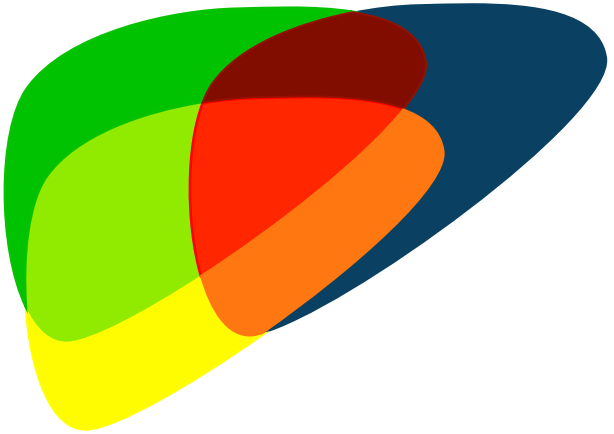
Noninvasive Diagnosis of NAFLD



Humaira Chaudhry, MD
Chair and Chief of Service
Associate Professor, Diagnostic Radiology
Rutgers New Jersey Medical School

RUTGERS
New Jersey Medical School

Outline

- Review of NAFLD
- US
- CT
- MR

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NAFLD

- Most common chronic liver disease worldwide
- Affects approximately 25% of the population
- Most patients remain asymptomatic, but 3-5% of Americans develop inflammatory component (i.e. NASH)

NAFLD

- Simple steatosis → NASH
- Liver disease can involve fatty deposition, fibrosis, inflammation, or a combination of these
- Increased overall mortality than the general population
  - cardiovascular complications leading cause of death
  - metabolic
  - liver-related causes
- cardiovascular risk amongst NAFLD patients correlates with steatosis severity
- NAFLD with advanced stage fibrosis or NASH also have increased liver-related morbidity and mortality
  - higher risk of progression to cirrhosis and cirrhosis-related liver transplantation
- changes in liver steatosis may also impact NAFLD progression
  - steatosis severity correlates with the risk of fibrotic progression in NAFLD
  - regression in NASH and reduction in steatosis severity is associated with improvement in NASH

NAFLD

- Hepatic steatosis can progress to NASH, fibrosis, cirrhosis, and HCC
- Early detection and treatment can halt or even reverse NAFLD progression
- Patients with NAFLD who have combination of inflammatory changes and fibrosis have the poorest outcome

NAFLD Risk Factors

- Dyslipidemia
- Type 2 DM
- Obesity
- Age
- Genetics
- Diet
- Smoking
- Air pollution
- Gut microbiome

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NASH

Diagnosis of NAFLD

- Biopsy remains reference standard for diagnosis and grading
- Can evaluate features of NASH currently not detectable on imaging
  - specific patterns of inflammation
  - hepatocyte injury seen
- Histological steatosis graded on a semi-quantitative scale based on the number of hepatocytes containing microscopically discernible cytoplasmic fat droplets:
  - 0 (<5% hepatocytes)
  - 1 (5–33% hepatocytes)
  - 2 (33–66% hepatocytes)
  - 3 (>66% hepatocytes).
- Shortcomings of biopsy:
  - Observer dependent
  - Costly
  - Invasive – risk of morbidity and mortality
  - Inappropriate for screening
  - Relatively small core size of biopsy also introduces sampling errors, especially as steatosis is known to be heterogeneous

Liver biopsy is a suboptimal tool for screening, monitoring, and research.

Diagnosis of NAFLD

- Imaging
  - US
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  - CT

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Ultrasound

- Wide range of ultrasound parameters for the diagnosis of NAFLD
  - qualitative assessment of echogenicity
  - hepatorenal index
  - attenuation coefficient
  - backscatter coefficient
  - sound speed estimation
  - transient elastography
  - shear-wave elastography
- For detection of fibrosis, US elastography is a capable option, but additional laboratory evaluation is needed to identify the inflammatory component

Ultrasound

- Normal liver parenchyma is the same as or slightly more echogenic than the adjacent kidney and spleen.
- Ultrasound beam scattering by lipid droplets in steatosis causes more echo signals to return to the transducer, creating the appearance of a "bright" or hyperechoic liver.
- Fat also attenuates the beam which decreases beam penetration into tissue.
  - Attenuation leads to poor visualization of structures within the steatotic liver parenchyma such as intrahepatic vessels, bile ducts and liver lesions.
- Remains relatively insensitive to detection of mild steatosis.
- Sensitivity and specificity of ultrasound at detecting moderate to severe steatosis, using histology as reference standard, are 80–89% and 87–90%, respectively.
  - Sensitivity and specificity drops to 65 and 81%, respectively, when all grades of steatosis are considered moderate to severe steatosis, using histology

Ultrasound

- Advantages
  - Safety
  - wide availability
  - little associated patient discomfort
  - Cost
    - abdominal ultrasound is low compared to CT or MR
  - Unlike CT and MRI, liver iron has little effect on the ultrasound beam.

Ultrasound

- Disadvantages
  - Large body habitus ->steatosis may be overestimated due to beam attenuation by overlying fat rather than liver fat.
  - Echogenicity of the liver may be confounded by fibrosis, inflammation, and other features of chronic liver disease.
    - Fibrosis and fat can superficially resemble each other by causing coarsening of the echotexture and increased echogenicity of the liver.
    - In the setting of chronic liver disease, it may be difficult to ascertain the extent that hyperechogenicity is attributable to steatosis, fibrosis, or both.

Ultrasound

- Disadvantages cont'd.
  - Imprecise qualitative classifications of mild, moderate, and severe steatosis.
  - Conventional ultrasound is operator- and reader-dependent → variable results and reproducibility.
  - Liver steatosis can be diffuse, focal or mixed
    - ultrasound may not visualize the entire liver due to shadowing from ribs, gas, and other patient factors
  - Ultrasound measurements are indirect indices of fat
    - values depend on calibration and acquisition parameters
    - variations between manufacturers, machines and operators that confound interpretation of results

Ultrasound

- Ultrasound is appropriate as an initial screen for steatosis.
- A diagnostic test such as CT, MRI or biopsy may be considered as a next step to differentiate between disease states (fibrosis and fat) and to accurately quantify severity.

US Elastography

- Liver fibrosis stage in NAFLD associated with disease-specific mortality, liver-related outcomes, and transplantation.
  - Exponential increase in the risk of liver-related mortality with increasing fibrosis stage.
  - Advanced liver fibrosis stage associated with extrahepatic malignancies and vascular events.
- Quantifying liver fibrosis in patients with NAFLD to determine prognosis and guide treatment decisions is an important part of the clinical workup.

- Liver stiffness measurement is a promising surrogate biomarker of liver fibrosis stage
  - transient elastography (TE)
  - ultrasound-based 2D shear wave elastography (2D SWE)
- For patients with biopsy-proven NAFLD, TE and 2D SWE exhibited comparable and very good to excellent diagnostic accuracy for advanced fibrosis and comparable but lower accuracy for significant fibrosis.

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CT

- Attenuation is a relevant factor in determining final image brightness on CT
- CT images generated by X-ray photons traversing tissues and exposing a detector opposite the beam
- The denser the tissue, the more attenuated the X-ray is and the brighter the corresponding image pixel

CT

- CT scanners calibrated to yield pixel value measurements relative to water using a unit of measurement known as the Hounsfield Unit (HU)
  - Water is defined as 0 HU
  - air is defined as −1000 HU
- Unenhanced CT → normal liver parenchyma is about 60 HU and hyperattenuates relative to the spleen
  - With increased steatosis, the liver tissue becomes hypoattenuating relative to the adjacent fat-free spleen
  - In severe steatosis, the normally hypoattenuating intrahepatic vessels may appear bright relative to the steatotic liver and mimic the effect of contrast enhancement

CT

- Absolute liver HU less than 40 or liver-minus-spleen difference of less than −10 HU have been used to diagnose steatosis
  - sensitivity and specificity ranging 46–72% and 88–95%
- Retrospective evaluations of steatosis at unenhanced CT have established absolute liver HU less than 48 as highly specific for moderate to severe steatosis
- Like ultrasound, the diagnostic performance of CT decreases with lesser severity of steatosis.

CT

- Contrast enhanced CT
  - liver-minus-spleen difference of less than or equal to 19 HU has been found to diagnose moderate to severe steatosis with modest sensitivity and high specificity on portal venous phase post-contrast
  - contrast-enhanced CT is generally not used for clinical assessment of steatosis due to the overlap in HU between normal and abnormal liver tissues and to the HU dependence on scan delay and contrast protocol.

CT

- Advantages
  - fast acquisition
  - ease of performance
  - straightforward analysis
  - quantitative results.

CT

- Disadvantages
  - CT cannot accurately diagnose mild steatosis
  - CT uses tissue density as an indirect index of steatosis and relies on calibration which is known to vary between scanners, manufacturers, and reconstruction algorithms
  - X-ray beam attenuation is not specific for steatosis.
    - Liver density is influenced by the presence of materials such as iron, glycogen and less well-understood factors including hematocrit, copper and other metallic ions. All of these can alter X-ray beam attenuation.
    - The spleen is an imperfect reference standard as it can be affected by hemosiderosis and haemochromatosis
  - Ionizing radiation
  - Most CT examinations performed for clinical care are performed following intravenous contrast injection.
    - Quantification of steatosis on conventional post-contrast images involves specific contrast protocols and imaging delay which limits its utility as a standard metric.

CT

- Due to exposure to ionizig radiation and low sensitivity for mild steatosis, CT is not recommended as a primary modality for measuring liver steatosis.
- If CT is done for other purposes, then radiologists can assess for steatosis using conservative thresholds.
- Widespread availability and quantitative metric of CT make it potentially useful for identifying patients with steatosis in retrospective studies

CT Future Directions

- Dual energy CT (DECT) has promise in separating the fat component from water and in reconstructing virtual unenhanced CT images.
  - Exploits the observation that different tissues have characteristic attenuation profiles across a range of photon energies
  - Most tissues exhibit decreased attenuation as the incident photon energies increase
  - In contrast, fat preferentially attenuates high-energy photon over low-energy photons for the photon range used in conventional CT imaging.
  - DECT uses the characteristic attenuation profiles of different tissues, including fat, to decompose images specific for different material composition
    - "fat maps" may be recreated from a study done at different energy levels.
  - Characteristic attenuation profile of iodinated contrast may be utilized to "subtract" contrast enhancement from studies and create virtual unenhanced images

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MR

- MRI is considered the most sensitive and specific technique for assessing steatosis.
- Unlike ultrasound and CT, which measure steatosis by proxy, MRI measures the signal intensity of protons at different resonance frequencies.
  - Water resonates at a single frequency, while triglycerides in steatosis exhibits more complex behavior
  - MRI exploits the difference in proton resonance frequencies of water and triglycerides by acquiring images at echo times at which water and triglycerides are nominally in and out of phase

MR

- Hepatic steatosis assessment on MRI has evolved from early methods that only gave qualitative estimates (i.e. dual echo chemical shift imaging) to more advanced and fully quantitative methods
- Accurate and precise steatosis measurement
- Proton Density Fat Fraction (PDFF)
  - (liver fat signal)/(total signal)
- Prior studies in children and adults with known or suspected NAFLD have shown that MRI-PDFF have high intra- and interexam repeatability across scanners and magnets.

MR

- Advantages
  - MRI measures the PDFF → fundamental property of tissue and requires no internal calibration or reference standard
  - Advanced sequences can address biological confounders such as iron overload by simultaneously measuring and correcting for R2*
  - Can be acquired quickly

MR

- Disadvantages
  - Areas of motion and parallel image artifact negatively impact measurement accuracy. These regions need to be identified and avoided when placing ROIs.
  - Magnitude data-based MRI does not readily differentiate fat fraction greater than 50% from fat fraction less than 50%.
    - Though rare, human liver fat fraction does occasionally exceed 50%.
  - Limited ability of current MRI techniques for R2* correction.
    - In cases of extreme iron overload, the signal loss may be so fast that it is not feasible to measure the oscillation
    - Limited knowledge about proton pool variability between patients and within patients over time.

MR

- Disadvantages cont'd
  - Availability
    - Software packages capable of processing PDFF maps may not be readily available due to budgetary and hardware constraints in some imaging facilities.
    - Commercially available on new MR platforms
  - Claustrophobia, implanted devices, and discomfort of MR
  - Cost

MR

- If a PDFF technique is available, it should be the method of choice in all patients for whom assessment of liver steatosis is clinically requested.

Summary

	Advantages	Disadvantages	Recommendations
Ultrasound	Safe Widely available Low cost	Indirect measurement Qualitative Operator and calibration dependent Inaccurate for mild steatosis Inaccurate steatosis grading Confounders: obesity, fibrosis Imprecise localization	Clinical care: initial screen Clinical trials: do not recommend
CT	Fast acquisition Easy to perform Straightforward analysis Quantitative	Indirect measurement Variable calibration Inaccurate for mild steatosis Confounders: iron, glycogen Ionising radiation Requires standard acquisition if contrast-enhanced	Clinical care: retrospective with conservative thresholds Clinical trials: do not recommend
MRI-PDFF	Direct measurement Precise fat quantification Highly sensitive and specific Corrects for confounders Fast acquisition	Relatively limited access Claustrophobia Implantable devices	Clinical care: study of choice (if available) Clinical trials: study of choice (if available)

References

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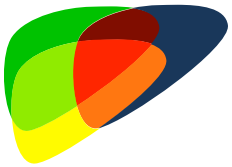

Thank you!

chaudhhu@njms.rutgers.edu