) in comparison with CAP, using histopathology as the reference standard.

METHODS

Patients

A total of 182 consecutive patients with hepatitis C virus (HCV) or NAFLD-related CLD who had undergone UGAP, CAP, computed tomography (CT) and a LB at our institution between April 2016 and July 2017 were involved in this study. CLD refers to ongoing inflammation in the liver for a period of at least 6 mo (Lefton et al. 2009). The inclusion criteria were the ability to provide informed consent and age from 18 to 80 y. HCV-related CLD was diagnosed based on the results of a histologic analysis and the detection of HCV antibodies in serum using a third-generation enzyme-linked immunosorbent assay (Abbott Labs, Abbott Park, IL, USA). The diagnosis of NAFLD was based on the presence of steatosis on LB. Exclusion criteria were alcohol use (consumption of ≥40 g/d alcohol for men and ≥20 g/d for women over the preceding 12 mo); viral hepatitis except for HCV; and other causes of chronic liver disease, such as primary biliary cholangitis, autoimmune hepatitis and untreated hypothyroidism (Chalasani et al. 2012).

The study was approved by the local ethics committee of Iwate Medical University (H26-124). Patients provided their written informed consent before the beginning of the study, in accordance with the principles of the Declaration of Helsinki (revision of Fortaleza, 2013).

Ultrasound-guided attenuation parameter

The AC was calculated based on the reference phantom method reported by Yao et al. (1990). This method utilizes an ultrasound phantom with known attenuation and backscatter coefficients to compensate for the characteristics of transmission and reception beamforming, which depend on the ultrasound system. Under the same conditions of transmission and reception, the echo signals from the tissue, $S_0(f,x)$ (target), and the phantom, $S_p(f,x)$ (reference), are described as

$$-\frac{1}{2f}\log_{10}\frac{s_0(f,x)}{s_\mathrm{p}(f,x)}+\alpha_\mathrm{p}x=\alpha_0 x \quad (1)$$

where f is the frequency used, x is the length of depth direction of the region of interest (ROI), and α_0 and α_p are the ACs of the tissue and the phantom, respectively.

The UGAP was evaluated on the day the patients underwent LB. A LOGIQ E9 XDclear 2.0 ultrasound scanner (GE Healthcare, Wauwatosa, WI, USA) was used with a C1-6-D convex array probe (frequency: 4 MHz). The custom-made phantom by Gammex Inc. (Middleton, WI, USA) was used as a reference (AC = 0.44 dB/cm/MHz). A single calibration of the ultrasound system, using a specific acquisition set up (4.0 MHz of the fundamental B-mode), was performed. The same acquisition setup was used for collection of data for each patient. The results of the one-time calibration were used to compute the UGAP value. One of the two radiologists (H.K. and Y.M.) performed the procedure. Both radiologists had 20 y of experience in performing liver US examinations, and they were blinded to the patient's histologic and clinical data. We acquired B-mode images of the liver parenchyma. Scanning was performed between the ribs in the right liver lobe (segment 5).

Radiofrequency-based ultrasound echo signals were transferred into a consumer PC and analyzed using a dedicated prototype software program with MATLAB (The MathWorks, Inc., Natick, MA, USA). One of three ultrasound engineers (T.O., S.N. and N.K.) opened each image and set the ROI on the liver parenchymal area, avoiding obviously large vessels (Fig. 1A). The average of 10 consecutive scanning rasters was processed; this was followed by a smoothing curve with a low-path filter