Imaging of Nonalcoholic Steatohepatitis: Advantages and Pitfalls of Ultrasonography and Computed Tomography

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Abstract

Objective The present study was performed to clarify the ability of ultrasonography (US) and computed tomography (CT) to detect steatosis and advanced fibrosis in nonalcoholic steatohepatitis (NASH) patients, and to assess the influence of steatosis, fibrosis, and obesity on the radiological detection of steatosis and advanced fibrosis.

Methods One hundred and eighteen biopsy proven NASH patients underwent US and CT within 6 months before or after biopsy. The ability of US and CT to detect histological steatosis and advanced fibrosis was assessed. To evaluate whether fibrosis and obesity interfered with the detection of moderate to severe histological steatosis by US and CT, we analyzed 88 NASH patients with moderate to severe steatosis. To evaluate interference with the detection of advanced fibrosis by steatosis and obesity, we analyzed 59 NASH patients with advanced fibrosis.

Results The sensitivity of US for detecting moderate to severe histological steatosis in patients with mild histological fibrosis was 100%, but this was reduced to 77.8% in patients with advanced histological fibrosis ($p=0.001$). The sensitivity of CT was 69.8% in patients with mild histological fibrosis and 48.9% in those with advanced histological fibrosis ($p=0.047$). The sensitivity of US and CT for moderate to severe histological steatosis was similar in each body mass index group. The sensitivity for detecting advanced fibrosis was markedly decreased by severe steatosis and obesity in the case of both US and CT.

Conclusion If we are aware of these disadvantages of US and CT, it is useful for diagnosing steatosis and fibrosis in NAFLD patients.

Key words: NASH, NAFLD, ultrasonography, computed tomography

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is increasingly being recognized as the most common cause of chronic liver disease worldwide. NAFLD represents a wide spectrum of conditions, ranging from simple steatosis that generally follows a benign and nonprogressive clinical course to nonalcoholic steatohepatitis (NASH), which sometimes progresses to cirrhosis and hepatocellular carcinoma (HCC) (1-5). In Japan, annual health checks have shown that 10-30% of Japanese adults demonstrate evidence of NAFLD by ultrasonography (US) (6, 7). It has been reported that almost 10% of persons with NAFLD will have NASH, so the

prevalence of NASH is estimated at 1-3% of the adult Japanese population, an extremely large number of potential patients. Unfortunately, there are no accurate noninvasive diagnostic methods for NASH, such as biochemical markers or imaging techniques, therefore liver biopsy is necessary to make a definite diagnosis, although the procedure is associated with pain, risks, high cost, and sampling errors (1, 2, 8-11).

In general practice, NAFLD (which includes simple steatosis and NASH) is a convenient term for the diagnosis and management of these patients. Diagnosis of NAFLD is based on the detection of steatosis by imaging techniques and the exclusion of other liver diseases, such as alcoholic liver disease or viral hepatitis. The response of NAFLD to

treatment is usually evaluated by the changes in transaminases and from imaging findings. Therefore, imaging studies are extremely important, both for diagnosing NAFLD and for monitoring patients over time.

Abdominal US is currently the most common method employed for qualitative assessment of hepatic steatosis, because it is noninvasive, widely available, cheap, and provides useful information (12). Computed tomography (CT) scanning and magnetic resonance imaging (MRI) both seem to be sensitive techniques for the quantification of steatosis, but MRI is still less widely available and more expensive than CT. In general practice, therefore, detection of steatosis is generally done by US, after which CT is performed for more objective and quantitative assessment of the severity of steatosis based on the liver/spleen attenuation ratio (13).

Several studies have assessed the sensitivity, specificity, and positive and negative predictive value of US for detecting steatosis, and the reported sensitivity ranges around 80-100% (8-10, 12). In patients with morbid obesity, however, a sensitivity of less than 40% has been reported, presumably due to the technical difficulty of performing US in such patients (14). Moreover, recent studies have shown that US is not accurate for detecting hepatic steatosis in patients with chronic liver disease due to the presence of fibrosis (15). These factors often exist in NASH patients. Therefore, evaluation of the influence of obesity and fibrosis on the detection of steatosis is needed.

To date, few studies have involved the evaluation of steatosis in NASH patients by both US and CT (16-19). Assessment of the severity of hepatic fibrosis is essential for determining the prognosis and making treatment decisions in patients with NASH. It is also suspected that the detectability of fibrosis is decreased in NASH patients with severe steatosis. Accordingly, the present study was performed to clarify the ability of US and CT to detect steatosis and advanced fibrosis in NASH patients, and to assess the influence of steatosis, fibrosis, and obesity on the radiological detection of steatosis and fibrosis.

Methods

From 1990 to December 2007, 384 Japanese patients were diagnosed as having biopsy proven NASH at Tokyo Women's Medical University. Among them, 126 patients underwent liver biopsy, and also underwent US and CT within 6 months before or after biopsy. All patients gave informed consent to participation in the study. Eight patients were excluded due to a change in the severity of obesity (change of their BMI by more than 1) between the time of liver biopsy and imaging, leaving 118 patients for whom clinical data were collected retrospectively.

Diagnosis of NASH was based on the following criteria: 1) steatohepatitis on liver biopsy, 2) intake of less than 100 g of ethanol per week (confirmed by the attending physician and family members who were in close contact with the patient), and 3) appropriate exclusion of other liver diseases

(viral hepatitis, autoimmune hepatitis, drug-induced liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, biliary obstruction, and metabolic liver diseases such as Wilson's disease and hemochromatosis) (1, 2).

A complete history was obtained and physical examination was performed in all patients. The following laboratory parameters were measured: albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltranspeptidase, platelet count, and prothrombin time.

All liver biopsy specimens were examined to assess the severity of steatosis and fibrosis, and the NAFLD activity score (NAS) was calculated (20, 21). Mild steatosis was defined as 10-29% of hepatocytes containing fat, moderate steatosis was 30-69% involvement, and severe steatosis was more than 70% involvement. Mild fibrosis was defined as F0-2 and advanced fibrosis was defined as F3-4 (bridging fibrosis and cirrhosis).

All 118 patients were examined by US and CT. US was used to detect the presence of steatosis and advanced fibrosis. Hepatic steatosis was defined as being present in patients with at least two of the following findings: increased hepato-renal contrast, liver brightness, deep attenuation, and vascular blurring. Advanced fibrosis was defined as existing in patients with at least two of the following: a blunt liver edge, surface nodularity, caudate lobe hypertrophy, a coarse echo pattern, increased definition of portal veins, splenomegaly, ascites, and varices (12, 22).

CT was performed with a multi-detector row helical scanner. On non-enhanced scans, the liver-to-spleen attenuation ratio was measured and the presence of steatosis was indicated by a ratio of less than 0.9 according Japanese criteria (13). Advanced fibrosis was defined by the presence of at least two of these features on CT scans: surface nodularity, a prominent caudate lobe associated with a shrunken right lobe, a decrease in the volume of the medial segment of the left lobe, splenomegaly, ascites, and varices (12, 13).

The ability of US and CT to detect mild to severe histological steatosis and advanced histological fibrosis was assessed and the sensitivity of each modality was calculated. Unfortunately, specificity could not be calculated because there were no control patients.

To evaluate whether fibrosis and obesity interfered with the detection of moderate to severe histological steatosis by US and CT, we analyzed 88 NASH patients with moderate to severe steatosis (Fig. 1). The patients were divided into a group with mild histological fibrosis and another group with advanced histological fibrosis to evaluate interference with the detection of moderate to severe histological steatosis by fibrosis. To examine the influence of obesity, we divided the patients into 3 groups according to the body mass index (BMI): BMI<25, BMI of 25-30, and BMI>30.

To evaluate interference with the detection of advanced fibrosis by steatosis and obesity, we analyzed 59 NASH patients with advanced fibrosis. The patients were divided into three groups with mild histological steatosis, moderate stea-

Figure 1. To evaluate whether fibrosis and obesity interfered with the detection of moderate to severe histological steatosis by US and CT, we analyzed 88 NASH patients with moderate to severe steatosis. To evaluate interference with the detection of advanced fibrosis by steatosis and obesity, we analyzed 59 NASH patients with advanced fibrosis.

Table 1. Patient Profile

		NASH n=118
		Median (range or %)
Age (years)		54 (14~89y.o.)
Sex		M52 (44.1%) F66 (55.9%)
BMI (kg/m ²)		27.3 (19.3~42.6)
Obesity (BMI≥25 kg/m ²)		87 (73.7%)
Severe obesity (BMI≥30 kg/m ²)		39 (33.1%)
Diabetes		58 (49.2%)
Hyperlipidemia		62 (52.5%)
Hypertension		53 (44.9%)
Alb	(g/dL)	4.3 (2.6-5.5)
T-bil	(g/dL)	0.6 (0.2-6.0)
AST	(IU/L)	51 (12-260)
ALT	(IU/L)	70 (10-302)
ALP	(IU/L)	265 (112-1407)
γ-GTP	(IU/L)	75 (17-1543)
Plt	(×10 ⁴ /μL)	18.5 (3.7-45.1)
Prothrombin time	(%)	97 (45.5-100)
Fibrosis	F0-2	59 (50.0%)
	F3-4	59 (50.0%)
	Mild	30 (25.4%)
Steatosis	Moderate	25 (21.2%)
	Severe	63 (53.4%)
Activity	Mild	25 (21.2%)
	Moderate	59 (50.0%)
	Severe	34 (28.8%)

nosis, or severe steatosis. We also examined the influence of obesity.

Statistical analysis

Statistical analysis was done using SPSS software (version 11.0).

We assessed the relation between the liver/spleen attenuation ratio on CT and the severity of steatosis by analysis of variance (ANOVA), and we analyzed the sensitivity of detecting steatosis and fibrosis, as well as the influence of each factor by the chi-square test.

Results

Baseline demographic, clinical, and laboratory data for the NASH patients are shown in Table 1. The median age was 54 years, with a range of 14 to 89 years. There were 52 men and 66 women. Thirty-one patients had a BMI of less than 25, 48 patients had a BMI of 25-30, and 39 patients had a BMI of more than 30. Liver biopsy showed that 25.4% had mild steatosis, 21.2% had moderate steatosis, and, 53.4% had severe steatosis. In the case of fibrosis, 50.0% of NASH patients had mild fibrosis and 50.0% had

Figure 2. Scatter diagram of the liver/spleen attenuation ratio on CT in relation to the severity of histological steatosis. There was a significant difference of the liver spleen attenuation ratio between each stage of steatosis defined by liver biopsy ($p<0.001$).

advanced fibrosis. The NAFLD score was 3-4 in 4.2% and 5 or more in 95.8%.

Steatosis and imaging modalities

[Sensitivity of detecting steatosis]

Figure 2 displays the liver/spleen attenuation ratio obtained by CT in relation to the severity of steatosis. CT could precisely evaluate steatosis, and there was a significant difference of the ratio between each stage as defined by liver biopsy ($p<0.001$).

The sensitivity of detecting mild to severe steatosis in 118 NASH patients was 79.7% by US and 46.6% by CT. US was more accurate for identifying the existence of steatosis ($p<0.001$). US could not detect steatosis in 24 NASH patients, including 14 patients with mild histological steatosis and 10 patients with moderate histological steatosis. All 10 patients with moderate steatosis had advanced fibrosis and the US diagnosis was only advanced fibrosis in every case. Among the 14 patients with mild histological steatosis, 11 patients had advanced fibrosis and their US diagnosis was "advanced fibrosis without steatosis," while the other 3 patients had mild fibrosis and the US diagnosis was normal liver.

To evaluate the detection of each histological grade of steatosis, we analyzed 30 mild steatosis patients, 25 moderate steatosis patients, and 63 severe steatosis patients. US was more accurate for identifying the existence of each grade of steatosis. US detected 53.3% versus 10.0% for CT in patients with mild histological steatosis, while the rates were 64.0% versus 28.0% in moderate histological steatosis, and 98.4% versus 71.4% in severe steatosis. The difference between US and CT was statistically significant for each steatosis grade ($p=0.0003$ for mild steatosis, $p=0.0107$ for moderate steatosis, and $p\leq 0.0001$ for severe steatosis).

[Interference with detection of moderate to severe histological steatosis by fibrosis]

To evaluate interference with the detection of moderate to severe histological steatosis by fibrosis, we analyzed 88 patients with moderate to severe steatosis. Among them, 43 patients had mild fibrosis and 45 patients had advanced fibrosis.

The sensitivity of US for detecting moderate to severe histological steatosis in patients with mild histological fibrosis was 100%, but this was reduced to 77.8% in patients with advanced histological fibrosis (Fig. 3). The sensitivity of CT was 69.8% in patients with mild histological fibrosis and 48.9% in those with advanced histological fibrosis. The decrease in the sensitivity of detecting moderate to severe steatosis due to the presence of advanced fibrosis was statistically significant for both US and CT ($p=0.001$ for US and $p=0.047$ for CT). The extent of the decrease in sensitivity was similar for US and CT.

[Interference with the detection of moderate to severe histological steatosis by obesity]

Among the 88 patients, 21 patients had a BMI of less than 25, 35 patients had a BMI of 25 to 30, and 32 patients had a BMI of more than 30. The prevalence of advanced histological fibrosis was not significantly different in each BMI group (the prevalence of advanced histological fibrosis was as follows: BMI<25; 41.9%/25≤BMI<30; 50.0%/BMI≥30; 56.4%; $p=0.74$). Figure 4 shows the detection of moderate to severe histological steatosis by US and CT. The sensitivity of US for moderate to severe histological steatosis was similar in each BMI group. CT could more accurately identify the presence of moderate to severe histological steatosis in obese patients (BMI>30), but the difference was not statistically significant.

Figure 3. Comparison of the detection of moderate to severe histological steatosis between patients with mild fibrosis and advanced fibrosis. The decrease in the sensitivity of detecting moderate to severe histological steatosis due to the presence of advanced fibrosis was statistically significant for both US and CT.

Figure 4. Detection of moderate to severe steatosis by US and CT according to BMI. The sensitivity of US for moderate to severe histological steatosis was similar in each BMI group. CT could more accurately identify the presence of moderate to severe histological steatosis in obese patients, but the difference was not statistically significant.

Fibrosis and imaging modalities

[Sensitivity of detecting advanced fibrosis]

To evaluate the detection of advanced histological fibrosis, we analyzed 59 NASH patients with advanced histological fibrosis. The sensitivity of detection was 59.3% for US and 71.2% for CT. The difference of sensitivity between US and CT was not significant, but CT was better able to detect advanced fibrosis.

[Interference with detection of advanced fibrosis by steatosis]

To evaluate interference with the detection of advanced histological fibrosis by steatosis, we analyzed 59 patients with advanced histological fibrosis. Among them, 14 patients had mild steatosis, 19 had moderate steatosis, and 26 had severe steatosis.

Interference with the detection of advanced histological fibrosis by steatosis is shown in Fig. 5. The sensitivity for de-

tecting advanced fibrosis was markedly decreased by severe steatosis in the case of both US and CT (the sensitivity for mild/moderate/severe histological steatosis was 92.9/84.2/23.1% with US and 85.7/89.5/50.0% with CT). The loss of sensitivity was statistically significant for both modalities ($p < 0.0001$ for US and $p = 0.006$ for CT), but the decrease was greater for US.

[Interference with detection of fibrosis by obesity]

To evaluate interference with the detection of advanced histological fibrosis by obesity, we analyzed the patients with advanced fibrosis. The prevalences of severe histological steatosis were higher among the patients with BMI of more than 30. The difference was not statistically significant (the prevalence of severe histological steatosis was as follows: BMI < 25; 41.9%/25 ≤ BMI < 30; 52.1%/BMI ≥ 30; 64.1%; $p = 0.18$). Among the 59 patients, 13 patients had a BMI of less than 25, 24 patients had a BMI of 25 to 30, and 22 patients had a BMI of more than 30. Detection of advanced histological fibrosis by US and CT is shown in

Figure 5. Comparison of the detection of advanced fibrosis in patients with mild, moderate, and severe steatosis. The sensitivity for detecting advanced fibrosis was markedly decreased by severe steatosis in the case of both US and CT.

Figure 6. Sensitivity of US and CT for advanced fibrosis in relation to BMI. The sensitivity of both US and CT for detecting advanced fibrosis decreased as the BMI increased. The loss of sensitivity was statistically significant for US.

Fig. 6. The sensitivity of both US and CT for detecting advanced fibrosis decreased as the BMI increased. The sensitivity of detecting advanced fibrosis was as follows for US: BMI<25; 92.3%/25≤BMI<30; 54.2%/BMI≥30; 45.5%. For CT, it was: BMI<25; 92.3%/25≤BMI<30; 70.8%/BMI≥30; 59.1%. The loss of sensitivity was statistically significant for US (Fig. 6).

Discussion

NAFLD patients are usually asymptomatic and this condition is most often detected by US during an annual health check. Transaminases are not useful for making a diagnosis NAFLD because some patients have normal levels (6, 23). US also has several limitations because it is subjective, operator-dependent, poor at detecting mild steatosis, and poor at quantifying steatosis. Patients with detection of NAFLD by US underwent CT to confirm the presence of steatosis and to evaluate its severity by measurement of the liver/spleen attenuation ratio. Of course, CT has limitations with respect to the diagnosis of steatosis, including poor detection of mild steatosis, exposure to X-rays, and unavail-

ability for patients with hemosiderosis (24). Moreover, both imaging modalities could not distinguish NASH from simple steatosis. Therefore, patients were evaluated to assess the need for liver biopsy to make a diagnosis of NASH. Liver biopsy is usually performed in NAFLD patients who are suspected to have other liver diseases and/or in patients suspected to have NASH. Therefore, it is important to determine the strengths and weaknesses of US and CT for confirming hepatic steatosis and fibrosis in NAFLD patients.

Several researchers have attempted to develop US grading systems in order to improve agreement between observers and decrease operator bias, and to develop US diagnosing systems for NASH (25, 26). However, even if the results are reproducible, it is very difficult to use such models in clinical practice. Since there is no correlation between the severity of steatosis and the severity of fibrosis in NASH patients, we think that detecting the presence of steatosis is sufficient (27, 28).

The present study revealed that US could more accurately identify the presence of steatosis in NASH patients than CT. In Japan, a liver/spleen attenuation ratio of less than 0.9 is defined as indicating steatosis (13). This definition is quite

strict, so the sensitivity of detecting steatosis by CT was relatively low. Detection of changes in the liver/spleen attenuation ratio is very useful for monitoring NASH patients, even if they have more than 0.9 liver/spleen attenuation ratio. The most important role of CT in NAFLD patients is quantitative assessment of the severity of steatosis by measurement of the liver/spleen attenuation ratio, as previously reported (12).

It is well known that mild steatosis is difficult to diagnose by US. In the present study, the sensitivity of US for mild steatosis in NASH patients with mild fibrosis was 81.3%. The high sensitivity of US for mild steatosis was probably achieved because most of our patients with mild histological steatosis had more than 20% of their hepatocytes containing fat. Interference by the presence of advanced fibrosis reduced the sensitivity of both US and CT for the detection of moderate to severe histological steatosis in NASH patients. It is important to know that the sensitivity of US for detecting moderate to severe steatosis in NASH patients with mild fibrosis was 100%, however in 22.2% of NASH patients with advanced fibrosis, even moderate to severe steatosis could not be detected by US. If liver biopsy was not done, these patients would be diagnosed as having idiopathic hepatic fibrosis. Interestingly, obesity did not interfere with the detection of moderate to severe histological steatosis by US or CT. Even when the focus was on the detection of severe histological steatosis, the results were similar for US and CT. According to our findings, it is not problematic to detect hepatic steatosis in obese Japanese patients.

Concerning fibrosis, CT could more accurately identify the presence of advanced fibrosis than US. The sensitivity of detecting advanced fibrosis by US or CT was markedly decreased in patients with severe steatosis and obesity (BMI >

25) and this decrease was more significant for US. It is important to recognize these weaknesses of US and CT.

Several reliable and noninvasive bio-markers for predicting the presence of advanced fibrosis or cirrhosis in NASH patients have been reported (28-31). We previously reported that measurement of hyaluronic acid can accurately identify advanced fibrosis in Japanese NAFLD patients, while the platelet count can be used to identify cirrhosis.

Therefore, imaging modalities might be used together with these markers to diagnose fibrosis more accurately.

The first limitation of our study is that we attempted to clarify the ability of US and CT for diagnosing steatosis and advanced fibrosis in NASH patients, but there were no controls. Therefore, we could not assess the specificity of the two imaging modalities for steatosis and fibrosis, so our study focused on sensitivity.

The second limitation is that the US data were interpreted by several radiologists, thus increasing inter-observer variability. However, we wanted to assess the validity of US in general practice, so the use of several radiologists was more appropriate.

We confirmed that US could more accurately identify the presence of steatosis in NASH patients than CT. Concerning interference with the detection of steatosis by advanced fibrosis, the decrease of detection was marked for both imaging modalities. However, obesity did not affect the detection of steatosis. The sensitivity of US and CT for advanced fibrosis was decreased markedly in patients with severe steatosis and obese patients, and this decrease was more marked for US. Awareness of these disadvantages of the common imaging modalities is useful for diagnosing steatosis and fibrosis in NAFLD patients.

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