X-ray Corner

Imaging of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is defined by liver biopsy finding of macrovesicular fat with an absence of alcoholic intake (<20 gm or 2 drinks/day), or chronic hepatitis B, and C[1]. Spectrum of NAFLD includes hepatic steatosis, nonalcoholic steatohepatitis (NASH), chronic fibrosis, and cirrhosis.

NAFLD is strongly associated with obesity and diabetes type 2. Approximately 70-80% of obese people will have hepatic steatosis, and 15-30% will have NASH[2]. In the USA, the estimation is that by the year 2025, 50% of adults will become obese (BMI >30 kg/m^2), and more than 25 million people will develop NASH[3]. If the prediction is true, NASH will become the most common cause of chronic liver disease. Approximately 10% of obese people will develop cirrhosis[4] and patients with diabetes type 2 will die from cirrhosis twice as highs as normal population[5].

Natural history of NAFLD is not yet clearly understood. It is thought that only a small portion of fatty liver will progressed to NASH and most cases of NASH is developed de novo. About 40% of NASH will progress to fibrosis, but most will not show clinical or biochemical deterioration[6]. Only 3-10% of these patients will eventually become cirrhosis[7]. Thus, NASH is relatively benign compared to alcoholic steatohepatitis. NASH patient's 10-year-survival is about 60%, whereas that of alcoholic hepatitis is about 15%[6]. Pathogenesis of NASH is currently proposed by "2-hit" theory. The first hit is insulin resistance, which leads to hepatic steatosis. Fatty liver is less able to oxidative stress, which is second hit, leading to chronic inflammation or steatohepatitis[8].

Role of Imaging in NAFLD

Role of imaging includes assessment of hepatic fat content, detection of inflammation in NASH, demonstration of fibrosis, and diagnosis of NAFLD-related HCC. Only assessment of hepatic fat content will be discussed in this presentation with a slight touch on NAFLD-related HCC.

Assessment of hepatic fat content is usually used biopsy as a gold standard. Grading of hepatic steatosis depends on amount of intracellular fat; less than 5% is normal, 5-30% is mild grade, 30-60% is moderate grade and more than 60% is severe grade[9]. Even though biopsy is considered a gold standard for assessment of fat, it is invasive and impractical for screening, longitudinal monitoring or evaluating for treatment response. Imaging has a good role for all these purposes. Imaging technique for fat detection includes US, CT and MRI.

Fat Detection by US

Characteristic finding of fatty liver by US includes diffuse hyperechotexture of the liver parenchyma with poor visualization of the blood vessels. US has poor sensitivity for mild fatty liver and about 70-80% sensitivity for severe fatty liver[10]. It is a qualitative technique, but not able to quantitate the amount of fat. Advantages of US are low cost, easily accessible, and no radiation. Limitations of US include operator and equipment dependence, unreliability in the presence of iron and fibrosis, and inability for fat quantification.

Fat Detection by CT

Plain CT is the technique used to detect fatty liver.

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It shows diffuse low attenuation of the liver parenchyma. Diagnosis at plain CT is based on attenuation of the liver less than 40 HU, or 10 HU less than that of the spleen. CT is not sensitive for mild to moderate fatty liver with reported sensitivity of about 5-30%. Liver attenuation of less than 40 HU signifies more than 30% of intracellular fat, which is considered having a high morbidity after hepatic resection or a poor candidate as a liver donor[11]. Similar to US, CT is not able to accurately quantitate fat. Advantages of CT are easily accessible, easy to perform and cheaper than MRI. Limitations include radiation exposure, unreliability if there is depositional diseases (iron, glycogen, amyloid), and inability to quantitate fat.

Fat Detection by MRI

MRI is the best imaging modality to both detect and quantitate liver fat. Fat quantification is important to determine the severity of hepatic steatosis, to monitor patients over time, and to assess response to therapeutic intervention. Three MRI methods proposed in this presentation are:

1. Chemical shift imaging (in phase-opposed phase gradient)
2. Frequency selective imaging
3. MR spectroscopy (MRS)

Chemical shift MRI for fat assessment (Figure 1, 2)

Proton of fat and water has slightly different resonant frequency (225 Hz at 1.5 T). Therefore, their magnetization vectors are alternately in- and out-of phase with each other. Signal of fats are measured in both phases and fat signal fraction (FSF) is calculated as following:

FS = S Fat / S Fat + S Water
= S inphase - S outphase / 2 S inphase[12]

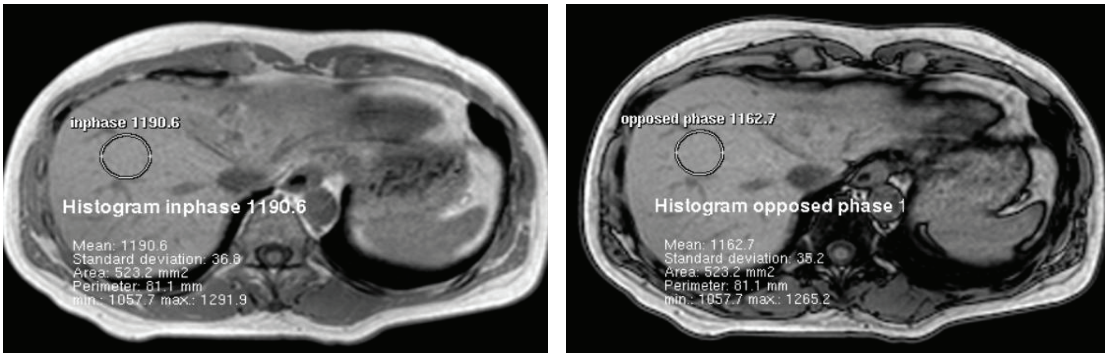

Figure 1. Chemical shift MRI for fat quantification in normal liver
Inphase signal = 1191, outphase signal = 1163
Fat signal fraction = 1191-1163/2 × 1191 = 1.2% fat

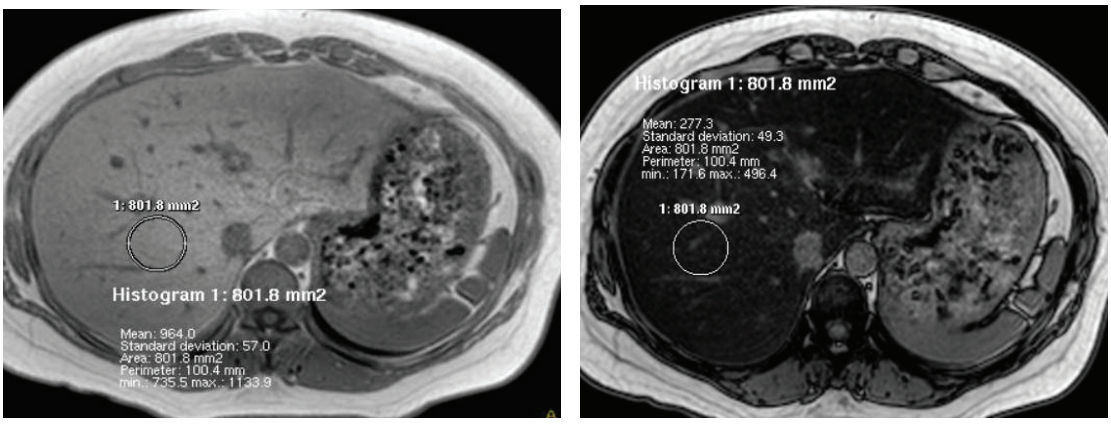

Figure 2. Chemical shift MRI for fat quantification in fatty liver
Inphase signal = 964, outphase signal = 277
Fat signal fraction = 964-277/2 × 964 = 36% fat

Chemical shift MRI is a rapid method and the technique is already existed in routine upper abdomen MRI protocol. It is a robust technique, unaffected by magnetic field inhomogeneity, and works well with different magnetic field strength. There are some weaknesses with this technique. It cannot distinguish between fat or water domination. Therefore, 30% and 70% FSF will show similar signal strength because it will have similar out-of-phase signal quantity[13]. Moreover, iron depositing within the liver will cause signal loss, which will interfere with signal loss from fat. Clinical use by this technique is recommended in conjunction with MRS.

Frequency selective MRI for fat assessment

In this MRI technique, 2 sets of imaging are acquired, which is non-fat suppression (NFS) and fat suppression (FS) sequences. Signal of fats are measured in both sequences and fat signal fraction (FSF) is calculated as following:

FSF = S Fat / S Fat + S Water

= S nfs - S fs / S nfs

This technique is easy to perform and is not as ambiguous over the range of 0-100% FSF as chemical shift technique. However, complete fat suppression is difficult and homogeneous magnetic field is needed. Moreover, inadvertent water suppression may easily occur. A large study is needed to validate and confirm this technique before it is recommended for a clinical use[12].

MR Spectroscopy (MRS) for fat assessment (Figure 3, 4)

In MRS, a specific target volume is excited with

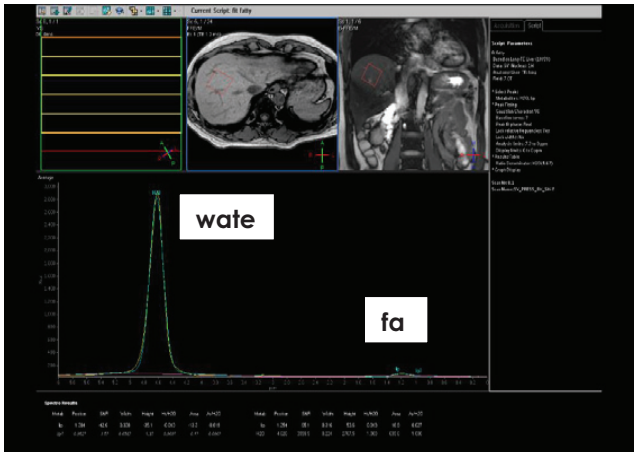

Figure 3. MRS for fat quantification in normal liver
Area fat = 11, Area water = 600
Fat signal fraction = 11/ (600/0.7) + 11 = 1.3% fat

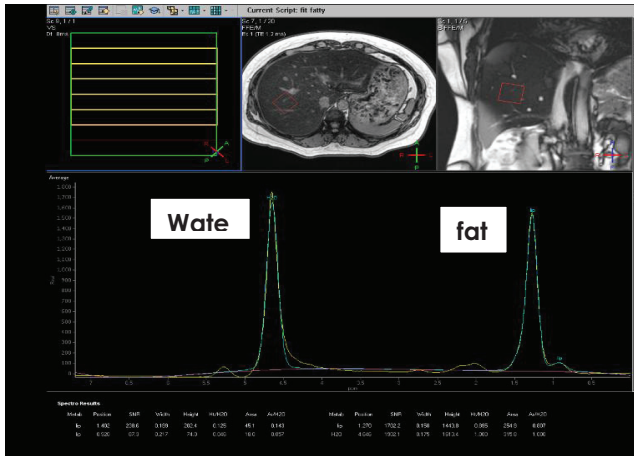

Figure 4. MRS for fat quantification in fatty liver
Area fat = 318, Area water = 316
Fat signal fraction = 318/ (316/0.7) + 318 = 41% fat

a spatially selective gradient excitation pulse combination such as STEAM (stimulated-echo acquisition mode) or PRESS (point-resolved spectroscopy). MR imaging spectrum represents the strength of signal at each frequency. Fat detection is straightforward and requires only identification of the spectral peak at resonant frequency specific to protons in triglyceride (1.3 ppm). Signal of fats are calculated using the area under the peak, and calculated as following:

FSF = A fat / (A water/0.7 + A fat)[14]

MRS is very sensitive and able to detect fat as low as 1%. It is the most accurate method for fat quantification. However, it needs skilled operator and good software program for complex data analysis. It is recommended to use in clinical routine if radiologist and technician have expertise in the subject.

Hepatocellular carcinoma (HCC) in NAFLD (Figure 5)

HCC in NAFLD-related chronic liver disease is about 18-27%[15]. However, there is evidence that HCC may develop in NAFLD before it has cirrhotic change. Even though, there is a risk of HCC in NAFLD, there is not yet a recommendation for HCC surveillance in NAFLD patients.

HCC in NAFLD is usually a solitary mass or one dominant mass with a few satellite nodules. It has smooth margin with capsule. Central necrosis may occur. Rapid arterial enhancement and rapid washout are similar to other typical HCCs. Background fatty liver may be helpful for the diagnosis of NAFLD-related HCC, but it may not be visualized if only mild fatty change is present.

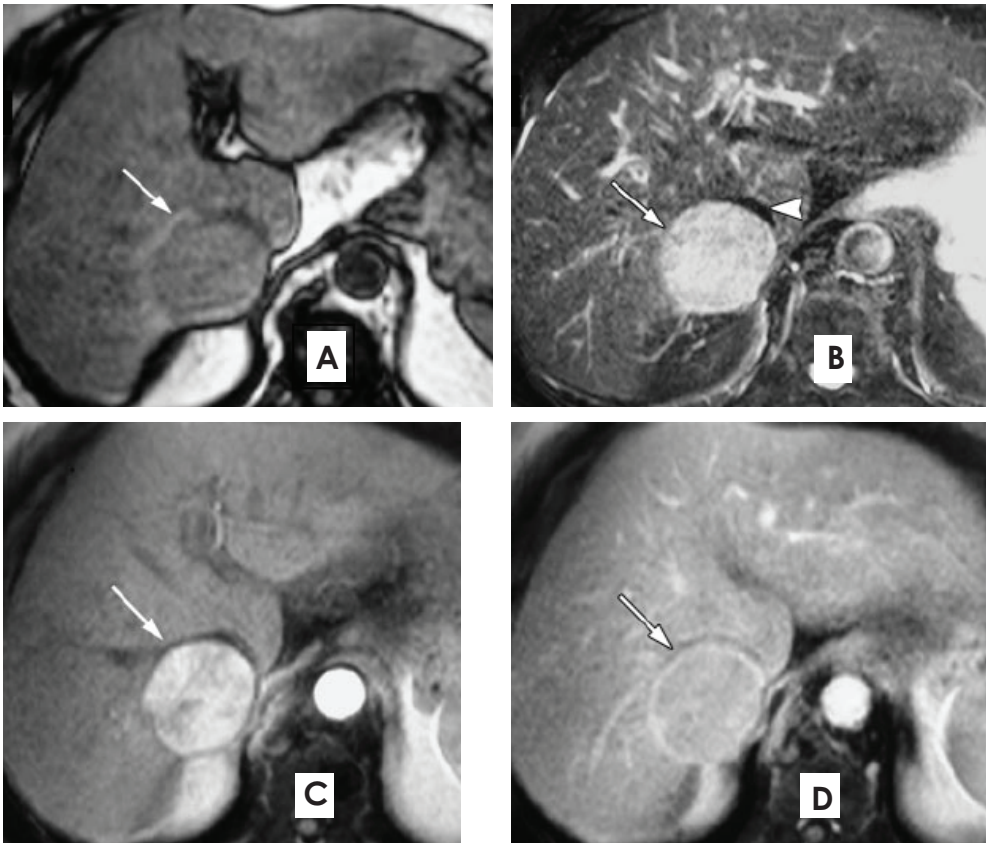

Figure 5. HCC in NAFLD in a 71-year-old obese man with diabetes. MRI shows fatty liver (A) containing a well-defined, encapsulated mass. This mass shows high SI at T2 (B), rapid enhancement (C) and rapid washout (D), consistent with HCC.

CONCLUSIONS

1. NAFLD is becoming a public health problem.
2. NAFLD may progress to cirrhosis with higher risk to develop HCC.
3. NAFLD may be reversible if detected and treated prior to severe fibrosis.
4. Noninvasive detection and quantification of liver fat is necessary to monitor response to treatment.
5. US and CT are able to detect liver fat but not for accurate quantification.
6. MRI is becoming an important tool for fat detection and quantification and MRS seems to be the most accurate method.

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