Clinical Gastroenterology and Hepatology 2015;13:561–568

Effect of Weight Loss on Magnetic Resonance Imaging Estimation of Liver Fat and Volume in Patients With Nonalcoholic Steatohepatitis

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BACKGROUND & AIMS: **Little is known about how weight loss affects magnetic resonance imaging (MRI) of liver fat and volume or liver histology in patients with nonalcoholic steatohepatitis (NASH). We measured changes in liver fat and liver volume associated with weight loss by using an advanced MRI method.**

METHODS: **We analyzed data collected from a previous randomized controlled trial in which 43 adult patients with biopsy-proven NASH underwent clinical evaluation, biochemical tests, and MRI and liver biopsy analyses at the start of the study and after 24 weeks. We compared data between patients who did and did not have at least 5% decrease in body mass index (BMI) during the study period.**

RESULTS: **Ten of 43 patients had at least a 5% decrease in BMI during the study period. These patients had a significant decrease in liver fat, which was based on MRI proton density fat fraction estimates (18.3% ± 7.6% to 13.6% ± 13.6%, $P = .03$), a relative 25.5% reduction. They also had a significant decrease in liver volume (5.3%). However, no significant changes in levels of alanine aminotransferase or aspartate aminotransferase were observed with weight loss. Thirty-three patients without at least 5% decrease in BMI had insignificant increases in estimated liver fat fraction and liver volume.**

CONCLUSIONS: **A reduction in BMI of at least 5% is associated with significant decrease in liver fat and volume in patients with biopsy-proven NASH. These data should be considered in assessing effect size in studies of patients with nonalcoholic fatty liver disease or obesity that use MRI-estimated liver fat and volume as end points.**

Keywords: Noninvasive; Steatosis; Biomarker; Response to Treatment.

Nonalcoholic fatty liver disease (NAFLD) has become an increasingly common problem. It now affects approximately 30%–40% of adults in the Western world,[1,2] including 60%–70% of obese adults,[3] and its prevalence may continue to rise with the worldwide obesity epidemic.[2] It is well-known that obesity, insulin resistance, and metabolic syndrome play a central role in the development and progression of NAFLD.[4–6] Although most patients with NAFLD have a relatively benign clinical course, 10%–20% have nonalcoholic steatohepatitis (NASH), which can lead to advanced fibrosis, hepatic decompensation, and liver-related mortality.[7–10]

Despite the increasing clinical relevance of NAFLD, few effective therapies have been identified for this disease. Treatment of NASH with thiazolidinediones may reduce liver steatosis and inflammation; however, their use has been associated with weight gain, cardiovascular complications, and bladder cancer.[11–15] In randomized controlled trials, vitamin E has also been effective in reducing steatosis and inflammation in NASH[13,16]; however, it is unclear whether this medication may be associated with an increase in all-cause mortality.[17] Other pharmacologic therapies including metformin,

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NAS, nonalcoholic fatty liver disease activity score; PDFF, proton density fat fraction; ROI, region of interest.

© 2015 by the AGA Institute
1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.08.039

omega-3 fatty acids, bile acids, and bile acid sequestrants have been ineffective in the treatment of NASH.[18,19]

Weight loss remains the mainstay of treatment for NAFLD and NASH. Several studies have shown a reduction in transaminases as well as histology-determined steatosis grade and inflammation in patients with NASH who had significant weight loss.[20,21] In retrospective and prospective cohort studies, bariatric surgery has also been effective in reducing steatosis, steatohepatitis, and fibrosis in patients with NAFLD.[22,23]

Although many studies have demonstrated that weight loss is an effective therapy for NAFLD and NASH, most have used intensive lifestyle or dietary interventions. It is underappreciated whether weight loss leads to a decrease in liver volume along with a parallel decrease in liver fat or whether the liver volume remains unchanged and a reduction in liver fat alone is seen. This study addresses that gap in knowledge.

In addition, many previous studies have relied on histologic findings of steatosis to determine changes in liver fat. More recently, magnetic resonance spectroscopy (MRS) has shown a quantitative reduction in liver fat with weight loss and dietary interventions.[24–26] Although MRS has been considered the gold standard for quantitative liver fat assessment in patients with NAFLD, recent studies have used an advanced chemical shift–based gradient-echo magnetic resonance imaging (MRI) technique that measures the proton density fat fraction (PDFF), a quantitative marker of fat content in tissue.[19,27–29] This technique has been validated with MRS and has been shown to be more sensitive than histology-determined steatosis grade in quantifying increases and decreases in liver fat content.[30,31] Unlike MRS, this technique creates a parametric fat map of the abdomen, which allows for assessment of changes in liver volume and fat content in other organs including the pancreas. Changes in liver volume in patients with NAFLD may be an important marker of disease progression as well as regression, because it has been linked to metabolic syndrome. Reduction in steatosis and size may be noted with treatment response as well as when patients develop cirrhosis.[32,33]

In this study, we aimed to determine the quantitative effect of weight loss on MRI-PDFF estimated liver fat and liver volume in patients with biopsy-proven NASH. We hypothesized that weight loss leads to reduction in both liver fat and volume.

Methods

Study Design and Patient Population

This is a secondary analysis of a randomized controlled trial of 43 adult patients with biopsy-proven NASH. The primary outcome was change in MRI-estimated liver PDFF and MRI-estimated liver volume between the start (week 0) and completion (week 24) of the study. All patients were diagnosed with NASH on the basis of liver biopsy as well as exclusion of other causes of liver disease.[34]

As part of the original study, all patients were randomized to receive either colesevelam, a bile acid sequestrant, or placebo during a period of 24 weeks.[19] Patients underwent clinical evaluation, physical examination, biochemical testing, and MRI at baseline and after 24 weeks. All patients provided written informed consent to participate in the study, and the study was approved by the University of California at San Diego institutional review board. All patients underwent a standard history and physical exam, biochemical testing, and MRI examination at University of California at San Diego. They also all underwent an alcohol history assessment by completing the AUDIT and Skinner Lifetime Drinking questionnaires.

Two cohorts for this secondary analysis were derived according to those who had at least a 5% decrease in body mass index (BMI) and those who did not have at least 5% decrease in BMI.

Inclusion and exclusion criteria and clinical and histologic evaluation are available in the Supplementary Material.

Magnetic Resonance Imaging Protocol

To quantify liver fat and volume, we used a previously described advanced chemical shift that based gradient-echo MRI technique that estimates PDFF, which is a standardized and objective measure of fat content.[27,30,31,35–38] It acquires multiple echoes at different echo times, with fat and water signals nominally in phase or out of phase with each other, and applies an algorithm to generate a PDFF parametric map depicting fat quantity and distribution throughout the liver. This method has been shown to reliably measure liver fat content when compared with other MR techniques and histology-determined steatosis, and it is sensitive in detecting changes in liver fat content.[31,36,39] To estimate PDFF across the entire liver, 3 regions of interest (ROIs) 300–400 mm^2 in area were placed in each of the 9 liver segments on the PDFF parametric maps (Figure 1). In addition, fat content in the pancreas (pancreatic PDFF) was measured by placing 1–2 ROIs of 100 mm^2 in the head, body, and tail of the pancreas in each slice of the PDFF parametric maps. These protocols have been described in prior studies.[27,31] The mean of all ROIs in the liver and pancreas was calculated to determine the average PDFF in each organ. Liver volume was calculated by measuring the liver area in each slice of the original MR images and integrating this across all MRI slices.

A single resident physician, who was trained in the MRI analysis, performed the measurements. The physician was blinded to clinical and histologic data and was under the supervision of the radiology investigator (C.S.).

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