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# Targeted Hepatic Sonography During Clinic Visits for Detection of Fatty Liver in Overweight Children:

A Pilot Study

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## Abstract

**Objectives**—The purpose of this study was to assess the feasibility and utility of targeted hepatic sonography to evaluate for hepatic steatosis during a subspecialty clinic visit.

**Methods**—In this pilot study, we performed targeted hepatic sonography on 25 overweight children aged 7 to 17 years consecutively seen in a pediatric obesity clinic. Long-axis images of the right lobe of the liver and a split-screen image of liver and spleen were taken. Images were interpreted in real time by the radiologist and shown to the family. Demographics, clinical measurements, and laboratory parameters were also collected from the specialty clinic visit on the same day.

**Results**—Sonography required a median of 4 minutes during the visit (interquartile range, 3–5 minutes). All consented patients completed the study. The median alanine aminotransferase (ALT) level was 23 U/L in those with no steatosis (n = 14), 26 U/L with mild steatosis (n = 6), and 41 U/L with moderate/marked steatosis (n = 5). Children with ALT levels of 25 to 50 U/L had very variable sonographic measures of hepatic steatosis. When the participants were categorized by the overall degree of fatty liver, hepatic steatosis was significantly associated with the aspartate aminotransferase level (P=.028), ALT level (P=.003), and diastolic blood pressure (P=.05) but did not correlate with age, sex, Latino race, or insulin resistance.

**Conclusions**—Targeted hepatic sonography added information not apparent from routine ALT screening and provided immediate feedback to clinicians and families about the effect of obesity on end organs. This examination could be a feasible, informative addition to screening for children at high risk for nonalcoholic fatty liver disease who are seen in clinics that specialize in obesity.

#### Keywords

nonalcoholic fatty liver disease; pediatric obesity; sonography

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The prevalence of nonalcoholic fatty liver disease (NAFLD) is estimated at 20% to 70% in obese children and adolescents.<sup>1,2</sup> Early NAFLD may be reversible but is almost always asymptomatic, making appropriate screening of high-risk children important.

In 2007, the American Academy of Pediatrics, American Medical Association, and Centers for Disease Control and prevention recommended aspartate aminotransferase (AST) and alanine aminotransferase (ALT) tests as initial screening for NAFLD in overweight and obese children. However, recent studies in adults with biopsy-proven nonalcoholic steatohepatitis suggest that patients can have substantial steatosis and fibrosis with aminotransferase levels in the "normal" range.<sup>3–5</sup> In addition, Schwimmer et al<sup>6</sup> recently found that the 95th percentile for ALT in healthy, nonoverweight adolescents from a nationally representative sample (National Health and Nutrition Examination Survey) was 25.8 U/L in boys and 22.1 U/L in girls. In an analysis of 424 children presenting to our pediatric obesity clinic between 2002 and 2008, 64% of boys and 47% of girls had ALT levels above this 95th percentile (E.R.P., R.H.L., and Nathan M. Bass, MD, PhD, unpublished data, 2011). The high prevalence of ALT levels above the 95th percentile in our clinic population suggests that current screening may miss a substantial proportion of NAFLD.

New European guidelines for pediatric NAFLD suggest initial screening with both sonography and AST/ALT testing in obese children.<sup>7</sup> Sonography is commonly used in the evaluation of hepatic steatosis, with good specificity but limited sensitivity.<sup>8,9</sup> However, the feasibility and utility of targeted sonography as an NAFLD screen during routine evaluation of high-risk children has not been evaluated. We performed a pilot study to investigate whether targeted hepatic sonography during an initial pediatric obesity clinic visit would provide a rapid, noninvasive method of identifying children with NAFLD that would otherwise not have been detected.

#### Materials and Methods

Approval was obtained from the Committee on Human Research at the University of California, San Francisco. Parents of all participants provided signed informed consent, and participants provided assent.

We included children 7 to 17 years of age consecutively attending intake visits to our pediatric obesity clinic with a parent or guardian. Inclusion criteria were a body mass index (BMI) at or above the 85th percentile for age and sex, which is the cutoff for overweight in children, and a parent/guardian fluent in English or Spanish because of the informed consent requirement. Patients were excluded if they had a known diagnosis of liver disease other than NAFLD. The targeted sonographic examinations were performed in a dedicated examination room in the time between provider interactions; families see 1 or 2 physicians, a nutritionist, and a physical activity coordinator during the obesity clinic visit. All sonographic examinations were done during an intake clinic session in which 15 to 18 new patients undergo initial evaluation.

Sonograms were taken with an Acuson Sequoia 3000 ultrasound system and a 4V1 (1.75–4 MHz) or 4V2 (2–4MHz) transabdominal transducer (Siemens Medical Solutions, Mountain View, CA). Long-axis images of the right lobe of the liver including the right kidney and a dual image of the liver and spleen for direct comparison of echogenicity were obtained. The span of the right hepatic lobe, from dome to inferior tip, was measured.

All images and measurements were taken and interpreted by an experienced sonologist (V.A.F.) who was blinded to the patient's laboratory data. The scan time was recorded. The targeted sonograms were reviewed, and a determination regarding the presence of hepatic steatosis was reached. If deemed present, then an assessment regarding the degree of fatty infiltration was made. Sonographic manifestations of fatty infiltration included increased echogenicity of the liver, obscuration of the margins of the portal triads, increased relative echogenicity of the liver compared with the right kidney or spleen, and attenuation of the sound beam, which in some cases required technical adjustments, such as the use of a lower-frequency transducer.<sup>9,10</sup> Based on a combination of these sonographic features, the cases were classified, by a single experienced observer (V.A.F.) who was blinded to clinical and laboratory data, as "mild," "moderate," or "marked" (Figures 1–3).

Images were interpreted in real time by the radiologist and shown to the family. Their interpretation was discussed with the family and clinic provider. Children with moderate to marked fatty liver on sonography, ALT levels of greater than 60 U/L, or other abnormalities on the targeted sonography were referred to pediatric hepatology. No children had other abnormalities detected on the targeted sonography.

Additional information including demographics, family history, clinical measurements, and laboratory parameters were collected from the clinic visit on the same day as the sonographic examination. Acanthosis nigricans, a darkening of the posterior cervical and axillary skin associated with insulin resistance, was assessed by the clinic physician. Diastolic and systolic hypertension were defined as blood pressure greater than the 95th percentile for sex, age, and height.<sup>11</sup> High-density lipoprotein (HDL) was classified as below or above the 5th percentile and triglycerides as above or below the 95th percentile for age and sex.<sup>12</sup> As a measure of insulin resistance, the homeostasis model assessment of insulin resistance was calculated using fasting blood glucose and insulin levels. We categorized children with homeostasis model assessment of insulin resistance values of 3.16 or greater as insulin resistant following the receiver operating characteristic analysis of Keskin et al.<sup>13</sup> We defined metabolic syndrome as at least 3 of the following: BMI above the 95th percentile, HDL below the 5th percentile, triglycerides above the 95th percentile, systolic or diastolic blood pressure above the 95th percentile for age and sex, and an impaired fasting glucose level of greater than 100 mg/dL following previously published definitions.<sup>14–16</sup>

Statistical analysis was performed with the Kruskal-Wallis test for continuous variables and  $\chi^2$  test for categorical variables.

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## Results

Twenty-seven families were approached to participate in the study; 26 consented, and 1 was excluded because of known glycogen storage disease, which increases hepatic echogenicity. All participants completed the scan. Based on qualitative feedback from the 3 attending physicians, 2 nutritionists, and an activity coordinator in the clinic, the process was easily integrated and did not disrupt other patient care.

Our analysis included 25 children. Table 1 details their demographics, clinical parameters, and routine laboratory screening. Three children had ALT levels of greater than 50 U/L; 2 were 15-year-old Latino males, 1 with an ALT level of 92 U/L and sonographic findings of mild hepatic steatosis and the other with an ALT level of 103 U/L and marked steatosis. The third was a 12-year-old white male with an ALT level of 59 U/L and marked steatosis.

Two of 12 children with ALT levels of less than 25 U/L had mild steatosis on sonography. The category of children with ALT levels of 25 to 50 U/L had very variable sonographic measures of hepatic steatosis. Overall, ALT was associated with hepatic steatosis and each of the parameters used to assess steatosis (Table 2).

When the participants were categorized by the overall degree of fatty liver, hepatic steatosis was significantly associated with AST, ALT, and diastolic blood pressure but did not correlate with several other clinical characteristics usually associated with NAFLD, including age, sex, Latino race, and insulin resistance (Table 3). Hypertension, hypertriglyceridemia, and low HDL were not more significantly common in those with steatosis. Overall, ALT increased with increasing fatty infiltration of the liver, even though 21 of 24 participants had ALT levels of less than 50 U/L (Table 3 and Figure 4). One child with no AST/ALT test results available was excluded from this analysis.

#### Discussion

In this pilot study, we found that targeted hepatic sonography was a tolerable and rapid method to assess for hepatic steatosis in overweight children and adolescents. The sonographic examination required minimal time during a routine clinic visit. It added diagnostic information by detecting steatosis in several children that would not have been referred for further workup based on ALT testing.

Sonography as an adjunct to screening may be most informative in children with ALT levels of 25 to 50 U/L, as they had very variable sonographic findings. Those with sonographic findings of hepatic steatosis did not differ systematically from those without steatosis by several known risk factors for NAFLD, including age, sex, Latino race, BMI *z* score, and insulin resistance.

Targeted liver sonography could give useful immediate feedback for physicians assessing clinic patients with other risk factors for NAFLD. Focused sonographic techniques for diagnosis are used by emergency department physicians assessing abdominal trauma and surgeons localizing for outpatient biopsies.<sup>17,18</sup> These physicians receive training in limited protocols to assess for specific diagnostic information. Integrating targeted liver sonography

into a specialty clinic visit would require equipment, a trained provider—either a physician or a sonographer—and ideally an expert available to interpret the images immediately.

The multidisciplinary design and clustering of new patient visits on specific days made sonography very feasible in our clinic. Our sonograms offered real-time visual feedback for health care providers and families about the potential effects of obesity on end organs. We did not assess the impact of this information on behavior changes in this pilot study. Interestingly, a survey of parents with overweight children found that parent's belief that their child's weight status was a "health problem" was the strongest predictor of their readiness to take action in lifestyle changes aimed at weight loss (odds ratio, 9.75; 95% confidence interval, 3.43–27.67). Targeted sonography for detection of NAFLD could be an opportunity for providers to offer immediate evidence to families of one health problem caused by obesity in their child. Providers would also need to be trained in discussing the limitations of sonography with families.<sup>19</sup>

The resources required make sonography impractical for a general pediatrician's office but may be useful in a clinic specializing in pediatric obesity and its comorbidities. For example, the American Academy of Pediatrics recommends a staged approach to treatment of overweight and obesity depending on how elevated the BMI percentile is and whether associated "health risks" are present, including elevated ALT as a proxy for NAFLD.<sup>20</sup> The combination of ALT and sonography may provide a more specific assessment of NAFLD to guide early management. Recent European guidelines for pediatric NAFLD support this approach.<sup>7</sup>

The main limitation of this pilot study was its small sample size, limiting the recommendations we can make about the utility of sonography in specific patient groups. We did not measure waist circumference or assess pubertal status, nor was our goal to address the accuracy or reliability of the sonographic determination of hepatic steatosis, as this has been evaluated by many other studies.<sup>8–10</sup> This investigation did not include more invasive or expensive procedures, such as computed tomography, magnetic resonance imaging, or percutaneous liver biopsy (the reference but imperfect standard for confirmation of NAFLD), to correlate with the sonographic findings. The assessment was based on the interpretation of a single experienced reader, which entails some subjectivity. Thus, interobserver variability in the determination of fatty liver was not investigated. The goal of our pilot study was to assess feasibility and utility on a small scale, but these issues should be addressed in future studies.

The sensitivity of sonography for hepatic steatosis is limited, but it is generally accepted as a screening tool for NAFLD given its high specificity, tolerability, and low cost.<sup>8,9</sup> In a cohort of obese adolescents with hepatic steatosis prevalence very similar to that of our population, Bohte et al<sup>21</sup> concluded that negative sonographic findings were sufficient to rule out substantial hepatic steatosis (high negative predictive value), but positive sonographic findings were not sufficient to judge steatosis presence or severity (low positive predictive value) in this population. Two recent meta-analyses that compared sonography to liver histology for steatosis diagnosis actually found that the sensitivity and specificity of sonography did not differ significantly from those of magnetic resonance imaging and

magnetic resonance spectroscopy.<sup>8,21</sup> The specificity of sonography did not differ significantly from computed tomography, magnetic resonance imaging, or magnetic resonance spectroscopy in studies using steatosis cutoffs of greater than 0% to 5% and greater than 25% to 33%; it was lower in studies using steatosis of greater than 10% to 20%.<sup>21</sup> Given the currently limited ability to predict which patients with fatty liver will have nonalcoholic steatohepatitis, limited treatment options, and the requirement of liver biopsy for further workup, a highly specific and less sensitive test may be reasonable for initial NAFLD screening in overweight children.

In patients with steatosis on sonography or persistently elevated aminotransferase levels, it remains essential to exclude other causes of liver disease before diagnosing NAFLD, particularly given the low positive predictive value in obese adolescents.<sup>21</sup> Other methods to quantify changes in liver fat and assess for steatohepatitis are still required.<sup>7,17</sup> For children with steatosis on sonography or elevated AST/ALT levels, and for children with other abnormalities on targeted sonography or symptoms suggestive of gallstone or liver disease, a full sonographic examination of the liver, spleen, and pancreas with Doppler imaging and referral to a pediatric hepatologist is important.

The need for available, affordable, noninvasive diagnostic tests will increase as the prevalence of obesity and of NAFLD in childhood continues to grow. Better biomarkers for NAFLD and nonalcoholic steatohepatitis are needed, but currently, AST and ALT remain the most widely available and used serum markers.<sup>19</sup> This pilot study investigated the use of sonography and AST/ALT for concurrent primary NAFLD screening in high-risk children, as recently recommended.<sup>7</sup> We found that targeted hepatic sonographic examinations can feasibly be incorporated into an outpatient specialty clinic visit. This adjunct screening test may be particularly useful in children with ALT levels above the National Health and Nutrition Examination Survey 95th percentile but below levels that usually trigger further NAFLD workup, for example, ALT levels of 25 to 50 U/L. Future research to define subgroups of children in whom sonographic screening would add useful diagnostic and prognostic information is needed.

#### Acknowledgments

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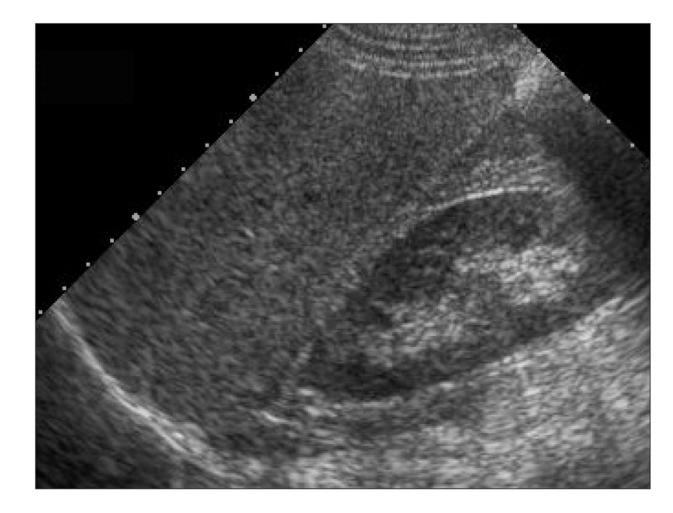
#### Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
HDL	high-density lipoprotein
NAFLD	nonalcoholic fatty liver disease

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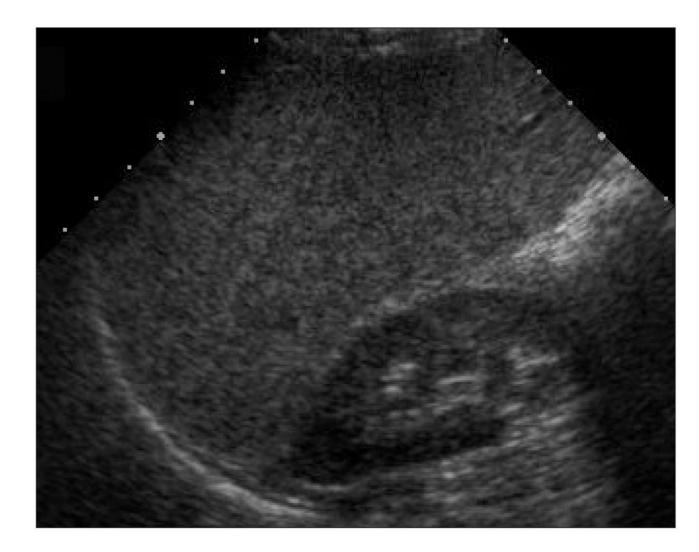
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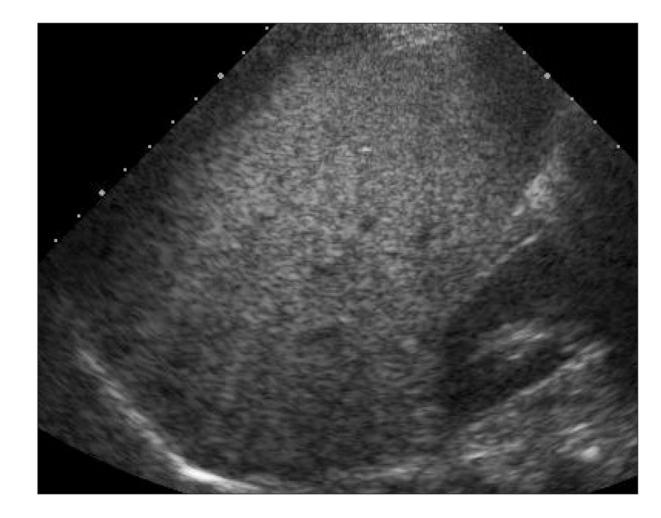
#### Figure 1.

Mild fatty infiltration of the liver, manifested as slightly increased echogenicity of hepatic parenchyma diffusely.



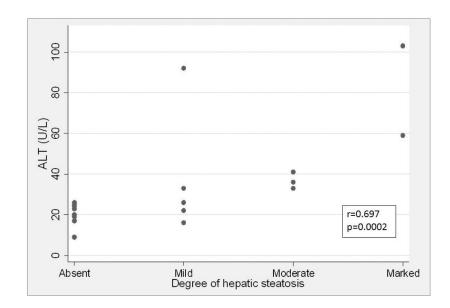
#### Figure 2.

Moderate fatty infiltration of the liver with increased echogenicity of the liver, particularly compared with the adjacent right kidney, and obscuration of the portal triad margins.



#### Figure 3.

Marked fatty infiltration of the liver with increased echogenicity and attenuation of the sound beam, requiring a decrease in the transducer frequency to improve penetration.



#### Figure 4.

Alanine aminotransferase levels increased with the degree of hepatic steatosis on sonography, but most children have ALT levels of less than 50 U/L even when liver fat is detected. The Spearman rank correlation coefficient and associated P were calculated.

#### Table 1

Characteristics of the Study Participants (n = 25)

Characteristic	Value
Age, y	$11.6\pm2.9$
Race	
White	16 (64)
African American	8 (32)
Asian	1 (4)
Latino	11 (44)
BMI, kg/m <sup>2</sup>	$32.4\pm6.2$
BMI z score	$+2.4\pm0.3$
Acanthosis nigricans	17 (68)
Family history of obesity	22 (88)
Family history of diabetes	17 (68)
Previously diagnosed NAFLD <sup>a</sup>	1
AST, U/L	24 (22–27)
ALT, U/L	24.5 (20-33)

Values are presented as mean  $\pm$  SD, number (percent), or median (interquartile range).

<sup>a</sup>One male patient with previously diagnosed NAFLD had an AST level of 56 U/L and an ALT level of 92 U/L on the day of sonography.

#### Table 2

#### Sonographic Findings by ALT Level<sup>a</sup>

Finding	ALT <25 U/L (n = 12)	ALT 25–50 U/L (n = 9)	ALT >50 U/L (n = 3)	P <sup>b</sup>
Scan time, min	3 (2-4)	4 (3-4)	4 (4–5)	.092
Overall hepatic steatosis		χ- γ		
None	10 (83.3)	3 (33.3)	0	.025
Mild	2 (16.7)	3 (33.3)	1 (33.3)	
Moderate/marked	0	3 (33.3)	2 (66.7)	
Liver echogenicity				
Normal	10 (83.3)	3 (33.35)	0 (0%)	.001
Mildly increased	1 (8.3)	3 (33.3)	1 (33.3)	
Moderately increased	1 (8.3)	3 (33.3)	0	
Markedly increased	0	0	2 (66.7)	
Liver/kidney echogenicity	v contrast			
Normal	11 (91.7)	4 (44.4)	0	.013
+	0	3 (33.3)	1 (33.3)	
++	1 (8.3)	2 (22.2)	1 (33.3)	
+++	0	0	1 (33.3)	
Sound beam attenuation				
None	11 (91.7)	6 (66.7)	0	.004
+	1 (8.3)	2 (22.2)	1 (33.3)	
++	0	1 (11.1)	1 (33.3)	
+++	0	0	1 (33.3)	
Portal triads obscured	1 (8.3)	3 (33.3)	3 (100)	.007
Liver span, cm	14.8 (13.6–16.0)	15.6 (13.7–16.0)	17.4 (15.4–18.2)	.279

Values are presented as median (interquartile range) or number (percent).

<sup>a</sup>One child with no steatosis was missing ALT test results and was excluded from this analysis.

 $^{b}$ Kruskal-Wallis test for continuous variables,  $\chi^{2}$  test for categorical variables.

#### Table 3

Association of Clinical and Laboratory Findings With Hepatic Steatosis

	Overall Hepatic Steatosis Grade			
Characteristic	None (n = 14)	Mild (n = 6)	Moderate/Marked (n = 5)	P <sup>a</sup>
Age, y	11.2 (9.5–14.6)	13.3 (10.6–15.2)	13.0 (12.2–15.6)	.170
Male	8 (57)	2 (33)	4 (80)	.297
Latino	4 (29)	4 (67)	3 (60)	.111
White	6 (38)	5 (31)	5 (31)	.039
African American	7 (50)	1 (17)	0	.079
BMI z score	+2.4 (2.3–2.6)	+2.3 (2.1-2.6)	+2.3 (2.3-2.4)	.790
Acanthosis nigricans	10 (71)	5 (83)	2 (40)	.452
AST, U/L	23 (21–25)	22.5 (22–27)	34 (26–38)	.028
ALT, U/L	23 (19–24)	26 (22–33)	41 (36–59)	.003
Fasting glucose, mg/dL	81 (77–83)	83 (81–85)	83 (82–93)	.372
Insulin resistant <sup>b</sup>	8 (62)	5 (83)	4 (100)	.257
Systolic blood pressure, mm Hg	97 (93–113)	112 (104–117)	120 (112–120)	.580
Diastolic blood pressure, mm $Hg^{C}$	62 (56–68)	55 (54–57)	68 (63–68)	.050
Triglycerides, mg/dL	90 (68–114)	132 (49–214)	172 (85–258)	.338
HDL, mg/dL	42 (36–46)	50 (45-60)	40 (38–42)	.198
Metabolic syndrome	0	1 (17)	1 (20)	.800
Scan time, min <sup>d</sup>	3 (3–3)	4.5 (4–5)	4 (4-4)	.111

Values are presented as median (interquartile range) or number (percent).

<sup>*a*</sup>Kruskal-Wallis test for continuous variables,  $\chi^2$  test for categorical variables.

 $^{b}$  Homeostatic model of insulin resistance value of 3.16 or greater.

<sup>c</sup>No patients with diastolic hypertension.

 $^{d}$ One patient with moderate steatosis required 10 minutes to scan, and 1 with mild steatosis required 7 minutes. All other scans lasted 2 to 5 minutes.