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

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Abstract

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.

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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.

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 $>\pm 5\%$ and change in stiffness was defined as $>\pm 20\%$ 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.

Results

The patient population ($n = 65$) was predominantly a non-Hispanic, Caucasian cohort of male adolescents, reflective of the population demographics of patients with NAFLD in our Midwestern geographic region (Table I). At the time of the first MRI, only 1 patient had a body mass index (BMI) below the 95th percentile for age and sex. The mean ($\pm$ SD) interval between first and last MRI was 27 (± 14) months. Baseline fat fraction data were available for 45 of 65 patients, as initially MRE were done without PDFF measurements at our institution.

Anthropometrics and Laboratory Investigations

For the population as a whole, although average BMI increased from the first to the last MRI (34.6 ± 6.7 vs 36.9 ± 7.4 kg/m², $P < .001$), BMI percentiles remained unchanged (98.5 ± 3.1 vs 98.6 ± 2.6 , respectively; $P = .51$). Mean ALT levels did not change significantly from the first to the last MRI; however, the proportion of patients with ALT < 50 U/L (< 2 times the upper limit of normal) increased with time (20% vs 37%, respectively, $P = .01$). Population average change in transaminases, markers of insulin sensitivity, and lipid profiles are shown in Table II. From the first to the last MRI study the proportion of patients receiving treatment for type 2 diabetes mellitus did not change significantly (10% vs 13%, respectively; $P = .157$), nor did the proportion of patients receiving treatment for dyslipidemia (5% vs 8%, $P = .317$).

Liver Volume

Across the study population, average liver volume increased from the first to the last MRI (2071 vs 2277 mL, $P < .01$, $n = 64$; however, liver volume per body weight decreased slightly (24 mL/kg vs 22 mL/kg, $P = .007$).

Change in liver volume was correlated with change in fat fraction ($r = 0.80$, $P < .001$) and change in ALT ($r = 0.39$, $P = .002$), although it was negatively correlated with change in high density lipoprotein (HDL) ($r = -0.40$, $P = .001$). There was a trend toward a significant correlation between change in liver volume and change in liver stiffness ($r = 0.23$, $P = .07$), change in serum insulin levels ($r = 0.26$, $P = .052$), and change in serum triglyceride levels ($r = 0.24$, $P = .054$). After controlling for HDL and age at first MRI study, change in ALT predicted change in liver volume (estimate=2.286, $P = .002$).

FF

FF was measured using the same technique in the first and last MRI in 24 subjects. Mean FF did not change significantly in these patients ($12\% \pm 10$ vs $10\% \pm 6$, respectively; $P = .340$). However, only 29% of these patients had a decline in fat fraction of $\geq 5\%$, as shown in Figure 1.

There was weak positive marginally significant correlation between FF change and ALT change ($r = 0.41$, $P = .053$). Change in FF was moderately inversely correlated with change in serum HDL levels ($r = -0.58$, $P = .004$), but not with change in serum triglycerides ($r = 0.37$, $P = .079$), serum low density lipoprotein ($r = -0.32$, $P = .143$) serum insulin ($P = .41$, $P = .100$), or BMI ($r = 0.17$, $P = .482$). Multivariable modeling showed that, after adjusting for HDL, insulin change predicted change in FF with an estimate that trended toward significance (estimate=0.222, $P = .061$). No other variables predicted change in FF.

Liver Stiffness

Paired liver stiffness data were available for the entire cohort ($n = 65$). Mean stiffness did not change significantly (2.55 ± 0.50 kPa vs 2.53 ± 0.59 kPa, respectively; $P = .818$). The majority of the cohort had stable liver stiffness over time ($<20\%$ change from baseline, Figure 1). An example of increased liver stiffness is shown in Figure 2 in a child who progressed from stage 1 fibrosis to cirrhosis over a 4-year time period, with a corresponding significant increase in liver stiffness on MRE. There was no significant correlation between change in FF and change in stiffness ($r = -0.23$, $P = .275$, $n = 24$).

There was no significant correlation between change in liver stiffness and ALT change ($r = .015$, $P = .90$). In the 10 (15%) patients with ALT decline of $\geq 50\%$, stiffness changed in a similar way as the entire study cohort (increased in 20%, decreased in 20%, and remained stable in 60%; $P = .999$). Stiffness change also did not correlate with change in serum levels of HDL ($r = .08$, $P = .548$), triglycerides ($r = .02$, $P = .858$), insulin ($r = 0.18$, $P = .180$), or BMI ($r = -.04$, $P = .762$). The only variable that significantly positively correlated with change in stiffness was time from first to last imaging study ($r = 0.39$, $P = .001$) suggesting a general trend toward increasing liver stiffness over time in our population. This correlation

was weak but persisted even after controlling for serum ALT, HDL, and insulin levels ($P = .002$).

Vitamin E Treatment

Nine patients (14%) received treatment with vitamin E between imaging studies. Vitamin E treatment was not associated with a different pattern of stiffness change compared with that seen in the untreated cohort. Specifically, of the 9 patients treated with vitamin E between MRI examinations, stiffness was unchanged in 4 (45%), increased in 3 (33%), and decreased in 2 (22%). In terms of FF, only 5 patients exposed to vitamin E had comparable paired FF studies. Of those, 2 remained stable and 3 had clinically significant improvement in their FF.

Discussion

In this study, we investigated changes in noninvasive imaging markers of liver disease severity in a real-world population of children with NAFLD, who had enough concerning clinical and/or laboratory features to undergo repeat MRI-PDFF/MRE studies. Over a mean of 27 months follow-up, less than one-third of a small cohort of patients with paired measurements had significant decreases in hepatic FF measured by MRI and only one-fifth of patients had significant decreases in liver stiffness. The majority of patients either had unchanged or worsening liver steatosis and/or stiffness. This occurred in the context of stable mean BMI z scores, serum ALT, glucose, insulin, and lipid profile levels. Importantly, serum ALT levels performed suboptimally in terms of reflecting change in hepatic steatosis or stiffness in this cohort.

In comparison with the histologic outcomes reported in the placebo arms of the TONIC and CyNCh clinical trials, a minority of patients in our cohort exhibited improvement in NAFLD over time, as measured by decline in hepatic stiffness (20%) or FF (29%). In the placebo arm of the TONIC trial, 47 children received counseling regarding lifestyle interventions plus placebo and had paired biopsies approximately 24 months apart.⁶ Ordinal NAFLD activity scores were used to determine change in disease severity over time.²⁷ The mean baseline steatosis score of those in the placebo arm was 2.1 (a score of 2 is equivalent to steatosis involving 33%–66% of hepatocytes) and the score improved by 1 point in 40% of patients. Liver fibrosis scores improved in 19%. Similar results were reported in the CyNCh trial, where 81 patients were included in the placebo arm and received lifestyle counseling.⁷ Their mean baseline steatosis score was 2.5 and a little over a year later, 41% of patients had improved steatosis by 1 or more point. Fibrosis stage improved in 28%.

Our study used MRI to assess hepatic steatosis, which generates a continuous variable (FF) and MRE which also generates a continuous measure of stiffness (kPa), whereas histology is graded ordinally, with steatosis grouped into score 0–3 (score 0 = <5% hepatocytes affected by steatosis, 1 = 5 to 33%, 2 = >33% to 66%, and 3 = >66%) and fibrosis by pattern and severity (eg, stages 0–4), thus the outcomes are not directly comparable. Further, although mean age and BMI were similar in our cohort compared with the clinical trial cohorts, our population was predominantly non-Hispanic (80%), in contrast with the TONIC and CyNCh trials in which the majority were of Hispanic ethnicity (61%–75%). Finally, the patients included in our study were monitored in routine clinical practice and not as part of a RCT,

which may have also impacted outcomes. Although our recommended clinical follow-up is also every 3 months in our NAFLD program for ongoing lifestyle counseling, adherence to clinical protocol may have been less strict than typically required in a clinical trial. Nonetheless, our results suggest that a smaller proportion of pediatric patients with NAFLD achieve improvement in clinical practice with routine lifestyle counseling, than patients enrolled in placebo arms of clinical trials.

In clinical practice, ALT is used to screen for liver disease and to determine disease severity despite known limitations.¹² ALT has been shown to have a low specificity for the diagnosis of NAFLD, even in overweight/obese children.²⁸ In addition, although NASH is more common in those with a serum ALT >80, a significant proportion of those with lower ALT values have NASH.²⁸ Schwimmer et al recently reported a weak but significant correlation between ALT and liver stiffness in a pediatric study assessing the utility of MRE to determine fibrosis in a cohort of 90 children with NAFLD.²¹ In our study, we found no such correlation, and only a trend toward a weak correlation between change in ALT and change in FF. In addition, although 71% and 80% of patients in our study had unchanged or worsened steatosis and stiffness, respectively, the proportion of patients with an ALT <50 U/L paradoxically almost doubled to 37%, although those with ALT decline of >50% from baseline was 15%. This discordance between improvement in ALT and lack of improvement or worsening in MRI measures of disease, suggests that ALT alone is an inadequate or even inaccurate measure of outcome, even in patients who appear to be at risk of more severe liver disease. Our study highlights further the limitations of ALT in the context of pediatric NAFLD and supports recent recommendations that imaging modalities, such as MRI/MRE, can be helpful in providing additional assessment of liver disease progression over time, particularly in clinical trials.^{29,30}

Assessing the natural history of pediatric NAFLD in the “real world” and not in the context of a clinical trial setting, as well as the inclusion of a representative population in terms of age, sex and race/ethnicity are strengths of this study. Limitations include its retrospective nature, which may have introduced selection bias given that, in the clinical setting, not all patients undergo routine assessments of liver disease severity with repeat imaging MRI-PDFF/MRE. Specifically, in our center, repeat MRI-PDFF/MRE studies are obtained in patients at increased risk of more severe liver disease, given persistently elevated ALT >80 U/L, as well as other comorbidities, such as type 2 diabetes mellitus, dyslipidemia, and obstructive sleep apnea, most often in the context of a rising BMI. This suggests that the results of our study may not be generalizable to patients with mild NAFLD and/or no metabolic risk factors. In addition, this study is limited by the differences in the methodologies used to measure FF that limited the number of comparable MRI examinations. Not all patients included in this study had histologic confirmation of NAFLD; however, they had imaging evidence of hepatic steatosis and had undergone an extensive work up for other liver diseases, rendering it unlikely that they suffered from a different/additional liver disease. Lastly, although a small number of patients received vitamin E between MRI/MRE studies, the proportion with significant change in liver stiffness was similar to those who had not received vitamin E.

Further studies are needed with paired liver biopsy and MRI to determine to what degree changes in magnetic resonance (MR) measures of fat fraction and liver stiffness reflect changes in liver histology over time. In addition, studies assessing the relationship between changes in MR measures of NAFLD and clinical outcomes will be important to determine if MR changes in disease severity more accurately reflect risk of clinical adverse events in children with NAFLD, such as adverse cardiovascular outcomes or incidence of diabetes. Alternate strategies to treat NAFLD are urgently needed to prevent patients from progressing to more severe liver disease, and MRI may be a useful modality to noninvasively determine which children are at greatest risk for disease progression.³¹

In summary, this study shows that, in a real-world clinical population, only a small proportion of children and adolescents at risk of more severe NAFLD mandating repeat MRI-PDFF/MRE studies over time, treated with standard of care lifestyle interventions have significant improvements in liver FF and stiffness as measured by MRI. Our study also shows that, even in patients at increased risk of more severe NAFLD, solely monitoring serum ALT levels may provide false reassurance to clinicians over time. MRI-PDFF/MRE is very likely a helpful addition to ALT when monitoring liver disease progression.

Glossary

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

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Figure 1.
Change over time in MRI/MRE findings.

Figure 2.

Axial T2-weighted, **A**, fat saturated image, **B**, color wave image, and **C**, elastogram at diagnosis show mild hepatomegaly with normal liver stiffness manifest as purples, blues, and greens in the elastogram (mean = 2.2 kPa). Axial T2-weighted, **D**, fat saturated image, **E**, color wave image, and **F**, elastogram 4 years later show further enlargement of the liver with subtly increased T2-weighted signal. Waves in the liver are appreciably longer, reflective of elevated liver stiffness and faster wave travel. Liver stiffness is markedly increased (reds and yellows in the elastogram) with mean liver stiffness of 5.5 kPa.

Table I.

Baseline characteristics of the study cohort (n = 65)

Characteristics	Results
Age, y	14 (± 3)
Male sex, n (%)	45 (69%)
Race/ethnicity; n (%)	
White, non-Hispanic	39 (60%)
Hispanic	13 (20%)
Other	11 (17%)
Unknown	2 (<1%)
Anthropometrics	
Weight [kg]	90 (± 28)
Height [cm]	159 (± 14)
BMI [kg/m ²]	34.6 (± 6.7)
BMI percentile	98.5 (± 3.0)
Median hepatic FF(range)	
Total [n = 45]	10% (1–49)
Chemical shift [n = 42]	10% (1–26)
mDixon [n = 3]	15% (12–49)
Median liver stiffness [kPa] (range) [n = 65]	2.50 (1.45–4.06)
Median liver volume [mL] (range) [n = 65]	1950 (1255–3004)

Results are presented as means $\pm$ SD unless otherwise indicated.

Table II.

Population biochemical variables over time

Variables (n available for paired comparisons)	At first MRI	At last MRI	P value
ALT (U/L; n = 65)	84 ($\pm$ 44)	79 ($\pm$ 66)	.554
AST (U/L; n = 65)	44 ($\pm$ 24)	38 ($\pm$ 28)	.075
GGT (U/L; n = 62)	40 (21)	41 ($\pm$ 32)	.848
ALP (U/L; n = 57)	227 ($\pm$ 126)	178 ($\pm$ 124)	<.001
Glucose (mg/dL; n = 62)	90 ($\pm$ 7)	91 ($\pm$ 14)	.843
Insulin (mIU/mL; n = 58)	24 ($\pm$ 14)	28 ($\pm$ 18)	.124
HbA1c (%; n = 58)	5.3 ($\pm$ 0.8)	5.3 ($\pm$ 0.5)	.628
Triglycerides (mg/dL; n = 64)	146 ($\pm$ 76)	148 ($\pm$ 97)	.827
LDL (mg/dL; n = 64)	88 ($\pm$ 34)	84 ($\pm$ 32)	.199
HDL (mg/dL; n = 64)	40 ($\pm$ 9)	42 ($\pm$ 10)	.061

ALP, alkaline phosphatase; *AST*, aspartate aminotransferase; *GGT*, gamma glutamyl transferase; *HbA1c*, hemoglobin A1C; *LDL*, low density lipoprotein.

Results are presented as means ($\pm$ SD).