REVIEW

Bedside ultrasound in the diagnosis of nonalcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the United States. While the American Association for the Study of Liver Diseases guidelines define NAFLD as hepatic steatosis detected either on histology or imaging without a secondary cause of abnormal hepatic fat accumulation, no imaging modality is recommended as standard of care for screening or diagnosis. Bedside ultrasound has been evaluated as a non-invasive method of diagnosing NAFLD with the presence of characteristic sonographic findings. Prior studies suggest characteristic sonographic findings for NAFLD include bright hepatic echoes, increased hepatorenal echogenicity, vascular blurring of portal or hepatic vein and subcutaneous tissue thickness. These sonographic characteristics have not been shown to aid bedside clinicians easily identify potential cases of NAFLD. While sonographic findings such as attenuation of image, diffuse echogenicity, uniform heterogeneous liver, thick subcutaneous depth, and enlarged liver filling of the entire field could be identified by clinicians from bedside ultrasound. The accessibility, ease of use, and low-side effect profile of ultrasound make bedside ultrasound an appealing imaging modality in the detection of hepatic steatosis. When used with appropriate clinical risk factors and steatosis involves greater than 33% of the liver, ultrasound can reliably diagnose NAFLD. Despite the ability of ultrasound in detecting moderate hepatic steatosis, it cannot replace liver biopsy in staging the degree of fibrosis. The purpose of this review is to examine the diagnostic accuracy, utility, and limitations of ultrasound in the diagnosis of NAFLD and its potential use by clinicians in routine practices.

Core tip: Ultrasound is a non-invasive, widely available, and accurate tool in the detection of Non-alcoholic fatty liver disease (NAFLD). Ultrasound should be used as the first-line diagnostic test in patients with abnormal liver enzymes when other causes are excluded. Clinical risk factors, when used with ultrasound findings, have high accuracy in identifying NAFLD patients. We present an algorithm for chronic abnormal liver enzymes that illustrates the use of ultrasound in reducing the need for liver biopsy in the diagnosis of NAFLD. Clinicians should be aware of the known limitations of ultrasound, including the inability to grade or stage fibrosis in NAFLD patients.

INTRODUCTION

The potential role of ultrasound by the clinician is increasing. The estimated prevalence of non-alcoholic fatty liver disease (NAFLD) is approximately 34%. Strongly associated with metabolic syndrome, the incidence of NAFLD will continue to rise with the projected progression of the obesity epidemic[1,2]. NAFLD includes a wide spectrum of disease activity, from simple steatosis to non-alcoholic steatohepatitis (NASH)[3,4]. Simple steatosis has a benign and potentially reversible course, however, NASH can progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma[3,4]. The diagnosis of NAFLD remains under recognized as most patients are asymptomatic until late stages of disease[5]. Liver biopsy is the gold standard in diagnosing NAFLD and the most accurate tool for grading fibrosis, however is invasive and carries the risk of complications[2,3]. Bedside ultrasound, as a non-invasive and readily available tool, has an important role in diagnosing NAFLD. In this paper we present a review of current knowledge and literature on the utility of beside ultrasound in the diagnosis of NAFLD by the clinician.

CHARACTERISTIC SONOGRAPHIC FEATURES OF NAFLD

High diagnostic accuracy can be achieved by the ultrasound when sonographic features unique to NAFLD are standardized and used to aid in diagnosis. Bright hepatic echoes, increased hepatorenal echogenicity and vascular blurring of portal or hepatic vein have been classified as unique sonographic features of NAFLD. In a prospective study by Dasarathy *et al*[6], real time ultrasound was performed followed by a liver biopsy to evaluate the accuracy of ultrasound in hepatic steatosis. When steatosis was greater than 20% on biopsy, these sonographic features were able to predict the presence of NAFLD with greater than 90% sensitivity. Lower levels of fat content resulted in reduction of sensitivity[6]. A sonographic scoring system used by Hamaguchi *et al*[7] was developed based on similar pre-determined imaging findings. By using hepatorenal echo contrast, liver brightness, deep attenuation and vascular blurring, they were able to report similar sensitivities in detecting histologically proven NAFLD[7].

Subcutaneous tissue thickness, measured as the distance between the skin surface and the liver surface, has been shown to be another characteristic sonographic finding. When compared to other non-NAFLD liver diseases, NAFLD patients had thicker subcutaneous tissue, with a mean measurement of 25.6 ± 5.6 mm. In comparison, the non-NAFLD patients had a mean subcutaneous tissue thickness of 19.5 ± 5.2 mm. NAFLD was unlikely when the subcutaneous tissue thickness was less than 20 mm[8]. Along with subcutaneous tissue thickness, Riley *et al*[9] defined five characteristic sonographic findings for NAFLD that can be identified by the clinician:
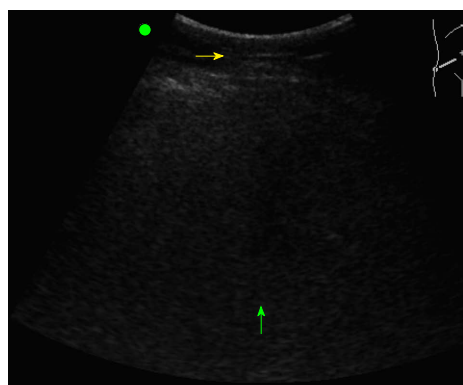

Figure 1 Bedside ultrasound image displaying sonographic characteristics on non-alcoholic fatty liver disease. Attenuation of image (green arrow), diffuse echogenicity, uniform heterogeneous liver, thick subcutaneous depth (yellow arrow), and enlarged liver filling of the entire field as described by Riley *et al*[9].

(1) attenuation of image quickly within 4-5 cm of depth, making deeper structures difficult to decipher; (2) echogenic diffusely but particularly important to note brightness within the first 2-3 cm of depth; (3) liver uniformly heterogeneous; (4) thick subcutaneous depth (> 2 cm); and (5) liver fills entire field with no edges visible (viewed as helpful but not necessary for diagnosis), as shown in a prototypical bedside ultrasound image in Figure 1. Using these characteristic sonographic findings, bedside ultrasound yielded a sensitivity of 80% and specificity of 99%.

EASE OF CLINICAL USE AND INTERPRETATION

These typical sonographic features can be identified by the clinician with the use of bedside ultrasound. Ultrasound can result in an immediate diagnosis and development of a plan of care at the initial visit. Riley *et al*[9] demonstrated that clinical providers could be trained to identify ultrasound images consistent with NAFLD after a brief 20-min session. Healthcare providers were subsequently able to reliably identify NAFLD using the prototype image with substantial inter-observer agreement, $\kappa = 0.76$[9].

ULTRASOUND AS A DIAGNOSTIC TOOL

In patients with chronic hepatitis, an algorithm weighing the relative importance between characteristic ultrasound findings and clinical risk factors has been proposed for the diagnosis of NALFD, as shown in Figure 2. To use the algorithm, viral hepatitis, autoimmune liver disease, alcoholic liver diseases, and genetic diseases must first be excluded. Clinical risks include any of the following: diabetes, body mass index (BMI) greater than 30, hepatomegaly, and hyperlipidemia[10]. Ultrasound features include any 4 of the following 5 sonographic features: (1) attenuation of image quickly within 4-5 cm of depth;
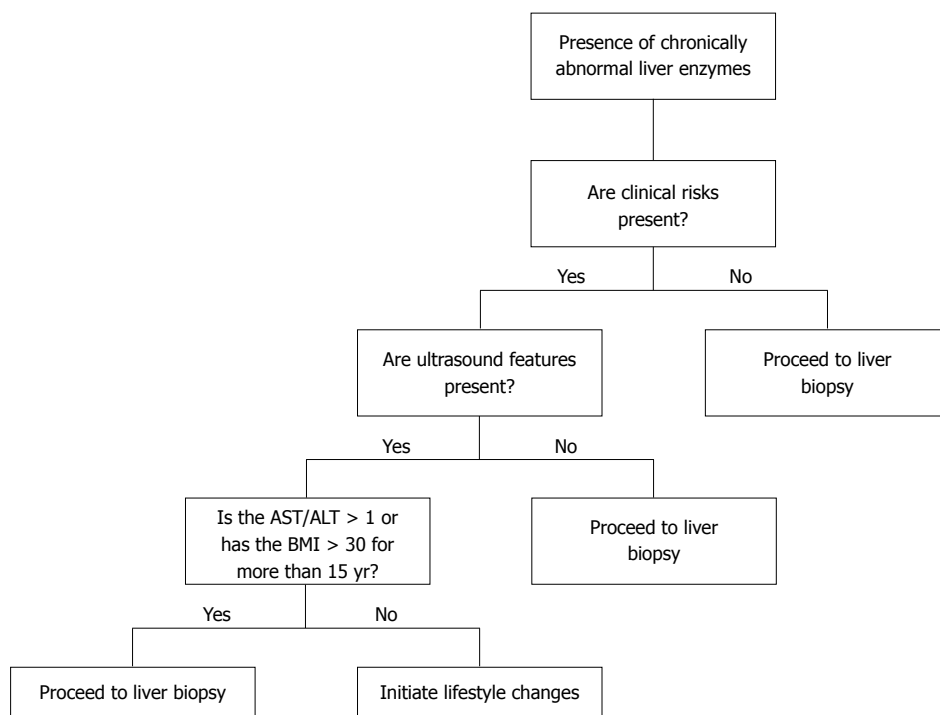
Figure 2 Diagnostic algorithm for suspected non-alcoholic fatty liver disease. The algorithm illustrates the use of ultrasound in reducing the need for liver biopsy in the diagnosis of non-alcoholic fatty liver disease. BMI: Body mass index; AST/ALT: Aspartate aminotransferase/alanine aminotransferase.

(2) echogenic diffusely but particularly important to note brightness within the first 2-3 cm of depth; (3) liver uniformly heterogeneous; (4) thick subcutaneous depth (> 2 cm); and (5) liver fills entire field with no visible edges[9]. Characteristic features for NAFLD on ultrasound were found to be the strongest independent predictor on multivariable analysis. Other clinical risk factors with significant correlation with the biopsy-proven diagnosis of NAFLD on multivariate analysis include the presence of diabetes, BMI > 30, hepatomegaly, female gender, age > 55, and triglyceride greater than 250[10]. The severity of hepatic steatosis on ultrasound in the presence of metabolic syndrome is a better non-invasive tool for monitoring liver disease than liver enzymes[11]. Normal alanine aminotransferase (ALT) level alone was not sufficient for exclusions of significant hepatic steatosis[12]. Aspartate aminotransferase (AST)/ALT ratio greater than 1, however, has been associated to findings of advanced fibrosis on liver biopsy[13]. The recognition of appropriate clinical factors in conjunction with characteristic ultrasound findings can lead to an accurate diagnosis of NAFLD without the use of invasive testing, and also identify those individuals that should go onto have a liver biopsy.

ULTRASOUND AS A SCREENING TOOL

The prevalence of NAFLD and NASH may be higher than previously predicted creating the need for an accurate, non-invasive, and easily available modality for the diagnosis of NAFLD in the asymptomatic patient[12,14]. When Williams *et al*[14] used ultrasound to screen asymptomatic individuals in the general population without known liver disease or significant alcohol use, they found non-alcoholic fatty liver disease to be more prevalent than previously reported. All individuals who had ultrasound findings suggestive of fatty liver had a liver biopsy to confirm their diagnosis. Using ultrasound as a screening tool, they found NASH and NAFLD to be present at 12.2% and 46% of the population, respectively.

Detection of NAFLD in potential living donor liver transplantation is an important part of the routine pre-transplant work-up[12]. During the evaluation of living donors, invasive procedures for healthy donors should be minimized. It is well-recognized that the diagnostic accuracy of ultrasound diminishes with less than 20% hepatic steatosis. Identification of living donor candidates with a higher degree of hepatic steatosis by ultrasound may allow them to forgo unnecessary liver biopsy needed for such assessment[15]. A study by Lee *et al*[12] evaluated 589 living donor candidates with ultrasound, CT scan, and liver biopsy. They found a higher incidence than previously reported. In their study, 51.4% living donor candidates has greater than 5% steatosis and 10.4% had greater than 30% steatosis. Ultrasound had a sensitivity of 92.3% when steatosis was greater than 30% when screening this population for a pre-transplant work-up.

In comparison to other non-invasive imaging techniques, ultrasound has comparable sensitivities, greater ease of use, availability, and lower cost in screening for moderate to severe degrees of NAFLD. Although other modalities such as dual-gradient echo magnetic resonance imaging (DGE-MRI) is more accurate with sensitivity and specificity greater than 90% when hepatic steatosis was greater than 5%, the difference between DGE-MRI's sen-

Table 1 Strength and weakness of ultrasound to diagnosis non-alcoholic fatty liver disease

Utility of ultrasound
  Non-invasive
  Ease of clinician use
  Ease of clinician interpretation
  Widely available
  Low cost
  Allows quick diagnosis
Limitations of ultrasound
  Cannot grade degree of fibrosis
  Limited use in pre-existing chronic liver disease
  Limited use in obese patients
  Low sensitivity when steatosis is less than 20%-30%

sitivity and ultrasound were statistically insignificant when steatosis was greater than 30%[1].

LIMITATIONS OF ULTRASOUND

Ultrasound is limited in its utility in several settings, as shown in Table 1. As previously mentioned, multiple studies have shown that ultrasound underestimates the prevalence of hepatic steatosis when less than 20% of steatosis is present. The sensitivity for detecting mild degrees of steatosis is low, ranging from 55%-90%[1,3,6,13,16,17]. Guajardo-Salinas *et al*[18] reported a low sensitivity in detecting all degrees of NASH in obese individuals (mean BMI 46-49) by ultrasound. In his retrospective chart review of ultrasound reports, the right upper quadrant ultrasound was an unreliable tool for screening fatty liver, with a sensitivity of 40%. In another study evaluating the diagnosis of NAFLD by ultrasound in obese patients undergoing bariatric surgery, de Moura Almeida *et al*[19] also found a low sensitivity of 64.9%. In this study, patients had an average BMI of 43.8. Low sensitivities in both these studies may be a result of the lack of clearly defined characteristic sonographic findings for the diagnosis of NAFLD. Nonetheless, severe obesity may also limit the ability to reliably detect liver echogenicity due to thick layers of subcutaneous fat[19,20].

When used in the setting of other chronic liver diseases, such as chronic hepatitis C, ultrasound had unacceptably low sensitivity and specificity in identifying hepatic steatosis[2,21]. Perez *et al*[21] revealed in their chronic hepatitis C patients that ultrasound had only a sensitivity of 32% for detecting fat on biopsy in these patients. These low sensitivities suggest that ultrasound should not be the only modality used in detecting co-existing NAFLD in patients with chronic hepatitis C.

Perhaps the most important limitation of using ultrasound alone is its inability to correlate with the degree of fibrosis[20]. Ultrasound scoring systems fall short of distinguishing between progressive NASH and benign steatosis. Studies have shown poor correlation between sonographic findings and the histological stage of fibrosis on biopsy[2,20]. Ballestri *et al*[22] developed the ultrasound fatty liver indicator (US-FLI), a scoring system based on

ultrasound findings that could predict the presence of steatosis. Although this score showed significant correlation with metabolic derangements, the US-FLI had poor performance in predicting the presence of NASH. Similarly, when Charatcharoenwitthaya and Lindor[23] evaluated various radiologic modalities in NASH, they found that neither ultrasound, CT scan, nor MRI were able to distinguish between NASH and other degrees of NAFLD. Other studies have also shown that ultrasound cannot be used to grade degrees of fibrosis and cannot replace needle biopsy in distinguishing simple steatosis from steatohepatitis[24,25].

DISCUSSION

Ultrasound represents a non-invasive, widely available, and accurate tool in the detection of NAFLD. Although there is limited data available to support the use of ultrasound as a screening tool, ultrasound can be a powerful tool in the setting of known liver abnormality. Ultrasound should be used as the first-line diagnostic test in patients with abnormal liver enzymes. Standardized, characteristic sonographic findings are able to reliably identify patients with NAFLD. Clinical risk factors, when used with ultrasound findings, have high utility in identifying NAFLD patients and initiating an early plan of care. In a study by Riley *et al*[26], the risk of advanced fibrosis was increased in patients with a BMI greater than 30 for over 15 years. In this clinical setting, with abnormal liver enzymes and ultrasound findings suggestive of NAFLD, these patients would benefit from a liver biopsy to identify the degree of fibrosis.

Bedside ultrasound can be incorporated into the training of clinicians and used in hepatology practices at outpatient visits. There is also potential use of ultrasound when screening liver donor candidates. Ultrasound can be used to exclude candidates with existing hepatic steatosis without putting them through liver biopsy. An early ultrasound and diagnosis will allow a potential liver donor candidate with hepatic steatosis to initiate early intervention and re-evaluation at a later date.

In conclusion, the bedside ultrasound is a powerful and useful diagnostic tool in the detection of NAFLD. It is an accurate and reliable method that can reduce the need for liver biopsy in the appropriate clinical setting. Clinicians should be aware of the known limitations when interpreting ultrasound, most importantly the inability to grade or stage degree of fibrosis in NAFLD patients. While bedside ultrasound cannot replace liver biopsy in monitoring the progression from simple steatosis to NASH, its accessibility, ease of use, and low-side effect profile make it an appealing diagnostic tool when used in the appropriate clinical setting. As the incidence of NAFLD continues to rise, we expect an increase in the use of bedside ultrasound by clinicians as it becomes integrated into the routine practices of gastroenterologists and hepatologists.

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