Emerging Imaging Techniques in Hepatic Steatosis

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Disclosures- Conflict of Interests

• Nothing to disclose
Background and Significance

- Nonalcoholic fatty liver disease (NAFLD) is an important public health concern and a risk factor for cardiac disease, diabetes and cancer.
- Though patients with hepatic steatosis can be asymptomatic for years, a subset will progress to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatoma.
- NAFLD includes a spectrum of histopathological changes ranging from simple steatosis to NASH to cirrhosis.
- Liver biopsy is considered a gold standard, however, ultrasound, CT and MR can be used to diagnose NAFLD noninvasively.
- Other diffuse hepatocellular diseases such as Hepatitis C, hemochromatosis, A1-antitrypsin can confound imaging findings.
- Emerging quantitative assessment methods such as elastography and MR appear promising, however prospective studies are warranted for validation.
Learning Objectives

• Prevalence and histopathologic activity scores of NAFLD
• Understand typical, atypical findings and differential diagnosis of NAFLD on ultrasound, CT and MR
• Learn emerging quantitative assessment methods such as MR and elastography
NAFLD in USA

The number of overweight or obese increased from 857 million in 1980 to 2.1 billion in 2013 (30% world’s population) Lancet, May 28, 2014

In severely obese: prevalence of steatosis 91% and NASH 37% J Hepatol 2006:45;600-606
Diabetes, Obesity, Cardiovascular disease (CVD) and Cancer are common diseases with tremendous impact on health worldwide. Epidemiologic evidence suggests that these diseases share many risk factors.

Radiology 2012, 264, 21-37
Radiology 2016, 279, 443-457

Diagram of the comparison of the various staging systems for liver fibrosis. Stars represent periportal fibrosis, lines represent bridging fibrosis, and circles represent nodularity. This chart shows the four stages of the METAVIR system, the six stages of the Ishak system, and the four stages of the Batts-Ludwig (Batts-L.) system. Note how each system has one “extra” stage 0 that describes a normal liver. While each stage ends with a stage 4 or 6 cirrhotic nodular liver, the actual descriptions of the stages between normal liver and cirrhosis differ. The Ishak system discriminates between early (stage 5) cirrhosis and established or advanced cirrhosis (stage 6), which differ in prognosis and incidence of clinical events. Four-stage (five if including normal liver) systems such as METAVIR and Batts-Ludwig do not take into account the fibrosis spectrum of a cirrhotic liver.
Typical Imaging Findings of NAFLD

- **US:** Increased echogenicity with obscured hepatic vasculature and deeper parenchyma and diaphragm in severe cases
- **CT:** Large areas of geographic decrease in attenuation (< 40 HU) best appreciated on unenhanced scan
- **MR:** Drop of signal on out-of-phase imaging
- Emerging quantitative assessment methods such as MRS (MR spectroscopy) and MRE (MR elastography) or US elastography are not yet used in routine clinical practice

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Typical Findings of Steatosis on US and CT

35-yr old woman with BMI of 30, hypertension and hyperlipidemia. She was noted to have ALT elevation. US images (a & b) show increased echogenicity of liver parenchyma obscuring details and suboptimal visualization of deeper anatomy including diaphragm. Axial CT images (c & d) demonstrate geographic low attenuation of liver parenchyma with subtle ill-defined areas of relative fat sparing. Subjects with significant steatosis > 33% are not considered eligible for liver donation.
38 yr-old diabetic woman with BMI of 34, presented RUQ pain, to r/o GB ds. Ultrasound images (a & b) show focal hypoechoic areas adjacent to gallbladder manifesting as relatively hyperattenuating foci on CT axial (c) and coronal (d) views. These are consistent with focal fatty sparing which is typical around the gallbladder. Background liver shows diffuse steatosis. Note excessive subcutaneous fat. It is important to recognize this common pattern of fatty sparing to avoid pitfall.
Nonalcoholic Fatty Liver Disease (NAFLD)

37-year-old woman with diabetes, hypertension and hyperlipidemia (BMI 32). Coronal CT images (A&B) and axial image (C) show enlarged liver with diffuse decrease in attenuation (mean HU 30) and focal areas for fat deposition (arrows) adjacent to gall bladder which shows signal drop on out-of-phase MR image (D). Ultrasound image (E) shows increased echogenicity with posterior sound attenuation (arrow) and obscured diaphragm (arrowhead). Ultrasound is often used for screening for NAFLD however there is better inter-reader reproducibility with CT or MR
Steatosis and Focal Fat Sparing

Axial CT image (a) and US images (b & c) demonstrate focal fat sparing around the gallbladder, which is a common pattern. Axial CT image (d) shows nodular areas of fatty sparing mimicking apparently enhancing lesions, however a CT KUB from two years prior showed similar hyperattenuating areas with similar HU. In both cases the background liver shows diffuse steatosis. Unenhanced CT is cost-effective and more diagnostic in such a scenario. Hepatic steatosis or NAFLD is interpreted as homogeneous when greater than 90% of the liver is assigned to one steatosis grade. Heterogeneous involvement by NAFLD is not uncommon. In one study, involvement by steatosis was heterogeneous in 52% and homogeneous in 48% of subjects (Radiology 2012;264:88-96)
Atypical Imaging Findings of NAFLD

- An area of unusual focal fat sparing or focal fat mimicking a tumor
- Perivascular fat
- NAFLD associated with other focal mass or diffuse liver disease
Atypical Presentation of Steatosis

Ultrasound images from 2010 (a) & 2014 (b) show stable perivascular echogenicity consistent with perivascular steatosis. Axial CT (c) and MR (d) images confirm perivascular distribution of fat.

Axial (a) and sagittal (b) CT images and axial MR images (c-e) demonstrate fatty mass in caudate consistent with focal fat.
Focal fat in a 23 yr-old woman. Had multiple follow-up CT and US

Gray-scale and color doppler (a-c) US images demonstrate a subcapsular focal echogenic area through which the vessels run uninterrupted. Corresponding coronal CT image (d) shows a nonenhancing fat density area confirming focal fat. Inspite of these findings and patient’s young age many follow-up CT and one MR (not shown) were obtained over 3-yr period given somewhat unusual appearance (cost, radiation)
40-yr-old woman with poorly controlled diabetes, diagnosed as NASH at age 31 (images a-g). Axial CT images acquired during arterial (A), portal venous (B) and 3 minute delayed phase (C) demonstrate enlarged, nodular lobulated liver with heterogeneous enhancement. Enhancing nodule (A, arrow) without corresponding washout was biopsied and proven to be a regenerating nodule. Many other hypodense nodules (arrows) become apparent on delayed phases. Axial MR images acquired during arterial (D), portal venous (E) phase demonstrate findings similar to CT. Heterogeneous activity with SUV ranging from 1.72 to 5.4 is seen on axial fused PET CT image (F). Transverse ultrasound image (G) shows echogenic and heterogeneous liver parenchyma with partially obscured deeper structures including diaphragm.
42-yr old man with diabetes and known NAFLD. Coronal CT images during hepatic arterial, portal venous and delayed phases, show cirrhotic liver with nodular contours and heterogeneous enhancement. Relatively focal hypoattenuating nodules were stable over 3 years. Imaging findings of NASH overlap those of cirrhosis from other etiologies requiring integration of clinical and histopathological findings for a specific etiology.
NAFLD/NASH and Focal Hepatic Nodules

43-yr old woman with NASH and BMI of 30. US image (a) shows enlarged lobulated echogenic liver with a hypoechoic nodule and prominent internal vessel on color doppler. Axial CT (b) and MR (c) images confirm an enhancing nodule during arterial phase. While any enhancing nodule raises a cancer for HCC in cirrhotic liver, the nodule in this patient was proven to be FNH

27-yr old woman with steatosis and hemangiomas. Small homogeneously enhancing nodules following blood pool are shown on axial CT images (d, e). Background liver is fatty. These were relatively hypoechoic on US (not shown), therefore further characterization with MR was obtained using Eovist. It is important to note that findings for hemangioma may be atypical on US when superimposed on diffuse steatosis
Implications for Liver Transplant

- Organ shortage, lab/psychosocial issues, vascular, biliary anatomic variations, inadequate remnant liver volumes (<30%), abnormal histologic findings such as steatosis, fibrosis were main reasons for exclusion from donation

- NAFLD on bx in 51.4% among potential Korean donors (J Hepatol 2007;47:239-244). Clinically significant steatosis of at least 10% (previously 5%) and fibrosis score of at least F1
# Effect of Bariatric Surgery on NASH

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Baseline Wt./BMI</th>
<th>Surgery</th>
<th>Follow-up</th>
<th>Change in Wt./BMI</th>
<th>Effect on NASH (score)</th>
</tr>
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<tbody>
<tr>
<td>Dixon (30)</td>
<td>45.9 kg/m²</td>
<td>LAGB</td>
<td>29.5 months</td>
<td>31.5 kg</td>
<td>NASH 80% resolved (AASLD score)</td>
</tr>
<tr>
<td>de Almeida (16)</td>
<td>53.4 kg/m²</td>
<td>RYGBP</td>
<td>23.5 months</td>
<td>22.3 kg/m²</td>
<td>Complete regression lobular inflammation and Mallory bodies (Brunt criteria)</td>
</tr>
<tr>
<td>Barker (19)</td>
<td>47 kg/m²</td>
<td>RYGBP</td>
<td>21.4 months</td>
<td>52.4 kg</td>
<td>89% (17/19) resolved NASH (Dixon scoring)</td>
</tr>
<tr>
<td>Mattar (70)</td>
<td>56 kg/m²</td>
<td>RYGBP (41) LSG (23) LAGB (6)</td>
<td>15 months</td>
<td>103 lb</td>
<td>80% improved steatosis 37% resolved steatosis and inflammation 20% resolved fibrosis (Brunt)</td>
</tr>
<tr>
<td>Klein (7)</td>
<td>58 kg/m²</td>
<td>RYGBP</td>
<td>1 yr</td>
<td>45 kg</td>
<td>100% improved steatosis, no change in inflammation and fibrosis (Kleiner)</td>
</tr>
<tr>
<td>Mathurin (50)</td>
<td>47.1 kg/m²</td>
<td>Biliointestinal bypass, LAGB</td>
<td>1 yr</td>
<td>27 kg</td>
<td>75% resolved NASH (Brunt), fibrosis Increased</td>
</tr>
<tr>
<td>Mottin (90)</td>
<td>Not specified</td>
<td>RYGBP</td>
<td>1 yr</td>
<td>46.7 kg/m²</td>
<td>54.4% resolved, 27.8% improved steatosis</td>
</tr>
<tr>
<td>Clark (16)</td>
<td>51 kg/m²</td>
<td>RYGBP</td>
<td>305 days</td>
<td>118 lb</td>
<td>81% resolved (Brunt), 80% improved inflammation (12/15), 94% improved steatosis (15/16)</td>
</tr>
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LAGB = laparoscopic adjustable gastric banding; RYGBP = Roux-en-Y gastric bypass; LSG = sleeve gastrectomy.
Quantitative Assessment of NAFLD: Work-in-progress

Radiomics: Images Are More than Pictures, They Are Data

US Elastography and gray-scale ultrasound images of liver demonstrate normal (A), mild, 5-33% (B), moderate, 34-66% (C) and severe, >66% steatosis and corresponding increase in stiffness (given scores of 1, 2, 3 and 4) by elastography

The consistency of two methods was tested by κ and the κ value was 0.87 ($P = 0.001$)


Quantitative MR: MRI and MRS delineate both large and small droplets of fat in hepatocytes (small droplets not seen on standard histology). MR may underestimate fat in NASH due to fibrosis. Many MR signal confounders however: T1, T2* of water and fat
(a) FF map and (b) MR elastogram in a 51-year-old woman who donated the right lobe of her liver. At excisional liver biopsy, the liver demonstrated 2% macrovesicular fat and no evidence of hepatic fibrosis. The FF map (a) showed that the FF was 2.1%, and the LS value was 1.3 kPa on the elastogram (b), suggesting normal liver parenchyma without substantial fat infiltration.


Emerging data in mice shows an inverse linear relationship between CT HU (45) and MRS for FF (Invest Radiol 2012;47:603-610)
## Comparison of Elastography Modalities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TE</th>
<th>pSWE</th>
<th>2D SWE</th>
<th>MR Elastography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Point of care for clinician, technique well defined, rapid learning curve, repeatable, presently not recommended for spleen measurements</td>
<td>Can be an independent procedure or an add-on during liver US, direct visualization of liver region being insonated, quantitatively possibly less variability than 2D SWE, can be used to assess the spleen</td>
<td>Can be an add-on during liver US, direct visualization of the liver region being insonated, color display of a larger field of view, can be used to assess the spleen</td>
<td>Closest correlation to adequate liver biopsy, large sample of liver allows for assessment of spatial pattern of disease, no depth dependence of measurement, can be used to assess the spleen, can be performed in patients with obesity or ascites, cross-vendor standardization</td>
</tr>
<tr>
<td>Expense</td>
<td>Inexpensive</td>
<td>Inexpensive</td>
<td>Inexpensive</td>
<td>Expensive, unless performed as a limited MR elastography—only examination</td>
</tr>
<tr>
<td>Frequency for shear wave generation</td>
<td>40–50 Hz (&quot;S,&quot; &quot;M,&quot; &quot;XL&quot; probe dependent)</td>
<td>100–500 Hz</td>
<td>100–500 Hz</td>
<td>60-Hz standard, other frequencies possible.</td>
</tr>
<tr>
<td>Limitations</td>
<td>Needs dedicated machine, probe needs recalibration every 6–12 months depending on probe, failures due to ascites and obesity (obesity failures may be overcome with the use of extra-large probe), no grayscale image of liver (A-mode images are available), lower performance compared with ARFI techniques (36,55,56,57)</td>
<td>Less published material than TE owing to shorter time in use</td>
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<td>Failures due to iron overload (newer sequences will reduce these), failures due to claustrophobia, not as widely available as TE, higher charges for examination</td>
</tr>
<tr>
<td>Measurement location</td>
<td>Right intercostal space (dullest area of percussion)</td>
<td>Most often segment VII or VIII</td>
<td>Most often segment VII or VIII</td>
<td>Right lobe of the liver in four sections</td>
</tr>
<tr>
<td>Region of interest (ROI size)</td>
<td>About 4 cm³</td>
<td>About 0.5–1.0 cm³</td>
<td>About 20 cm³</td>
<td>About 250 cm³</td>
</tr>
<tr>
<td>Value reported</td>
<td>Median of 10 measurements, check IQR/median value &lt; 0.3</td>
<td>Median of 10 measurements*, check IQR/median value &lt; 0.3 if the stiffness value is &gt; 1.5 m/sec (7.1 kPa)</td>
<td>Median of 10 measurements*, check IQR/median value &lt; 0.3 if the stiffness value is &gt; 1.5 m/sec (7.1 kPa)</td>
<td>Mean or median of ROI measurements in four sections</td>
</tr>
<tr>
<td>Defining a good measurement</td>
<td>Machine does not report value if inadequate</td>
<td>Not &quot;x.xx&quot; or &quot;0.00&quot;</td>
<td>ROI area not colored</td>
<td>Confidence map shows areas that are above a threshold</td>
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</table>
pSWE image in a 59-year-old woman with a history of hepatitis C. Note the white box that is the ROI where the measurement is obtained. Image demonstrates one of the 10 measurements obtained in the same location. The median stiffness measure is 2.38 m/sec, consistent with cirrhosis. Diagnosis of METAVIR stage F4 was confirmed at liver biopsy.

Technical failure rate 16% compared to 6% for MRE
A 2D SWE image in a 48-year-old woman who had abnormal liver function tests at presentation. Note the split-screen image with the rectangular box, which is the field of view where shear wave measurements are obtained and color coded. The round circle is the ROI where the measurement is obtained. The system provides the maximum, median, minimum, and standard deviation of the stiffness measurements within the ROI. In this case, the mean value is 59 kPa.

Report: **low** (< 1.37m/s) risk for having clinically significant fibrosis (stage F0 or F1, no follow-up required, **moderate** risk (F2 or some F3, additional testing appropriate), or **high risk** (> 2.2m/s) (F3, F4, follow-up advised)
MR elastograms in three patients. A, MR elastogram in a 63-year-old woman with a history of autoimmune hepatitis shows that the liver (outlined) has no evidence of hepatic fibrosis, with a normal stiffness value of approximately 2 kPa. B, MR elastogram in a 52-year-old woman with chronic cholestatic hepatitis demonstrates increased hepatic stiffness with approximately twice the normal value at 4 kPa, indicating the presence of significant hepatic fibrosis. C, MR elastogram in a 46-year-old man with chronic hepatitis C infection demonstrates markedly increased hepatic stiffness, averaging over 6 kPa, as is consistent with the presence of advanced hepatic fibrosis (cirrhosis).
Usefulness of MRE in longitudinal clinical follow-up of liver fibrosis. A case of primary biliary cirrhosis shows progressively increasing liver stiffness on annual follow-up over a 2-year period. Note that there are no changes in liver surface contour or gross architecture.
MRE of a liver transplant. (A) Contrast-enhanced axial image, (B) wave image, and (C) stiffness map showing normal stiffness of the transplant, ruling out significant fibrosis.

Emerging computational algorithms - machine learning (type of AI that allows computers to learn without being explicitly programmed) for semiautomated volumetry and fat percentage
Summary

- NAFLD is an important public health concern
- NAFLD includes a spectrum of histopathological changes ranging from simple steatosis to NASH to cirrhosis
- Liver biopsy is considered a gold standard, however, ultrasound, CT and MR can be used to diagnose and follow-up NAFLD noninvasively
- It is important to recognize typical and atypical imaging findings of NAFLD
- Emerging quantitative assessment methods such as elastography and MR appear promising, however prospective studies are warranted for validation
• Thank you!