

**Innovations in Body MRI Course**  
**“Quantification of Diffuse Liver Disease Using MRI”**  
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**Target Audience:** abdominal radiologists interested in quantitative biomarkers of diffuse liver disease, as well as physicists developing quantitative biomarkers interested in clinical aspects of diffuse liver disease.

**Background:** Diffuse liver disease comes in many forms and result, typically from either a metabolic or infectious related injury to hepatocytes throughout the entire liver. Etiologies of liver disease include, but are not limited to:

1. **Non-alcoholic fatty liver disease (NAFLD).** NAFLD is now the most common cause of diffuse liver disease, affecting upwards of 20-30% of the American population. It is a feature of the metabolic syndrome, which includes a constellation of abnormalities that include obesity, diabetes type 2, dyslipidemia, hypertension and insulin resistance. Abnormal accumulation of intracellular triglycerides within hepatocytes, in combination with unknown secondary factor can lead to progressive hepatocyte injury, inflammation, fibrosis, and eventually cirrhosis.
2. **Viral hepatitis.** Chronic viral infection, particularly hepatitis B and hepatitis C are the most common causes of liver cancer worldwide. Chronic infection leads to progressive necroinflammation, fibrosis, and cirrhosis in patients with viral hepatitis are at high risk for developing cirrhosis and hepatocellular carcinoma (HCC).
3. **Alcoholic liver disease.** Alcohol abuse manifests with steatosis, steatohepatitis and eventually cirrhosis, HCC and portal hypertension.
4. **Wilson’s disease** is a genetic disease that leads to abnormally low levels of ceruloplasmin levels that lead to abnormal copper deposition within the liver (and other organs), with subsequent liver injury.
5. **Iron overload.** Iron overload in the liver is due to two main causes including genetic hemochromatosis and transfusion hemosiderosis. Regardless of the cause, excess iron in the liver causes hepatocyte injury, inflammation, fibrosis and eventual cause cirrhosis and HCC.
6. **Autoimmune diseases.** Autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and other autoimmune diseases can lead to features of diffuse liver disease.
7. **Glycogen Storage Diseases** are a constellation of genetic diseases leading to abnormal accumulation of intrahepatocellular glycogen levels and subsequent liver injury.

Although there are variations in the natural history and specific presentation of these various causes of diffuse liver disease, there is a common pathway with certain disease features, several of which can be quantified on using MRI. The presence of **intracellular triglycerides (ie: steatosis)** is easily detected and more recently quantified using quantitative biomarkers of liver fat (see below). As liver injury progresses, the development of **fibrosis and inflammation** can lead to changes in liver stiffness as well as restricted diffusion of water within the liver. As the disease progresses through the different stages of fibrosis, eventually cirrhosis, the end stage of fibrosis, occurs.

Patients with cirrhosis can develop multiple complications including the presence of ascites, hepatic encephalopathy. All patients with cirrhosis are at elevated risk of the development of primary liver cancer, *i.e.*, hepatocellular carcinoma (HCC). Patients with viral hepatitis are at an additional elevated risk of developing HCC compared to patients with cirrhosis from other etiologies.

One of the dreaded complications of cirrhosis includes the development of **portal hypertension**. Portal hypertension is defined as an increased pressure gradient between the portal veins and the systemic veins, when it exceeds 5 mmHg. When the portosystemic pressure gradient exceeds 10 mmHg, patients can develop portal systemic collaterals, *i.e.*, varices. When portal pressure exceeds 12 mmHg, patients are at elevated risk of rupture of gastroesophageal varices. Variceal rupture can result in dramatic exsanguination and is one of the most dreaded complications of portal hypertension.

Portal hypertension causes complex and dramatic changes in the hemodynamics of the liver including decreased portal flow and compensatory increased hepatic arterial flow. In some cases flow in the portal vein can completely reverse with complex flow through portal-systemic collaterals (varices). Further, abnormal response to challenges such as a meal in patients can also be seen in patients with cirrhosis and portal hypertension.

**MRI Biomarkers of Diffuse Liver Disease:** With the exception of **inflammation**, which is defined by the presence of white blood cells within the liver, there are several emerging quantitative MRI biomarkers of diffuse liver disease that have been developed over the past several years. These will be discussed in detail below and in the lecture.

**Fat:** MRI is exquisitely sensitive to the presence of fat and numerous techniques have been developed to quantify the triglyceride concentration within the liver. Emerging techniques have converged on the use of 2D and 3D multi-echo gradient-echo chemical shift based water-fat separation methods. When all confounding factors, such as T1, T2\*, spectral complexity of fat, eddy currents and noise bias are accounted for, extremely accurate measurements of the proton-density fat fraction (PDFF) can be achieved. PDFF is a protocol and platform independent biomarker that reflects a fundamental property of the tissue and is the preferred biomarker used to quantify the concentration of triglycerides in the liver. It is well validated against MR spectroscopy as well as biopsy and tissue triglyceride concentration in animal models of NAFLD. State-of-the-art fat quantification techniques will be discussed in this lecture.

**Iron:** Numerous techniques have been developed over the years to quantify the concentration of iron within the liver. These include spin-echo and gradient-echo based techniques. The most accurate quantification of liver fat can be achieved with gradient-echo techniques using R2\*-mapping. It is necessary to correct for the confounding effects of fat, noise model and macroscopic field inhomogeneities. Emerging correction methods for these confounding factors will be described. When these factors are addressed, R2\* based methods provide highly robust, reproducibly, and accurate measures of liver iron concentration.

**Fibrosis:** Diffusion weighted imaging has been investigated to quantify changes in the apparent diffusion coefficient (ADC) as a biomarker of fibrosis. Due to increased collagen deposition in the liver, fibrosis appears to reduce the ADC. Unfortunately early stages of fibrosis do not create sufficiently large changes in the ADC to be a reliable measure of early stage fibrosis. More compellingly, emerging methods for measuring liver stiffness through MR elastography techniques have shown the great promise to detect and quantify fibrosis. In this lecture the use of MR elastography to detect early stage fibrosis as well as differentiating less aggressive

isolated steatosis from more aggressive non-alcoholic steatohepatitis will be discussed through the examples that demonstrate the power of combined use of quantitative biomarkers of fat.

***Hemodynamics of the liver:*** Exciting new work has been developed by several groups to provide comprehensive assessment of the hemodynamics of the liver including anatomy, flow visualization, and quantification within both the hepatic arterial and portal venous systems. Approaches for quantifying the hemodynamics of the liver in patients with portal hypertension will be discussed including 4D flow-phase contrast techniques.

***Summary:*** These are exciting times for the development and translation of quantitative biomarkers of diffuse liver disease including accurate biomarkers of fat, iron, fibrosis and hemodynamics. The remaining challenge of determining a biomarker for hepatic inflammation will also be discussed and is an important challenge and opportunity for MRI to address, in order for MRI to provide comprehensive evaluation, equivalent to biopsy and histological examination.