# Assessment of Nonalcoholic Fatty Liver Disease Progression in Children Using Magnetic Resonance Imaging

Marialena Mouzaki, MD, MSc[1,2], Andrew T. Trout, MD[3], Ana Catalina Arce-Clachar, MD[1,2], Kristin Bramlage, MD[1,2], Pierce Kuhnell, PhD[4], Jonathan R. Dillman, MD, MSc[3], and Stavra Xanthakos, MD, MS[1,2]

**Objective** To assess liver disease progression using paired magnetic resonance imaging (MRI) measurements of liver fat fraction (FF) and stiffness.

**Study design** Retrospective cohort study including patients with nonalcoholic fatty liver disease who had undergone repeat MRI studies. Descriptive statistics were used, as well as Pearson or Spearman correlation when appropriate. Mixed model analyses were used to determine relationships between liver FF/stiffness and predictor variables.

**Results** Sixty-five patients (80% non-Hispanic, mean age 14 ± 3 years) were included. Time from first to last MRI was 27 ± 14 months. Over time, body mass index z score remained stable, and there were no significant differences in mean serum aminotransferases, insulin, glucose, triglycerides, low-density lipoprotein, and high-density lipoprotein (HDL) levels. However, the proportion of patients with alanine aminotransferase (ALT) < 50 U/L increased. MRI FF and stiffness decreased in 29% and 20% of patients, respectively, and increased in 25% and 22% of patients, respectively. There was a weak positive correlation between FF change and ALT change (r = 0.41, $P = .053$) and a moderate negative correlation between change in FF and change in serum HDL levels (r = -0.58, $P = .004$). After adjusting for HDL, increase in serum insulin was the only variable predictive of increase in FF ($P = .061$). There was no correlation between change in liver stiffness and change in ALT (r = .02, $P = .910$).

**Conclusions** MRI-determined hepatic FF and stiffness improved in a minority of patients overtime. ALT levels were not reflective of the change in FF or stiffness. MRI-based imaging is complementary in the assessment of NAFLD progression. *(J Pediatr 2018;■■:■■-■■).*

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent condition that affects up to one- third of children worldwide.[1] Among adults with NAFLD, 25% have nonalcoholic steatohepatitis (NASH) at diagnosis with variable stages of fibrosis.[2] Adult studies also suggest that liver disease progresses in a significant proportion of patients (34%-44%) over a short time frame, even in those who have mild disease at baseline.[3,4] In less than a decade, 5% of adult patients develop end-stage liver disease and 3% develop liver-related complications, such as hepatocellular carcinoma.[5] Adult data on the natural history of NAFLD, however, should not be extrapolated to children, given the differences between adult and pediatric NAFLD (eg, histopathology, duration of disease, prevalence, and severity of comorbidities, etc).

To date, the natural history of pediatric NAFLD has been described in the placebo arms of 2 randomized controlled trials (RCTs; Treatment of non alcoholic fatty liver disease in children [TONIC] and Cysteamine bitartrate delayed release for the treatment of nonalcoholic fatty liver disease in children [CyNCh])[6,7]; the literature is otherwise limited to case series.[8,9] Patients randomized to the placebo arms of these studies received lifestyle advice (diet and exercise), comparable with guidance offered in routine clinical practice. The results of these RCTs suggest that standard lifestyle interventions lead to histologic improvement in 22%-40% of patients in a span of 1-2 years, but resolution of NASH occurred in less than one-third of patients.[6] Although these data are important, they may not reflect the true natural history of NAFLD, as patients enrolled in clinical trials are selected based on stringent inclusion/exclusion criteria, are monitored closely, and may be more likely to adhere to the lifestyle interventions prescribed. Therefore, more research is needed to determine how children and adolescents with NAFLD progress over time in real-world populations, to be able to appropriately counsel patients and their families regarding the natural history of this disease and to determine which patients are at greatest risk for adverse outcomes.

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| ALT | Alanine aminotransferase | MRE | Magnetic resonance elastography |
| BMI | Body mass index | MRI | Magnetic resonance imaging |
| CyNCh | Cysteamine bitartrate delayed release for the treatment of nonalcoholic fatty liver disease in children | NAFLD | Nonalcoholic fatty liver disease |
| | | NASH | Nonalcoholic steatohepatitis |
| | | PDFF | Proton density fat fraction |
| FF | Fat fraction | RCT | Randomized controlled trial |
| HDL | High-density lipoprotein | TONIC | Treatment of non alcoholic fatty liver disease in children |
| MR | Magnetic resonance | | |

From the [1]Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center; [2]Department of Pediatrics, University of Cincinnati College of Medicine; [3]Department of Radiology, Cincinnati Children's Hospital Medical Center; and [4]Department of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Given that NAFLD is a histologic diagnosis, repeat liver biopsies are important to clearly delineate its natural history. However, liver biopsies are subject to the possibility of sampling error, as disease severity may vary across the liver parenchyma.[10,11] Further, in clinical practice, biopsies are not universally obtained because of their invasive nature and cost, the high prevalence of this condition, and the lack of disease-specific treatments.[12,13] In general, higher levels of alanine aminotransferase (ALT) elevation are more likely to trigger a biopsy, thus, cohorts with NAFLD enrolled on the basis of histologic confirmation alone may not reflect the full spectrum of disease, which can be present even in the setting of normal to mildly elevated liver enzymes.[14] Imaging studies are often used as surrogates for histology to determine disease severity and monitor progression. Of the imaging modalities available for assessment of hepatic steatosis, ultrasonography is most commonly used in clinical practice; however, it has been shown to be relatively inaccurate in both detecting and quantifying steatosis and should not be used for this purpose.[12,15] In contrast, magnetic resonance imaging (MRI)-proton density fat fraction (PDFF) can accurately and noninvasively detect and quantify hepatic steatosis independent of age, sex, and body mass index, can be achieved with a rapid (single breath hold, <1 minute) scan, and does not require intravenous contrast material.[16-19] Magnetic resonance elastography (MRE), which can be performed in the same examination as MRI-PDFF, allows the noninvasive measurement of liver stiffness, which reflects fibrosis and potentially also hepatic inflammation.[20] MRE has recently been found to be accurate in identifying advanced fibrosis in children and adults with NAFLD[18,21,22] Considering that hepatic fibrosis is the strongest predictor of long-term patient outcomes and that noninvasive serum biomarkers of fibrosis in pediatric NAFLD are inaccurate, MRE is currently the most reliable, clinically available, noninvasive approach to assess fibrosis progression, particularly in obese patients.[18,23,24]

The primary objective of this study was to define disease progression of pediatric patients with presumed (radiologic evidence of steatosis and/or elevated transaminases in the context of obesity and a negative work up for other liver diseases) or histologically confirmed NAFLD using paired MRI-PDFF/MRE studies. In addition, we aimed to explore the relationship between change in hepatic fat fraction (FF)/stiffness and change in clinical measures over the period of observation.

## Methods

This was a retrospective cohort study performed at Cincinnati Children's Hospital Medical Center with Institutional Review Board approval and a waiver of informed consent. Inclusion criteria were patients with presumed or histologically confirmed NAFLD who had had repeat MRI examinations from August 2010 to October 2017. Exclusion criteria included secondary causes of hepatic steatosis (eg, lipodystrophy), evidence of other concurrent liver diseases, and history of weight loss surgery. Patients with a hepatic FF <5% at baseline were also excluded, unless there was histologically confirmed NAFLD within 3 months of the MRI. All patients were undergoing evaluation and management in a pediatric clinical NAFLD program. Per program protocols, standard of care dietary and activity guidelines were provided to all patients by trained clinical staff, consistent with practice guidelines for management of pediatric NAFLD.[12]

Clinical records were reviewed for race/ethnicity, age, and anthropometrics (weight, height, and body mass index) at the time of the imaging examinations, and laboratory data obtained within 3 months of the MRI (eg, serum levels of ALT, aspartate aminotransferase, gamma glutamyl transferase, alkaline phosphatase, fasting glucose, insulin, hemoglobin A1C, lipid profile, albumin, platelets, and international normalized ratio). MRI examinations were reviewed to collect liver volume (mL), FF (%), and liver stiffness (kPa).

Per standard clinical practice, MRI examinations were performed without intravenous contrast material and covered the abdomen only. MRE was performed with an active-passive driver system operated at 60 Hz and utilizing either a 2-dimensional gradient recalled echo or 2-dimensional spin-echo echo-planar imaging elastography sequence. Four axial slices through the mid liver were obtained for generation of shear wave and elastogram images. Regions of interest for measurement of liver stiffness were drawn manually (guided by 95% confidence maps) by dedicated Department of Radiology imaging postprocessors, and overall liver stiffness was expressed as the weighted mean of the average liver stiffness values for each of the 4 elastograms. FF was quantified using either the MRI-PDFF (mDIXON technique) or by performing chemical shift MRI with a low flip angle, with the percentage of liver fat normalized to an adjacent volume of lipid emulsion with a known concentration of fat (20%). Utilization of one technique vs the other was dependent on scanner capability and sequence availability. Regions of interest for FF measurements were drawn by the same postprocessors.

### Statistical Analyses

Paired *t* test (2-sided) was used to compare continuous variables from first to last study, and McNemar testing was used to compare categorical variables. Pearson and Spearman correlations were used when applicable to determine associations between variables, and mixed linear models were used to assess relationships between FF/stiffness and predictor variables. Analyses were performed using Stata MP v 13.0 (StataCorp, College Station, Texas) and SAS v 9.4 M3 (SAS Institute, Cary, North Carolina).

For the purposes of comparison, clinically meaningful change in FF was defined as >± 5% and change in stiffness was defined as >± 20% based on repeatability data in the literature.[25,26] FF comparisons were made only if the same imaging technique was used to quantify fat in the baseline and follow-up examinations. Correlation coefficients were interpreted as follows: 0-0.19, very weak; 0.2-0.39, weak; 0.40-0.59, moderate; 0.60-0.79, strong; and 0.80-1.0, very strong. $P < .05$ was considered significant for all inference testing.



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