The purpose of this talk is to provide an overview of non-invasive MRI biomarkers of fat and iron in the liver. A review of the relevant physics of non-invasive MRI methods for fat and iron quantification are reviewed, and clinical examples discussed.

Fat Quantification:
Non-alcoholic fatty liver disease (NAFLD) is an emerging form of liver disease closely associated with the metabolic syndrome, a constellation of conditions including type II diabetes, obesity, dyslipidemia and hypertension, among others. Epidemiological studies have shown that NAFLD is the most common cause of liver disease in the US affecting an estimated 30% of the US population, including 75% of obese adults, and up to 10% of all children. NAFLD encompasses a spectrum of liver diseases including with isolated steatosis (intracellular accumulation of triglycerides in hepatocytes without inflammation or fibrosis), non-alcoholic steatohepatitis (NASH) (fat accumulation in hepatocytes with ballooning degeneration, inflammation and fibrosis), and cirrhosis (end-stage liver disease with stage 4 fibrosis). Current data suggest that between 5-15% of patients with NASH will eventually develop cirrhosis and 4% of patients with isolated steatosis eventually develop cirrhosis. NAFLD has also been shown to be an independent risk factor for cardiovascular disease in type 2 diabetics is associated with higher rates of malignancy, and may even play a causative role in the development of type II diabetes. Current treatment regimens focus on improving insulin sensitivity through weight loss and exercise, and insulin sensitizing drugs when lifestyle modification is inadequate.

The hallmark and earliest feature of NAFLD is steatosis. Currently, the gold standard for the diagnosis and grading of steatosis is liver biopsy. However, its widespread clinical applicability is limited because it is expensive, invasive, and suffering from relatively high sampling error. Steatosis is a heterogeneous disease feature, and the sampling error of biopsy likely reflects the inherent flaw of characterizing a heterogeneous disease with only 1/50,000th of the liver.

Imaging is playing an increasingly new role in the noninvasive diagnosis, grading, and treatment monitoring of NAFLD. Imaging techniques such as CT and ultrasound are semi-quantitative and have a limited role in accurately grading steatosis particularly at lower grades of steatosis. Proton MR Spectroscopy (MRS) is regarded by many as the non-invasive reference standard for quantifying hepatic triglyceride content. However, steatosis is well known to have a heterogeneous distribution, limiting the utility of MRS, which acquires a single voxel at one location. The inability to interrogate the entire liver may also negatively impact the ability of MRS to follow steatosis longitudinally because it is difficult to re-localize a voxel accurately at different time points. Furthermore, MRS requires sophisticated post-processing that may be impractical in a clinical setting. Volumetric MRI methods, however, can acquire images over the entire liver with high spatial resolution in a single breath-hold, providing complete coverage of the liver that facilitates co-registration of measurements from different days.

In recent years, several groups have investigated the clinical utility of chemical shift based water-fat separation MRI methods for quantifying hepatic steatosis using MRS as a reference standard. These studies have demonstrated excellent correlation with MRS and show great promise. Most investigators measure the “fat signal fraction” as a biomarker of liver triglyceride concentration. Fat signal fraction is the ratio of the signal from fat protons, to the sum of the proton signal from free water and fat. Fat signal fraction can be easily derived from chemical shift based water-fat separation methods and has the advantage of being independent of RF coil sensitivity profiles.
A quantitative biomarker of liver fat should be both platform-independent and relaxation parameter-independent, to provide accurate estimates of the concentration of triglycerides in the liver. Unfortunately, there are several important confounding factors that must be addressed for fat-fraction to quantify hepatic triglyceride content. If the effects of all confounding factors are removed, then the fat signal fraction will reflect the density of fat protons relative to all protons in fat and free water, ie: “proton density fat-fraction”. For the purposes of brevity, we will use the term “fat-fraction” in the remainder of this talk.

Several confounding factors have been identified and addressed by different groups. These factors include the effects of T1,[41,42], noise bias,[41] T2* decay,[42,43], spectral complexity of fat[42-44] and eddy currents.[45] This talk will review the use of chemical shift based water-fat separation methods to quantify fat. Quantification will be performed in a T1 independent manner with noise bias correction, T2* correction, spectral modeling of fat, and correction for the effects of eddy currents.

Iron Quantification:
Iron overload in the liver can result from a variety of causes, but is most commonly encountered in patients with genetic hemochromatosis, transfusional hemosiderosis and a chronic inflammatory state (eg. NASH, viral hepatitis, alcohol, etc). Genetic hemochromatosis is an autosomal recessive disease that is present in approximately 1:200 people in the United States, with variable penetrance depending on the specific mutation in the HFE gene. Mutations in the HFE gene lead to increased gastrointestinal absorption and subsequent accumulation of iron in the liver, pancreas and heart. If left unchecked, patients succumb either from fatal arrhythmias from cardiac iron overload (leading cause of death in these patients), develop hepatic cirrhosis and complications that include liver failure of the development of hepatocellular carcinoma (second leading cause of death), and diabetes mellitus type I from pancreatic dysfunction. Treatment with phlebotomy or chelator therapy is an effective means of lowering the total body iron content[46].

MRI of the liver plays an important role in the management of liver disease in patients with iron overload. First, conventional dynamic contrast enhanced methods are effective at screening for complications of cirrhosis, including HCC. In addition, conventional T2 and T2* weighted imaging provides an excellent means for qualitative detection of hepatic iron overload. In addition, iron overload can also be diagnosed with conventional IOP imaging - paradoxical signal dropout is seen on the in-phase image, because this image is acquired at a longer TE than the out of phase image and iron accelerates T2* and T2 decay. Signal dropout on the in-phase image is considered diagnostic of hepatic iron overload with very high specificity. Of note, this paradoxical dropout explicitly demonstrates why iron confounds the ability of IOP imaging to quantify fat: iron and fat have the opposite effect on signal dropout. The pattern of signal dropout in different organs can be used to distinguish the type of iron overload. For example, genetic hemochromatosis generally affects the liver and pancreas, and spares the spleen and bone marrow, while hemosiderosis (eg. from transfusional iron overload) affects the liver, bone marrow and spleen, while leaving the pancreas unaffected.

In recent years, MRI methods have been developed for the quantification of hepatic iron overload based on both T2* and T2 weighted imaging methods. A widely accepted and commonly used approach is that developed by Gandon et al,[47] based on an imaging-biopsy correlation study in 174 patients. This protocol uses a combination of 2D gradient echo images acquired with proton density weighting, T1 weighting, and escalating T2* weighting. Signal intensities measured with this protocol are fed into a calibration curve that provides accurate estimates of hepatic iron concentration. Although this approach is widely accepted and used, it has the disadvantage that it requires specific scanner dependent parameters such as TR, TE, flip angle and field strength (1.5T). This method also requires several breath-holds and multiple signal intensity measurements. A
convenient website is available where signal intensities can be entered and estimates of hepatic iron concentration are provided\textsuperscript{48}.

R2 (=1/T2) methods have also been described, the best known of which is the work of St. Pierre et al \textsuperscript{49} using the “Ferriscan” technique. This is a spin-echo based method that provides measurements of R2, and via a website data entry calculator provides estimates of hepatic iron content. The main disadvantage of this method is that the scan time is lengthy (20 minutes) and requires highly specific acquisition parameters.

More recent approaches for iron quantification have focused on direct measurement of T2* in the form of R2* (=1/T2*) mapping. Using a 3D multi-echo gradient echo acquisition, Wood et al. recently performed a study in 102 patients undergoing biopsy demonstrating a linear correspondence between R2* and hepatic iron concentration\textsuperscript{50}. This works provides a useful calibration between R2* and hepatic iron concentration. The primary advantage of this approach is that a fundamental tissue property (R2*) is measured and is, in principle, independent of acquisition parameters such as TR, TE and flip angle. The calibration between R2* and iron concentration will be dependent on field strength of course, and many investigators are currently evaluation the use of R2* measurements at 3T for iron quantification\textsuperscript{51}. Another primary advantage of R2* mapping is that rapid 3D multi-echo gradient echo sequences are now available for rapid R2* measurements within a single breath-hold. R2* values can be fit from the data in a fully automated manner, requiring no user input other than measuring R2* from the images and determining hepatic iron concentration from the calibration curve.

References:


