Ultrasound-Guided Attenuation Parameter

LOGIQ™ E10, E10s, P Series and LOGIQ Fortis™

Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) is growing worldwide with the increase in obesity.[1] Among the many forms of NAFLD, non-alcoholic steatohepatitis (NASH) has attracted attention, as it can progress to liver cirrhosis and hepatocellular carcinoma due to hepatocyte apoptosis, inflammation and fibrosis.[2] Traditionally, liver biopsy has been the gold standard for the diagnosis and assessment of hepatic steatosis. However, this method has some problems such as sampling error and inter-pathologist variability.[3] In addition, the invasive nature of the procedure creates a risk of complications. More recently, MR proton density fat fraction (PDFF) has been accepted as a non-invasive reference standard, but limited access and high cost prevent widespread use, especially with respect to regular follow up exams.

The liver echogenicity on ultrasound B-Mode is widely used for the detection of hepatic steatosis. However, this technique does not enable a quantitative assessment since liver texture or brightness may vary depending on the imaging parameters used or the examiner's technique. Therefore, an objective ultrasound quantification method is desired for steatosis grading in current and potential NASH patients. Recently, a novel non-invasive tool that utilizes attenuation of the sound wave was developed. However, it may be susceptible to multi-reflection artifacts from subcutaneous tissues as well as disruptive structures such as vessels or diaphragm since the measurement area is not guided by imaging.[4]

This paper describes Ultrasound-Guided Attenuation Parameter (UGAP), a real-time, image-guided method of measuring the attenuation of the sound wave. The principles of the method as well as the clinical evaluation results are presented.

Ultrasound Attenuation

When the ultrasound wave propagates in an organ, such as the liver, it is gradually weakened due to diffusion, scattering and absorption. Known as sound attenuation, this results in less signal returning to the ultrasound transducer, causing the image to get darker with depth. If an image of a healthy liver has uniform image brightness over depth, it is because of the time-gain compensation (TGC) capability of the ultrasound scanner, which applies a different gain for each depth (Figure 1). In the case of fatty liver, the presence of many lipid droplets in the hepatocytes becomes the dominant factor of the attenuation, sometimes causing insufficient echo signals in the deeper area.

The amplitude of ultrasound wave u propagating in the x direction is expressed as $u=u_0e^{-\alpha x}$, where u_0 is the amplitude at x=0 and α is attenuation rate. Since the sound attenuation increases nearly proportional to the frequency (ranging between 1 MHz to 10 MHz), the attenuation rate can be approximated by $\alpha = \alpha_0 f$, where α_0 is the attenuation coefficient (dB/cm/MHz) and f is frequency in [MHz].[5] Attenuation rate and attenuation coefficient are used primarily to evaluate ultrasound attenuation in human tissues.

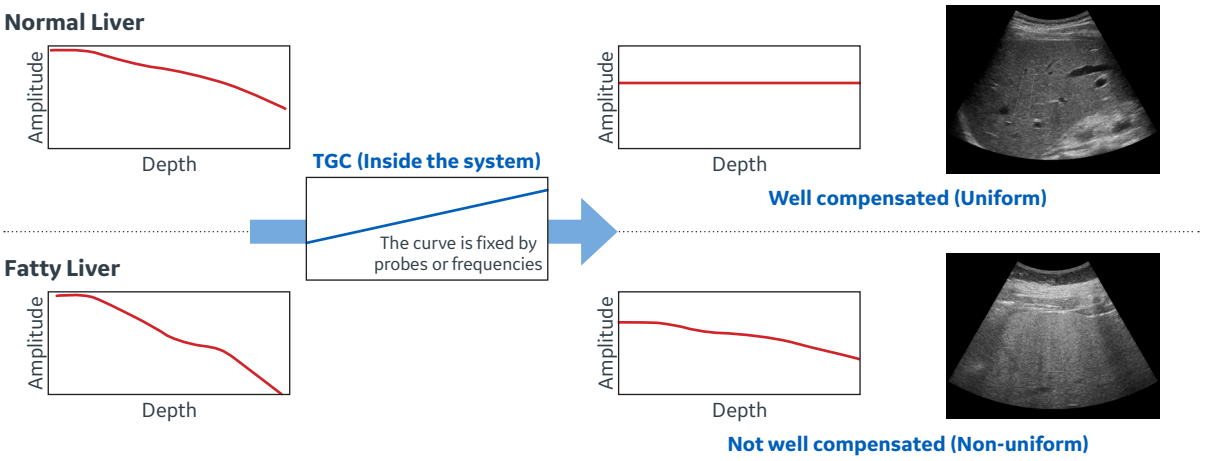


Figure 1. Ultrasound attenuation compensation by TGC.

Ultrasound Attenuation Evaluation Method by UGAP

Principle of Measurement[6]

As shown in Figure 1, measuring the attenuation slope would provide insight into liver attenuation. However, the sound profile in the real signal is not so simple, since it is curved as shown in Figure 2A. This complexity is caused by a focused sound beam from transmission as well as reception conditions. To cancel out or compensate for this complexity, several methods have been reported.[7] UGAP performs the compensation based on a Reference-Phantom Method (RPM)[8] (Figure 2). The profile of the echo amplitude for a tissue-mimicking phantom is measured in the depth direction and stored in the ultrasound system as a reference. In this case, a frequency of 3.5 MHz is used. This industry-standard phantom includes glass bead particles for attenuating materials and the attenuation coefficient is known. In the UGAP mode, the transmission and reception conditions are fixed to the same values as were used on the reference phantom, and the acquired echo profiles of the target (liver) are compensated by the reference data. As a result, the compensated sound profiles represent only decay caused by attenuation. If the compensated sound profile is flat, the attenuation is the same as the reference phantom.

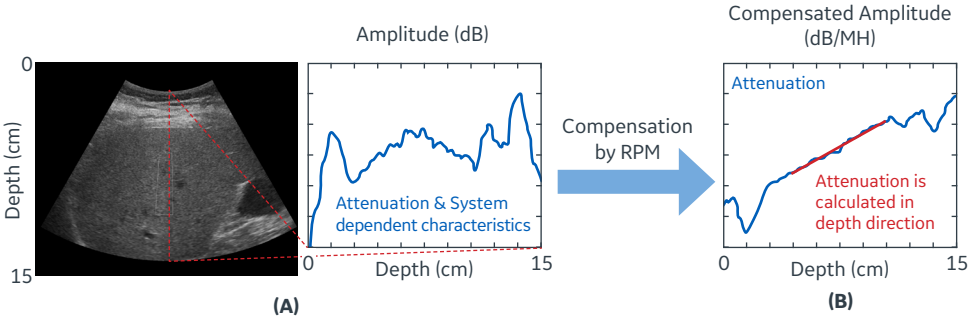


Figure 2. Compensation of ultrasound signal to enable UGAP measurement.

Measurement Algorithm

Although the system-dependent sound profile is compensated, there are still problems in performing a successful measurement. For example, structures such as large vessels and diaphragm may deform the slope profile. Or, multi-reverberation in the subcutaneous fat may generate artifacts into the liver parenchyma. Or, information needed to determine the slope may be diminished if the attenuation is very large. To avoid these problems, UGAP includes an automated measurement algorithm to find and then analyze the optimum measurement range. The start point of the range is determined by analyzing linearity and discontinuity of the echo profile close to the liver surface, thereby avoiding the multi-reverberation artifacts. In addition, the algorithm automatically detects and avoids depths where the signal-to-noise ratio (SNR) is insufficient. This enables the algorithm to employ the deepest usable end point. The diaphragm is also automatically excluded. Finally, the angle of the slope is measured across this optimum range to provide a representative attenuation coefficient. Because this measurement takes place on the raw data of a frozen or recalled image, it is not dependent on gain or other post processing settings. The goal of these automations is to make the UGAP measurement less dependent on the ROI position and more robust across various liver sizes and conditions.

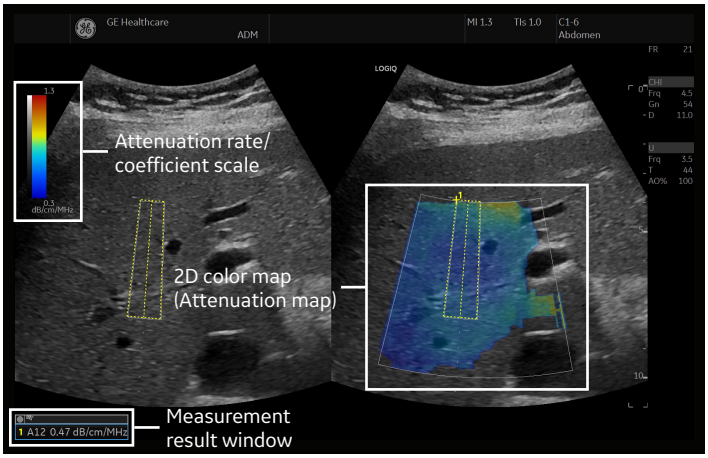


Figure 3. Example of B-Mode/Color dual display format.

Color Mapping for Measurement Guidance

To find the right scan-plane and ROI for measurement, B-Mode and two types of new color-mapped images are available in UGAP mode (Figure 3).

(a) Attenuation map: Displays color-coded local attenuation values for each pixel. When the measurement area (denoted by a trapezoid with a center line in Figure 3) has a uniform color, it is suitable to measure. The color will become inhomogeneous if the area includes a disruptive structure such as a large vessel.

(b) Quality map: Displays a color at pixels where signal quality is sufficiently high to perform a measurement. Even though the B-Mode texture may look homogeneous, a lack of color could be the result of unseen artifacts.

To aid in the acquisition and measurement of UGAP, various display formats are selectable: B-Mode only, B-Mode with color map overlay, and a dual display that shows both images side-by-side. Figure 3 shows an example of the B-Mode/Color map dual display. Examples of the color-coded attenuation for different degrees of steatosis are shown in Figure 4.

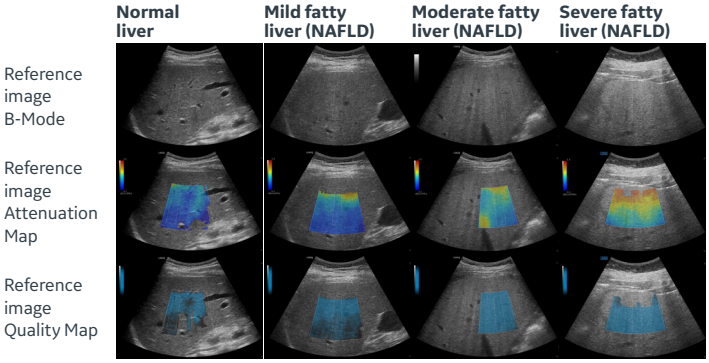


Figure 4. Examples of color-mapped attenuation images at different degrees of liver fat (Images courtesy of Prof. Sporea, Victor Babes University of Medicine and Pharmacy of Timisoara).

Evaluation of Steatosis Grade in Chronic Liver Disease by UGAP

This section summarizes the results of the multicenter prospective study reported by Nayoro City General Hospital, Ogaki Municipal Hospital, Yokohama City University Hospital, Tokyo Medical University Hospital, Iwate Medical University, Musashino Red Cross Hospital and Gifu Kyoritsu University Hospital.[9]

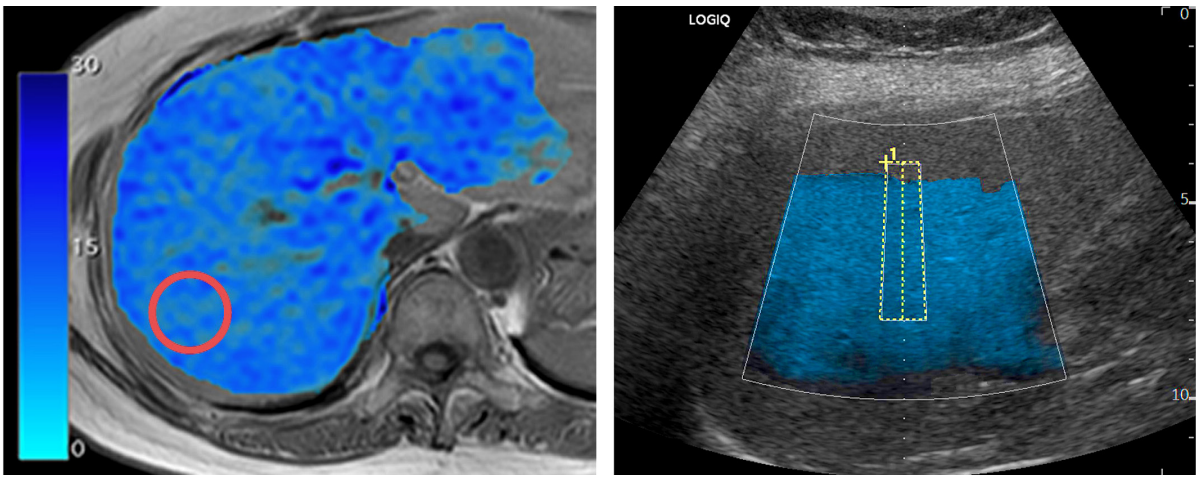
Materials and Methods

A total of 1,010 patients with chronic liver disease who underwent MRI-PDFF (Proton density fat fraction) and UGAP were enrolled. PDFF was measured using a multi-echo Dixon method (IDEAL-IQ sequence) with a single region of interest (ROI) (20 × 20 × 20 mm) placed in liver segment VII or VIII. (An example is shown in Figure 5A). Patients' sex, age, etiology, body mass index (BMI), skin capsule distance and steatosis grade are shown in Table 1.

Variable	Value
Subject (n)	1,010
Sex (Male/Female)	544/468
Age (y)	61.7 (52.0 – 72.0)
Etiology (NAFLD/ALD/HBV/HCV/AIH/Others)	515/90/133/124/38/110
BMI (kg/m^2)	26.2 (23.1 – 28.9)
Skin capsule distance (mm)	19.0 (15.5 – 22.0)
Steatosis grade (%)	
S0 (< 5.2%)	356 (35.2%)
S1 (5.3% < PDFF < 11.3%)	281 (27.8%)
S2 (11.4% < PDFF < 17.1%)	168 (16.6%)
S3 (PDFF > 17.2%)	205 (20.3%)

Table 1. Patients' sex, age, etiology, BMI, Skin capsule distance and steatosis grade.

UGAP measurements were performed using software equivalent to LOGIQ E10/E10s/P Series/LOGIQ Fortis. All measurements were performed within three months before or after MRI-PDFF, in fasting conditions for more than four hours, on patients in a supine position, with the right arm in maximum abduction, by intercostal approach, in the right liver lobe. A colored-coded attenuation map was used during measurement to confirm a homogenous area of the liver, free of large vessels. (An example is shown in Figure 5B). At least six measurements were performed. Reliable UGAP measurements were defined as the median value of six measurements performed in a homogeneous area of liver parenchyma, with an IQR/M < 0.30. UGAP values are expressed in dB/cm/MHz.



(A) **(B)**

Figure 5. Region of interest (ROI) and attenuation map of (A) MRI-based proton density fat fraction (PDFF) and (B) ultrasound-guided attenuation parameter (UGAP) measurements.

Results

All UGAP measurements were successful for 1010 cases. The mean MRI-PDFF was 10.8 ± 8.05% (range: 0.3 – 44.81%), and the mean UGAP value was 0.69 ± 0.12 dB/cm/MHz (range: 0.32 – 0.99 dB/cm/MHz). The relationship between UGAP and PDFF is shown in Figure 6. Significantly strong correlation was confirmed between UGAP and PDFF, Spearman's rank correlation coefficient was 0.785 ($p < 0.001$).

UGAP values in each steatosis grade are shown in Figure 7. The average values of UGAP in S0, S1, S2 and S3 steatosis were 0.59, 0.69, 0.77, and 0.83 dB/cm/MHz, respectively, as UGAP increased with increasing steatosis grade.

Receiver operating characteristics (ROC) curve of UGAP for diagnosis of S1 or higher, S2 or higher and S3 steatosis are shown in Figure 8: (A): ≥ S1, (B): ≥ S2, (C): S3. Area under the ROC curve (AUROC), 95% confidence interval (95% CI) and cutoff value of UGAP are shown in Table 2. The AUROCs of UGAP for the prediction of S1 or higher, S2 or higher and S3 steatosis were **0.901** (95% CI: 0.891 – 0.928), **0.912** (95% CI: 0.894 – 0.929) and **0.894** (95% CI: 0.873 – 0.916), respectively.

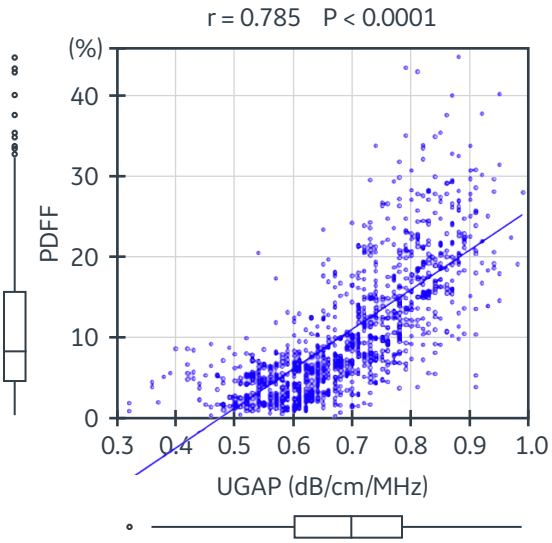


Figure 6. Relationship between UGAP and PDFF.

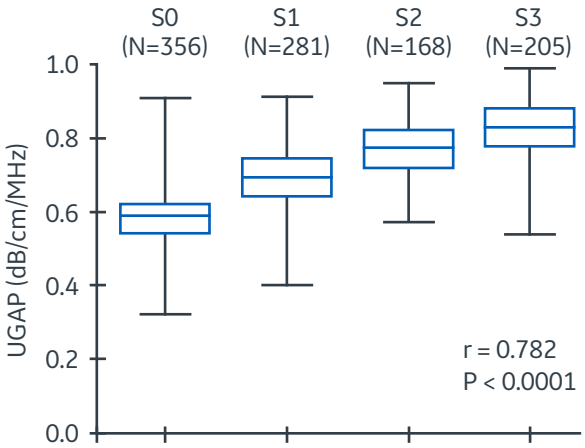


Figure 7. Measured UGAP values in each steatosis grade.

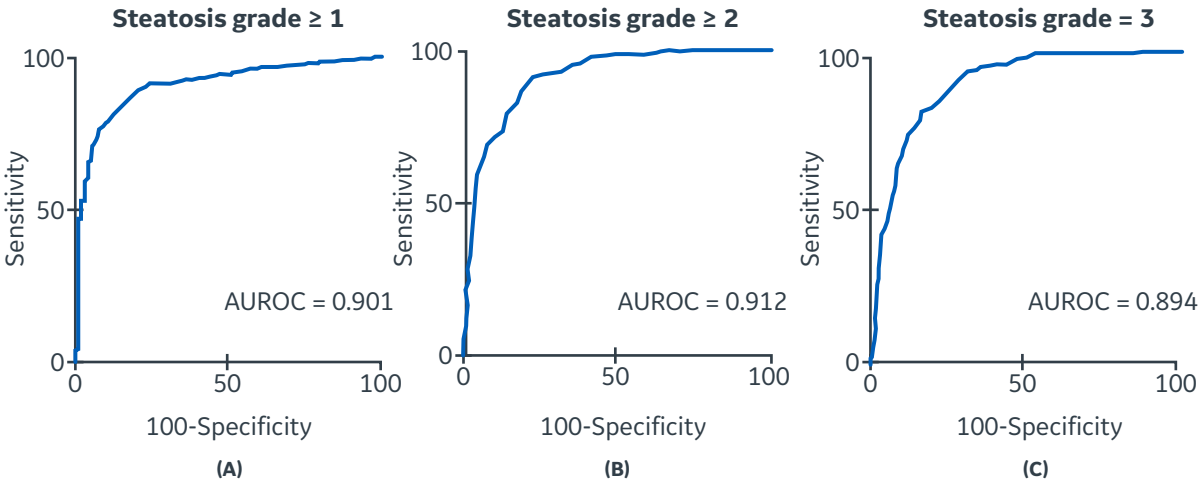


Figure 8. ROC of UGAP for diagnosis of steatosis grade (A) ≥S1, (B) ≥S2 and (C) S3.

	UGAP		
	≥ S1	≥ S2	S3
AUROC (95% CI)	0.901 (0.891 – 0.928)	0.912 (0.894 – 0.929)	0.894 (0.873 – 0.916)
Attenuation coefficient cutoff value (dB/cm/MHz)	0.65	0.71	0.77
Attenuation rate cutoff value (dB/m)	228	249	270

Table 2. AUROCs, 95% CI and cutoff values of UGAP for the prediction of ≥ S1, ≥ S2 and S3 steatosis.

Discussion

In this prospective study based on more than 1000 examinations – the largest to date – the results showed that UGAP has high accuracy at diagnosing and grading steatosis with MRI-PDFF as reference standard. Liver biopsy is still considered the gold standard for the evaluation of hepatic steatosis, but it is painful and costly. In addition, MRI-PDFF has the advantage of accounting for spatial variability of hepatic steatosis compared to biopsy which has potential for sampling error and may result in grading inaccuracies.[10] Recently, there have been several reports showing the utility of MRI-based PDFF for diagnosing hepatic steatosis, including reports showing the superiority of MRI-PDFF to VCTE-based CAP for diagnosing hepatic steatosis grade in NAFLD patients who underwent liver biopsy.[11] Therefore, MRI-PDFF is a precise and accurate non-invasive imaging biomarker for the diagnosis of hepatic steatosis.

The result of this study indicated that UGAP has significant linearity and negligible bias with respect to the reference standard of MRI-PDFF measurements over the entire range of observed steatosis severity. Therefore, it can be concluded that UGAP has excellent technical performance characteristics as a quantitative method of steatosis for widespread use in clinical trials and patient care.

Conclusion

UGAP is a new, non-invasive method for measuring a patient-specific, quantitative attenuation parameter that is well correlated to liver biopsy for discriminating hepatic steatosis among patients with CLD. The B-Mode image provides an anatomical guide while the attenuation and quality maps provide an attenuation quality guide. This combination provides extensive user assistance for proper placement of the UGAP measurement ROI. Lastly, automated algorithms optimize the results within the specified measurement ROI. As such, UGAP is an easy and fast tool that, in combination with 2D shear wave elastography, has the potential to aid in the initial diagnosis and follow-up care of CLD patients.

References

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