The utility of Xenon-133 liver scan in the diagnosis and management of nonalcoholic fatty liver disease


BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is an important and common condition affecting approximately 20% of the general population. Given the limitation of radiological investigations, diagnosis often requires a liver biopsy.

OBJECTIVE: To compare Xenon-133 (Xe-133) liver scanning with ultrasonography in the diagnosis of NAFLD.

METHODS: From January 2003 to February 2007, 258 consecutive patients with suspected NAFLD underwent Xe-133 liver scanning at Royal Victoria Hospital (Montreal, Quebec). Of these, 43 patients underwent ultrasonography and liver biopsy for the evaluation of NAFLD. Patients with other liver diseases and significant alcohol consumption were excluded. Two nuclear medicine physicians assessed liver Xe-133 uptake and measured the grade of steatosis using a standardized protocol. The degree of steatosis was determined from biopsy specimens assessed by two hepatopathologists.

RESULTS: NAFLD was identified by liver biopsy in 35 of 43 patients (81.4%). Xe-133 scan demonstrated 94.3% sensitivity (95% CI 81.4% to 98.4%) and 87.3% specificity (95% CI 52.9% to 99.4%) for the presence of NAFLD. The positive and negative predictive values for detection of steatosis by Xe-133 scan were 97.1% (95% CI 85.1% to 99.8%) and 77.8% (95% CI 45.3% to 93.7%), respectively. The positive and negative likelihood ratios were 7.54 (95% CI 1.20 to 47.26) and 0.07 (95% CI 0.02 to 0.26), respectively. Two patients with NAFLD (5.7%) who had a negative Xe-133 scan result had histologically mild steatosis (<10%). The grade of steatosis on liver biopsy was highly correlated with the results of the Xe-133 scan (r=0.87; P<0.001). The sensitivity and specificity of ultrasound in diagnosing steatosis were 62.9% and 75%, respectively.

CONCLUSION: Xe-133 liver scan proved to be a safe, reliable, non-invasive method for diagnosing and quantifying hepatic steatosis, and was superior to ultrasound.

Key Words: Nonalcoholic fatty liver disease; Ultrasonography; Xenon-133 liver scan

L’utilité de la scintigraphie hépatique au Xenon-133 pour le diagnostic et la prise en charge de la stéatose hépatique non alcoolique

HISTORIQUE: La stéatose hépatique non alcoolique (SHNA) est un trouble important et courant qui touche environ 20 % de l’ensemble de la population. Étant donné les limites des explorations radiologiques, il faut souvent procéder à une biopsie hépatique pour poser le diagnostic.

OBJECTIF: Comparer la scintigraphie hépatique au Xenon-133 (Xe-133) à l’échographie pour diagnostiquer une SHNA.

MÉTHODOLOGIE: De janvier 2003 à février 2007, 258 patients consécutifs atteints d’une SHNA présumée ont subi une scintigraphie hépatique au Xe-133 à l’Hôpital Royal Victoria de Montréal, au Québec. De ce nombre, 43 ont subi une échographie et une biopsie hépatique pour évaluer la SHNA. Les patients atteints d’autres maladies hépatiques et consommateurs d’alcool étaient exclus. Deux médecins spécialisés en médecine nucléaire ont évalué le captage du Xe-133 dans le foie et mesuré le niveau de stéatose au moyen d’un protocole standardisé. Deux hepatopathes ont évalué le degré de stéatose d’après les biopsies.

RÉSULTATS: La biopsie hépatique a permis de repérer une SHNA chez 35 des 43 patients (81,4 %). La scintigraphie au Xe-133 a démontré une sensibilité de 94,3 % (95 % IC 81,4 % à 98,4 %) et une spécificité de 87,5 % (95 % IC 52,9 % à 99,4 %) à l’égard de la présence de SHNA. Les valeurs prédictives positives et négatives relatives à la détection de stéatose par la scintigraphie au Xe-133 étaient de 97,1 % (95 % IC 85,1 % à 99,8 %) et de 77,8 % (95 % IC 45,3 % à 93,7 %), respectivement. Les rapports de vraisemblance positif et négatif étaient de 7,54 (95 % IC 1,20 à 47,26) et de 0,07 (95 % IC 0,02 à 0,26), respectivement. Deux patients atteints d’une SHNA (5,7 %) dont les résultats de la scintigraphie hépatique au Xe-133 étaient négatifs présentaient une stéatose bénigne sur le plan histologique (moins de 10 %). Le niveau de stéatose à la biopsie hépatique était fortement corrélé avec les résultats de la scintigraphie au Xe-133 (r=0,87; P<0,001). La sensibilité et la spécificité de l’échographie pour diagnostiquer la stéatose évoluaient à 62,9 % et à 75 %, respectivement.

CONCLUSION: La scintigraphie hépatique au Xe-133 s’est révélée une méthode sécuritaire, fiable et non effectrice pour diagnostiquer et quantifier la stéatose hépatique, et elle était supérieure à l’échographie.

Nonalcoholic fatty liver disease (NAFLD) is a common clinicopathological condition characterized by mild elevation of liver enzyme levels and significant fat deposition in the hepatocytes of a patient without a history of significant alcohol use (1). NAFLD refers to a wide spectrum of liver damage including simple steatosis, Nonalcoholic steatohepatitis (NASH), with or without cirrhosis (1-3), lies at the most severe end of the NAFLD continuum. NAFLD is the most common cause of chronic liver diseases in Western countries. NAFLD affects 10% to 39% of the general population in various countries. The prevalence increases to 57.5% (4) to 74% in obese individuals (5,6). NAFLD affects 2.6% of children (7) and 22.5% (7) to 52.8% (8) of obese children. Approximately 26% of adults in the United States are obese and, as this percentage continues to rise, the prevalence of NAFLD is expected to increase concomitantly (9).

NASH is a common explanation for abnormal liver test results in blood donors, and it is the cause of asymptomatic elevation of amino-transferase levels in up to 90% of cases once other causes of liver disease are excluded (10). It is the most common cause of abnormal liver test results among adults in the United States (11).

Recent studies have found that NASH is a strong predictor of cardiovascular disease and may play a central role in the cardiovascular risk of the metabolic syndrome (12).
Several studies have demonstrated that hepatic steatosis—i.e., NAFLD—does not progress to cirrhosis (2,9). On the other hand, nearly 20% of patients with NASH develop cirrhosis within five to 10 years (2,13,14), and more develop fibrosis slowly, with late-onset cirrhosis (2,14).

Pathological examination of liver specimens remains the gold standard for establishing a diagnosis of NAFLD (15), and is currently the only means of staging the disease and, thus, providing important prognostic information. Serial biopsies are also used to determine the effect of medical treatment (3,15).

Although considered to be the standard, liver biopsy is an invasive procedure associated with morbidity and, rarely, mortality (16). Many hepatologists are reluctant to perform a biopsy on asymptomatic patients. Because of its patchy nature, hepatic steatosis may be missed or underestimated at biopsy, and missing such a diagnosis would result in a delay in diagnosis (17). Furthermore, given the lack of effective medical treatment for patients with NAFLD, a liver biopsy may not be necessary to diagnose asymptomatic patients with clear risk factors (e.g., diabetes mellitus, hyperlipidemia and obesity) (2).

Therefore, it is necessary to develop a noninvasive method to quantify hepatic fat, and to determine how this method correlates with histological fat quantification and disease severity.

Ultrasonography often reveals a hyperechoic texture or a bright liver because of diffuse fatty infiltration (1). However, this is a nonspecific finding that cannot stage the disease, and should not be used to diagnose NAFLD. Other imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), are useful in demonstrating hepatic steatosis, at least when fat accumulation is moderate to severe (18-21). A recent study reported the overall sensitivity and specificity for ultrasound (US), CT and MRI in detecting pathologically confirmed fatty liver to be 56% and 82%, respectively (22). Another study showed that magnetic resonance spectroscopy can be used to measure hepatic triglyceride content and, thus, could quantify hepatic fat and grade hepatic steatosis (23,24). However, these tests may underestimate less-severe steatosis and cannot distinguish between simple steatosis and NASH. In addition, CT is associated with radiation exposure, and MRI is costly and not readily available for mass screening. Similar to US, focal fat infiltration may present diagnostic difficulties on CT (25,26).

Accordingly, there is a need to develop simple, inexpensive, reproducible, noninvasive and safe tests that can accurately diagnose and grade hepatic steatosis.

Xenon-133 (Xe-133) gas is highly fat-soluble and, therefore, concentrates in fatty tissues. Xe-133 has been used to detect lipid tumours in various parts of the body (27). Previous studies have demonstrated Xe-133 uptake by fatty liver (28-31). In fact, several investigators have quantified radioactive xenon uptake in fatty livers using either visual grading or hepatic retention ratio and correlated this with the amount of fat in hepatic cells (32-35). Xe-133 gas is inexpensive and safe, and is associated with a very low radiation risk (36).

Since early 2002, Xe-133 liver scanning has been routinely used at the Royal Victoria Hospital (Montreal, Quebec) for the evaluation of all patients with suspected NAFLD, and the institution is proficient in using this mode of liver scanning and interpreting the results. However, the usefulness of Xe-133 liver scan in the diagnosis and management of NAFLD has not been well studied. Accordingly, the present study was conducted to compare Xe-133 liver scan with US for the diagnosis of NAFLD.

METHODS

Patient selection

A review of the computerized nuclear medicine database for Xe-133 liver scanning revealed 258 consecutive patients who underwent a Xe-133 liver scan as part of their initial work up for NAFLD between January 2003 and February 2007. At the same time, all of these patients underwent ultrasonographic liver examinations. These patients were closely followed, and their baseline demographic information and prediagnosis history were recorded. Of these, 43 patients underwent liver biopsy after Xe-133 and US liver scans. All liver biopsies were interpreted by two experienced liver pathologists, with differences reconciled by consensus.

Approval to review the medical records and images was granted by the institutional review board.

The following criteria for patient enrollment were used:

1. Abnormal liver enzyme levels or clinical features suggestive of diffuse liver disease.
2. Documented history of minimal alcohol intake (<20 g/day).
3. Other causes of liver disease, such as chronic viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson disease, α1-antitrypsin deficiency, primary biliary cirrhosis and drug-induced liver disease, were excluded.

Extensive clinical and laboratory data including age, sex, body mass index (BMI) and history of diabetes mellitus or hyperlipidemia were recorded. The laboratory evaluations included a serum hepatic profile (aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, total protein and albumin levels, and international normalized ratio), serum glucose, lipid profile, viral serologies for hepatitis B and C, autoantibodies (antinuclear antibody, antismooth muscle antibody, antimitochondrial antibody), serum protein electrophoresis, iron profile ( ferritin, transferrin saturation), and ceruloplasmin and α1-antitrypsin levels.

BMI was calculated using the standard formula: weight (kg)/(height [m]²). Obesity was defined as a BMI ≥30 kg/m² for both men and women.

Liver US assessment

All patients underwent US examinations as part of their initial evaluation for NAFLD. The examinations were interpreted by one of two experienced US radiologists according to standard examination protocols. High-resolution US systems equipped with 3.5 MHz transducers were used for all patients.

The sonographic criteria for grading diffuse fatty infiltration of the liver were as follows: grade 0 (normal) — normal liver echo texture; grade 1 (mild) — slight, diffuse increase in fine echoes in hepatic parenchyma, normal visualization of diaphragm and intrahepatic vessel border; grade 2 (moderate) — moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm; grade 3 (severe) — marked increase in fine echoes with poor or nonvisualization of the intrahepatic vessel borders, diaphragm and posterior portion of the right lobe.

Xe-133 liver scan assessment

All Xe-133 scans were performed in the same nuclear laboratory and interpreted by two specialists with more than five years experience using this technique, and following a standard protocol.

Xe-133 liver scan was performed using a digital gamma camera (Maxxus F23, GE Healthcare, USA) linked to a minicomputer. The patients breathed a 155 MBq (5 mCi) of Xe-133 for 5 min from a closed-circuit rebreathing system—the equilibrium phase. The system was then opened to room air and patients began a 10 min washout phase. All counting data were acquired in frame mode (128×128 matrix) at 1 min per frame in the hepatic region, and both lung bases in anteroposterior view with the patient supine for 5 min during the equilibrium phase and at 3 min per frame for 10 min during the washout phase.

The assessment of the Xe-133 liver scan by the nuclear medicine specialist included qualitative assessment based on the visual grading, which is the visualization of hepatic uptake of the Xe-133 and quantitative assessment using hepatic xenon retention compared with the intensity of the lung at the end of the washout phase.

Hepatic steatosis was graded from 0 to 3: grade 0 corresponded to no radioactivity noted in hepatic area at any time, while grade 3 corresponded to radioactivity comparable with the greatest activity in the lung (Figures 1A to 1D).

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Indication for liver biopsy
All biopsies were performed following evaluation by US and Xe-133 scans of the liver. The indications were either for diagnosis of NAFLD/NASH in patients who continued to show abnormal liver tests despite lifestyle changes, or those whose initial workup was inconclusive. Pathological assessment was performed based on the grading and staging system developed by Brunt et al (37). The degree of fatty infiltration was assessed and graded based on the percentage of involved hepatocytes: mild (up to 33%); moderate (33% to 66%); and severe (>66%, as in Table 1). The grades and stages of NASH were assessed using the same protocol (37). Briefly, fibrosis was staged as follows: stage 0 – no fibrosis; stage 1 – zone 3 perisinusoidal fibrosis, focal or extensive; stage 2 – perisinusoidal fibrosis, focal or extensive, and periportal fibrosis, focal or extensive; stage 3 – bridging fibrosis, focal or extensive; and grade 4 – cirrhosis.

Statistical analysis
The sensitivity, specificity, positive and negative predictive values, likelihood ratios and accuracy of the Xe-133 and US liver scans for prediction of steatosis were calculated, with the assumption that the histological examination is the gold standard for diagnosis of hepatic steatosis. Pearson’s product-moment coefficients were calculated to determine the correlation of the grades of steatosis between histology and Xe-133 liver scan findings.

RESULTS
Clinical and demographic data for the 43 patients analyzed are presented in Table 1. A diagnosis of NAFLD was made in 35 of 43 patients (81.4%)

<table>
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<tr>
<th>Table 1</th>
<th>Demographic and clinical data of 43 patients who underwent liver biopsy, and Xenon-133 and ultrasound scans</th>
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<tr>
<td>Median age, years (range)</td>
<td>56 (36–80)</td>
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<tr>
<td>Male/female, n/n (% female)</td>
<td>28/15 (34.9)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (95% CI)</td>
<td>29 (23–45)</td>
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<tr>
<td>Diabetes, %</td>
<td>23</td>
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<th>Table 2</th>
<th>Xenon-133 liver scan versus liver biopsy in the diagnosis of steatosis (n=43)</th>
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<tr>
<td>Liver histology</td>
<td>Steatosis present</td>
</tr>
<tr>
<td>Any steatosis (n=43)</td>
<td>33</td>
</tr>
<tr>
<td>Steatosis &gt;33% (n=32)</td>
<td>32</td>
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<th>Table 3</th>
<th>Performance characteristics for the detection of steatosis on Xenon-133 liver scan (n=43) compared with liver biopsy</th>
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<tr>
<td>Liver</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>histology</td>
<td>Positive</td>
</tr>
<tr>
<td>Any steatosis (n=43)</td>
<td>94.3 (81.4–98.4)</td>
</tr>
<tr>
<td>Steatosis &gt;33% (n=32)</td>
<td>100 (92.3–100)</td>
</tr>
</tbody>
</table>

Data presented as % (95% CI) unless otherwise indicated.
Invasive positive test for fibrosis would be the most likely to benefit from a liver biopsy. This should be assessed in future studies. It is probable that individuals with an abnormal Xe-133 scan and non-invasive methods, such as tissue elastography or biochemical assays, for the assessment of fibrosis. It would be a limitation of our study. However, a previous report showed very high degree of intra- and inter-observer agreement on the severity of steatosis using the Xe-133 hepatic retention ratio method (34).

No studies have examined the degree of intra- and inter-observer agreement in the visual grading of Xe-133 retention at the end of the washout phase, which is the method used at our institution. This may be a limitation of our study. However, a previous report showed very high degree of intra- and inter-observer agreement on the severity of steatosis using the Xe-133 hepatic retention ratio method (34).

One major limitation of Xe-133 scan is that it only detects fat; therefore, it is not expected to distinguish between different subtypes of NAFLD, nor provide information about liver morphology. Therefore, combining Xe-133 scan with US is a useful, noninvasive method of establishing the diagnosis of NAFLD. Although it correlated well with the histological grade of NASH, it does not predict the stage of disease are excluded by clinical and laboratory evaluation, Xe-133 liver scan is inexpensive, simple, readily available, safe and a more accurate method of diagnosing hepatic steatosis compared with historically reported for these other two modalities (20). The present study showed that Xe-133 scanning could reliably rule in or rule out the presence of moderate to severe hepatic steatosis. Despite this, and compared with other imaging modalities, Xe-133 scan was more accurate in diagnosing mild grades of steatosis.

Because the majority of NAFLD patients are obese, the accuracy of US and noncontrast-enhanced CT in diagnosing steatosis was significantly worse with increasing BMI (20,36). In the present study, Xe-133 scan was able to detect steatosis in this population with high accuracy. In addition, all patients with steatosis and advanced fibrosis (stage 3 to 4) had a positive Xe-133 scan, unlike US, in which steatosis and fibrosis can have similar appearance (38-41). No studies have examined the degree of intra- and inter-observer agreement in the visual grading of Xe-133 retention at the end of the washout phase, which is the method used at our institution. This may be a limitation of our study. However, a previous report showed very high degree of intra- and inter-observer agreement on the severity of steatosis using the Xe-133 hepatic retention ratio method (34).

One major limitation of Xe-133 scan is that it only detects fat; therefore, it is not expected to distinguish between different subtypes of NAFLD, nor provide information about liver morphology. Therefore, combining Xe-133 scan with US is a useful, noninvasive method of establishing the diagnosis of NAFLD. Although it correlated well with the histological grade of NASH, it does not predict the stage well. It may be useful to assess how it performs when combined with either US or perhaps with newer noninvasive methods, such as tissue elastography or biochemical assays for the assessment of fibrosis. It is probable that individuals with an abnormal Xe-133 scan and non-invasive positive test for fibrosis would be the most likely to benefit from a liver biopsy. This should be assessed in future studies.

**SUMMARY**

Xe-133 liver scan is inexpensive, simple, readily available, safe and a more accurate method of diagnosing hepatic steatosis compared with other imaging modalities. The value of a liver biopsy for the diagnosis of NAFLD in routine clinical practice remains controversial, especially in the presence of a generally good prognosis for most patients with NAFLD, the lack of an established form of effective therapy, and the risks and costs associated with the biopsy. Therefore, once ongoing alcohol use (≥20g/day to 30 g/day) and other common causes of liver disease are excluded by clinical and laboratory evaluation, Xe-133 scan with ultrasound scan may be a useful noninvasive way to establish a diagnosis of NAFLD.

**DISCLOSURE:** The authors have no financial disclosures or conflicts of interest to declare.
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