Treatment of patients with Fatty Liver
– Importance of early diagnosis of Fatty Liver and clinical role of Ultrasound –

Masahiro Ogawa, M.D.
Head, Ultrasonography Suite,
Department of Gastroenterology,
Nihon University Hospital
Tokyo, Japan

Introduction

Because fatty liver is an asymptomatic condition, it is often the case that it is first identified during a routine health checkup. Nevertheless, if left untreated, it can progress to hepatic cirrhosis or liver cancer. Fatty liver is also frequently associated with metabolic syndrome.

In this paper, I would like to introduce the importance of diagnosing fatty liver in the early stages and assesses the clinical value of ultrasound in the diagnosis and management of patients with this condition.

Current approach to the treatment of patients with fatty liver

Fatty liver is pathologically characterized by the accumulation of neutral lipid in the liver. Typically it is asymptomatic in its early stages, so patients with this condition do not visit hospitals to seek care. Most patients are identified during routine health checkups performed at hospitals and workplaces. Fatty liver may also occasionally be detected in examinations performed in patients receiving treatment for lifestyle diseases such as diabetes.

In recent years, the number of patients with fatty liver identified in health checkups has been increasing.[1,2] This is also true at our facility, where it is found in 30% to 40% of patients receiving health checkups.

Fatty liver was previously thought to be caused by drinking excessive amounts of alcohol. But today, the condition known as Nonalcoholic Fatty Liver Disease (NAFLD) is widely recognized.

Importance of early diagnosis of fatty liver

NAFLD can be categorized into two main types: Nonalcoholic Steatohepatitis (NASH), which tends to progress to more serious diseases, and Nonalcoholic Fatty Liver (NAFL), which tends to remain relatively stable. In patients with NASH, which accounts for 10% to 20% of those with NAFLD,[3] fibrotic changes tend to become more severe over a period of 5 to 10 years before the development of hepatic cirrhosis. Some of these patients may even develop liver cancer.

The diagnosis of NASH is based on the pathological findings of lipid droplets in 5% of hepatocytes combined with ballooning degeneration and the presence of inflammation in the hepatic lobules.[4] The most important factor in determining the prognosis is the severity of fibrotic changes,[5] and it is understood that the severity of fatty degeneration shows no correlation with the prognosis.[6]

Nevertheless, in patients with fatty liver, the progression of fibrotic changes can be prevented by medical intervention to modify the patient's lifestyle, such as dietary instructions and exercise guidance. Such intervention should be aimed at halting the progression of fibrotic changes before they lead to irreversible changes in the liver. This is why the early diagnosis of patients with fatty liver is of such great clinical importance.

In addition, many patients with fatty liver also suffer from metabolic syndrome. In other words, fatty liver can be considered to be an early diagnostic sign of metabolic syndrome, and if it is identified in the early stages, treatment of metabolic syndrome can be instituted promptly to avoid the development of advanced atherosclerosis. This can be expected to reduce mortality rates and improve the prognosis of patients

with cardiovascular diseases, cerebrovascular diseases, and medical conditions in which hemodialysis is required.
As mentioned above, the early diagnosis of fatty liver is extremely important for the treatment of patients with hepatic diseases and metabolic syndrome.

Most commonly used methods for diagnosing fatty liver and their characteristics

The methods most commonly employed for the diagnosis of fatty liver include liver biopsy, CT, MRI Proton Density Fat Fraction (MRI-PDFF), FibroScan® with Controlled Attenuation Parameter (CAP), and diagnostic ultrasound. Each of these methods has both strengths and weaknesses.

Liver biopsy was previously the gold standard for the evaluation of fatty liver. However, there is a risk of sampling error because the amount of tissue collected is quite small, and the diagnostic accuracy may also be reduced because the findings tend to vary depending on the physician who performs pathological examination.[7] Liver biopsy is also an invasive procedure with a high risk of complications. For these reasons, there has been a shift toward diagnostic imaging methods in recent years.

In CT examinations, the liver-to-spleen ratio can be used to identify fatty liver accurately and objectively regardless of the CT scanner used. A liver-to-spleen ratio of 0.9 to 1.1 with a hepatic fat content of 30% or more based on pathological examination[8-10] has been determined to be the absolute threshold for the diagnosis of fatty liver. Of course, one of the main disadvantages of CT is X-ray exposure.

MRI-PDFF is a noninvasive method that can be used to evaluate the entire liver with excellent reproducibility and accuracy.[6,11] However, due to its high cost and long examination times, it is not possible to perform MRI-PDFF in all patients. In addition, because MRI systems use powerful magnets, there are some limitations in the examination of patients with implantable devices such as cardiac pacemakers. It is also difficult to examine patients who suffer from claustrophobia.

FibroScan® with CAP is another noninvasive method that can provide objective indices for quantitatively evaluating the severity of fatty degeneration. However, one challenge is that the degree of fatty degeneration in the liver may be nonuniform, so the measurement values obtained may vary depending on the particular regions examined and therefore not accurately reflect the true clinical condition of the entire liver.

Ultrasound is a noninvasive and cost-effective method that has now assumed the main role in screening for fatty liver. Because examinations can be performed quickly and easily, ultrasound is also ideal for follow-up. In the past, it was generally thought that ultrasound findings were relatively unreliable and tended to vary depending on the specific scan settings and the skill of the operator, However, thanks to recent technological advances such as the introduction of diagnostic ultrasound systems incorporating Attenuation Imaging (ATI), which is a new technology for visualizing the frequency-dependent ultrasound attenuation coefficient within tissues, it has now become possible to quantitatively evaluate the degree of fatty degeneration.

In fact, based on the practice guidelines for NAFLD/NASH established by the Japanese Society of Gastroenterology in cooperation with the Japan Society of Hepatology,[3,12] the Subcommittee on diagnostic criteria for ultrasound in fatty liver established the diagnostic criterion for fatty liver based on ultrasound findings as "large lipid droplets observed in 5% or more of hepatocytes" in the May 2019 edition. They also designated methods for quantitatively measuring ultrasound attenuation as the standard for the quantitative evaluation of fatty degeneration. ATI was specifically mentioned as one such method.

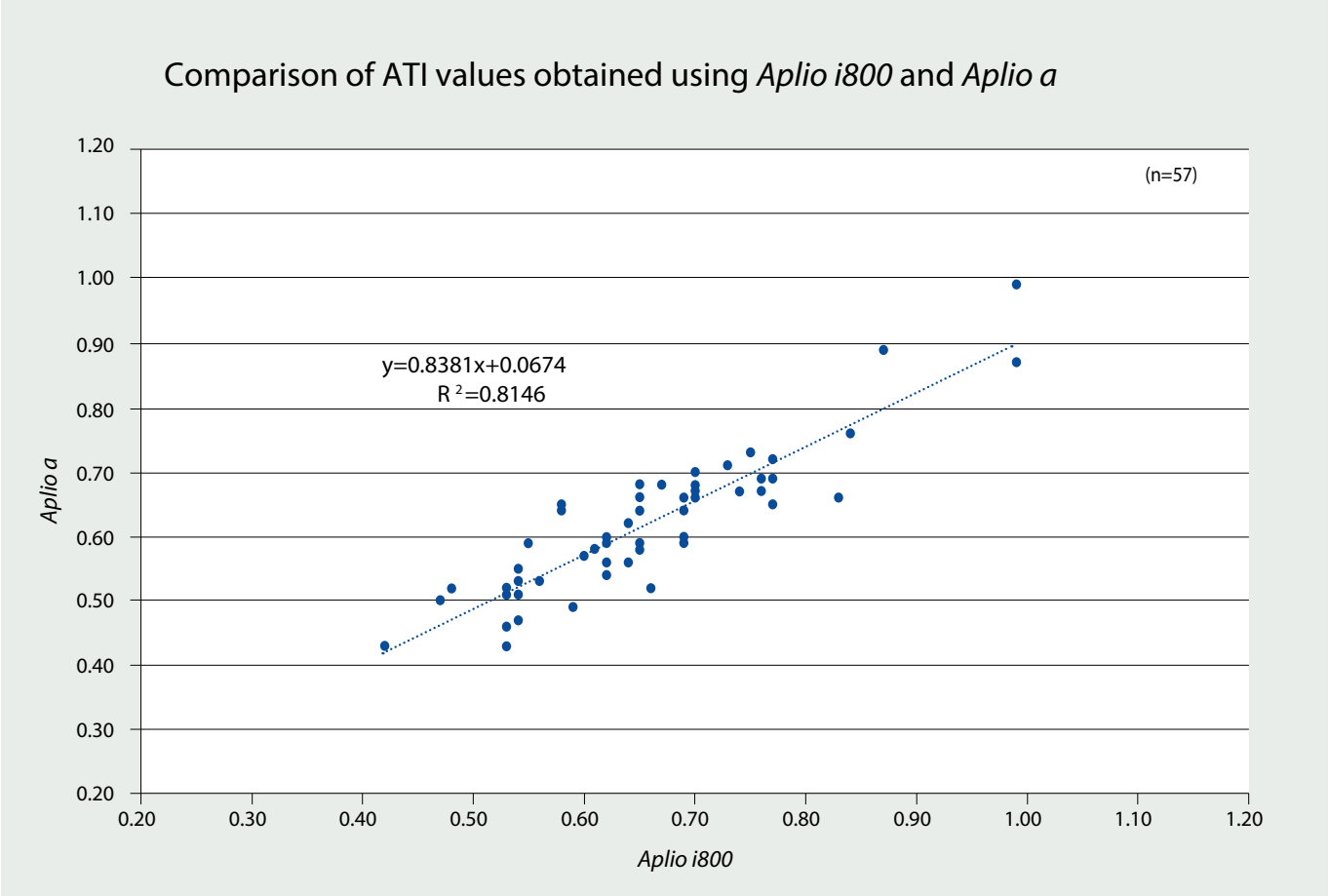
Figure 1 *Aplio a*

Usefulness of diagnostic ultrasound system *Aplio a* in routine clinical practice

ATI function

Studies have shown good agreement between the findings obtained using ATI (which is a function for the quantitative evaluation of fatty degeneration incorporated in diagnostic ultrasound system *Aplio i800*) and a variety of other measurement methods such as MRI-PDFF, FibroScan® with CAP, and liver biopsy[13-15]. However, *Aplio i800* is a high-end system, and it would be desirable for healthcare facilities to employ less expensive midrange models that are able to play a wide range of roles in routine clinical practice.

For this reason, we are currently conducting a study to compare the ATI measurement results obtained using *Aplio i800* with those obtained using *Aplio a* (Fig. 1), which is a midrange system designed for routine clinical use that also includes some of the advanced features of the high-end *Aplio i800* system. The subjects in this study are patients who are receiving regular follow-up ultrasound examinations at our hospital. Patients who are unable to receive ultrasound examination and patients who receive ultrasound examination for any reason other than evaluation of the liver are excluded from the study. In each patient, measurement of fatty degeneration is performed 5 times using both the *Aplio a* system and the *Aplio i800* system, and the mean values are then calculated. The measurement ROI is set at a depth of 4 to 7 cm, with special care taken to ensure that the measurement ROI does not include any reverberation artifacts or acoustic shadows. We are continuing to gather data and are performing ongoing statistical analysis to assess the correlations between the mean values obtained using the two systems. Initial data collected in 57 subjects to date show a good correlation between the values obtained using *Aplio a* and those obtained using *Aplio i800* (Fig. 2).



Data courtesy of Dr. Masahiro Ogawa

Figure 2 Comparison of ATI values obtained using *Aplio i800* and *Aplio a*

Advanced SWE

The display monitor used in *Aplio a* is slightly smaller than that used in *Aplio i800*, but this also means that *Aplio a* is lighter and more compact. In addition to ATI and the thin-convex transducer (PVT-475BT), *Aplio a* includes a number of advanced applications inherited from *Aplio i800*, such as Shear Wave Elastography (SWE), Superb Micro-vascular Imaging (SMI), and Protocol Assistant.

In particular, SWE allows tissue stiffness to be quantitatively analyzed by measuring the shear wave propagation velocity. This is extremely useful for assessing the severity of fibrotic changes, which is a major factor in determining the prognosis of patients with liver disease (Fig. 3). When fatty liver progresses to cirrhosis, the amount of fat actually decreases, which may mistakenly be thought to indicate clinical improvement. This is why it is important to evaluate tissue stiffness in the liver using SWE. In *Aplio a*, ATI (for measurement of fatty changes) and SWE (for measurement of fibrotic changes) can be performed using a single button, and there is no need to change transducers. This imaging technique, known as Advanced SWE, is original technology developed by Canon which allows fatty changes and fibrotic changes in the target region to be evaluated at the same time (Fig. 4).

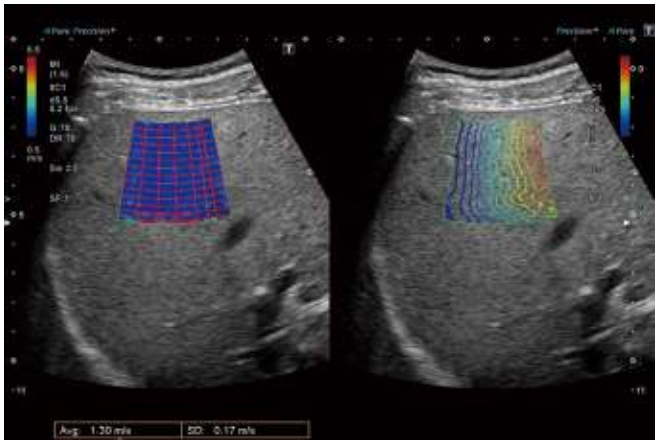


Figure 3 Shear Wave Elastography (SWE)

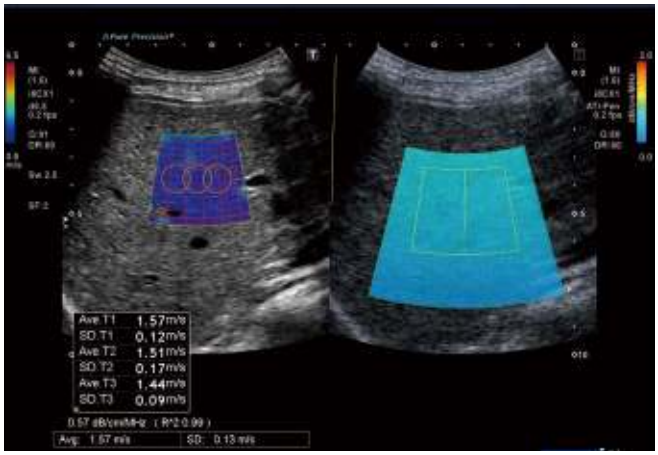


Figure 4 Advanced SWE

Superb Micro-vascular Imaging (SMI)

SMI is superior to color Doppler, power Doppler, and Advanced Dynamic Flow (ADF) for visualizing low-velocity blood flow. It can clearly depict vascular structures and obtain accurate blood flow measurements for evaluating patients with suspected cirrhosis based on B-mode ultrasound findings as well as for establishing a definitive diagnosis in patients with tumorous lesions. The SMI function provided in *Aplio a* also features a remarkably large ROI.

Thin-convex transducer

The thin-convex transducer (PVT-475BT) used with *Aplio a* employs a monocrystalline substance known as polymethylpentene resin, which allows the thickness of the transducer head to be reduced to as little as 9 mm (Fig. 5). As a result, intercostal scanning can be performed much more easily in liver examinations. The light weight of the transducer also helps to minimize operator fatigue.

Protocol Assistant

Protocol Assistant is also available in *Aplio a*. This feature includes a variety of operator support functions, such as functions for showing the operating procedures that should be performed to visualize the required regions or planes for observing changes in lesions, functions for registering reference images, and search functions for reviewing changes in clinical data over time. The use of Protocol Assistant helps to prevent required images from being accidentally omitted during examinations or mistakenly excluded from quantitative evaluation. It also allows physicians to provide clear explanations to their patients while showing them the actual changes in their medical condition over time using both images and numerical data. This is particularly useful in small clinics where physicians tend to care for the same patients over many years.

Figure 5 Conventional transducer (left) and thin-convex transducer, PVT-475BT (right) The contact surface of the thin-convex transducer is only 9 mm thick, half that of the conventional transducer.

***Aplio a*: a powerful tool for detecting fatty liver in the early stages and for enhancing patient awareness of their disease**

There has been remarkable progress in diagnostic ultrasound systems in recent years. Of course, *Aplio i800* is a better system than *Aplio a*, but both systems can provide images that allow a certain degree of objective evaluation when employed in an appropriate manner. In particular, with the introduction of Protocol Assistant, just the right amount of essential data is collected and displayed, allowing the operator to easily observe changes over time based on the search results. Moreover, the ability to present clear explanations while displaying high-quality images and numerical data obtained by ATI and SWE at different times helps to enhance patient understanding of their medical condition and improve patient satisfaction. It also increases the confidence that patients have in their caregivers.

As mentioned above, the early detection of fatty liver is a great benefit to patients because it allows treatment to be instituted without delay in order to prevent the progression of hepatic diseases and metabolic syndrome. When considered from this viewpoint, *Aplio a*, which includes functions such as ATI which allow patients with fatty liver to be evaluated easily and economically, is expected to serve as a powerful tool for the early detection of fatty liver, which can be considered to be the hepatic manifestation of metabolic syndrome, as well as for enhancing patient awareness of their disease.

References:

1. Sasamori N. *Journal of Japan Hospital Association 2003*; 50(12): 1867-1942.
2. Eguchi Y et al. *J Gastroenterol 2012*; 47: 586-595.
3. *Japan Society of Hepatology: Evidence-based Clinical Practice Guidelines for Nonalcoholic Fatty Liver Disease / Nonalcoholic Steatohepatitis 2015. Bunkodo, 2015.*
4. Bedossa P et al. *J Hepatol 2012*; 56: 1751-1759.
5. Boursier J et al. *J Hepatol 2016*; 65: 570-578.
6. Bannas P et al. *Hepatology 2015*; 62: 1444-1455.
7. Rockey DC et al. *Hepatology 2009*; 49: 1017-1044.
8. Yajima Y et al. *Tohoku J EXP Med 1982*: 337-342.
9. Park SH et al. *Radiology 2006*; 239: 105-112.
10. Iwasaki M et al. *Transplantation 2004*; 78: 1501-1505.
11. Noureddin M et al. *Hepatology 2013*; 58: 1930-1940.
12. *Japanese Society of Gastroenterology: Evidence-based Clinical Practice Guidelines for Nonalcoholic Fatty Liver Disease / Nonalcoholic Steatohepatitis 2014. Nankodo, 2014.*
13. Ferraioli G et al. *Clin Transl Gastroenterol 2019*; 10(10): e00081.
14. Iijima H et al. *Kanzo 2018*; 59(1): 65-67.
15. Tada T et al. *Ultrasound Med Biol 2019*; 45(10): 2679-2687.

Acknowledgement:

This English version is created based on the article published in Medical Tribune on the Web, March 15, 2021.

CANON MEDICAL SYSTEMS CORPORATION
https://global.medical.canon

MWPUS0011EA 2021-08 CMSC/SZ/Produced in Japan