

2. SPECIFIC AIMS: TECHNICAL DEVELOPMENT OF QUANTITATIVE BIOMARKERS OF FATTY LIVER DISEASE WITH MR

Non-alcoholic fatty liver disease (NAFLD) is an emerging condition increasingly recognized as the most common type of chronic liver disease. It afflicts an estimated 90-100 million (>30%) people in the United States alone^{30,31} including 10% of children³²⁻³⁶. *The overall goal of this work is to develop, validate and translate to clinical practice, non-invasive quantitative biomarkers for accurate diagnosis and grading of NAFLD using magnetic resonance imaging (MRI).* This proposal responds to the NIDDK program announcement PA-09-181. One of this PA's objectives is to develop "non-invasive methods, such as imaging" to define "the extent and rate of progression of steatosis [fatty infiltration] of the liver". We will accomplish these goals with a multidisciplinary team of scientists, radiologists, hepatologists, and pathologists from academia and industry. NAFLD is closely linked to the "metabolic syndrome", a constellation of conditions that includes obesity, diabetes and insulin resistance. The hallmark feature of NAFLD is intracellular accumulation of triglycerides within hepatocytes (steatosis). In many NAFLD patients, steatosis progresses to liver injury, with inflammation and fibrosis. Eventually these patients develop cirrhosis and succumb to liver failure and/or hepatocellular carcinoma (HCC), necessitating liver transplant. With the current epidemic of obesity and diabetes, NAFLD is expected by many to overtake hepatitis C as the leading indication for liver transplantation in the next decade. Early detection and quantitative assessment of NAFLD requires *accurate and precise quantification of steatosis, the earliest feature of NAFLD.* In addition, accurate quantification of hepatic fibrosis, which reflects the degree of liver injury, is necessary to determine prognosis and guide therapies that attempt to arrest or reverse liver damage. Unfortunately, biopsy, the current gold standard for measuring steatosis and fibrosis, is risky, expensive and has high sampling variability. Imaging methods, such as ultrasound, CT and MRI that can detect steatosis are limited by poor sensitivity early in disease, and inaccuracy from confounding factors that limit their clinical utility. *Safe, inexpensive and accurate biomarkers for diagnosis and grading of NAFLD would have tremendous potential to improve patient care. The limitations of biopsy and current imaging methods have been a major barrier to early diagnosis and pre-emptive treatment of NAFLD. In this proposal, we aim to quantify steatosis through the development of novel MR imaging methods that quantify hepatic steatosis (fat-fraction).* We will develop a quantitative approach for measuring fat, based on the foundation of an established chemical shift based fat-water separation method designed for qualitative fat suppression, that address previous shortfalls in MRI, particularly in areas of high magnetic susceptibility such as the abdomen. Using these methods as a foundation, new quantitative methods will be developed. *These methods will address important confounding factors that prevent current fat water separation methods from providing accurate measurements of fat. Addressing these challenges and validating new solutions will form the basis of this proposal.* Confounding factors include the effects of NMR relaxation parameters (T1, T2*), noise related bias, multiple spectral peaks of fat, and eddy currents. Importantly, new methods will be developed to address the effects of iron overload, which impacts the MR signal through accelerated signal decay (shortened T2*). Iron overload commonly coexists with steatosis in patients with NAFLD, and *therefore as a secondary goal, we aim to measure T2* (as a biomarker of iron), and fat-fraction, simultaneously.* In this proposal we will develop and validate new MRI biomarkers of steatosis, and secondarily, biomarkers of hepatic iron overload. Specifically, we aim to:

1. *Develop, implement, and validate quantitative MRI biomarkers of hepatic steatosis (fat-fraction) and iron overload (T2*) in a single breath-hold (!20s), with complete liver coverage.*
2. *Perform pre-clinical validation of biomarkers for steatosis and iron overload in: a. the ob/ob mouse model of hepatic steatosis, with super-imposed iron overload. b. explanted human livers rejected for transplant due to the presence of steatosis.*
3. *Prospectively evaluate patients referred for biopsy for suspected NAFLD, to evaluate the accuracy of fat-fraction and T2* measurements through a co-registered biopsy/imaging correlation pilot study.* This proposal responds to the NIDDK program announcement PA-09-181 for development of "Non-Invasive Methods for Diagnosis and Progression ..." of diseases of interest to the NIDDK, which includes NAFLD. We aim to meet the urgent need for biomarkers that non-invasively quantify hepatic steatosis, and secondarily iron, without the inaccuracy, danger, and cost of biopsy. *Successful development of these MRI biomarkers will provide an unprecedented opportunity for pre-emptive intervention for the prevention and treatment of an important and increasingly prevalent cause of cirrhosis, liver failure and HCC.*