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OBSERVATION

# Overview of screening methods for fatty liver disease in children

Caroline Anitha Devadason, Ann O Scheimann

Caroline Anitha Devadason, Ann O Scheimann, Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University, Baltimore, MD 21287, United States
Author contributions: Devadason CA did research and wrote manuscript; Scheimann AO helped with manuscript development and writing/editing.
Correspondence to: Ann O Scheimann, MD, MBA, Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University, Baltimore, MD 21287, United States. ascheim1@jhmi.edu
Telephone: +1-410-9558769 Fax: +1-410-9551464
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## Abstract

The prevalence of obesity and obesity related comorbidities including diabetes and nonalcoholic fatty liver disease (NAFLD) has been rising globally. Nonalcoholic fatty liver disease is emerging as a common liver disease among adults which can lead to the eventual development of complications including cirrhosis and hepatocellular carcinoma. With the rise of obesity in children, the development of detection methods for the presence of NAFLD is becoming imperative. Although the gold standard for diagnosis is liver biopsy, practical issues limit pediatric use and warrant development of noninvasive or minimally invasive screening tools for the detection and staging of NAFLD. A variety of diagnostic methods have been studied including use aminotransferases, imaging studies and serologic markers which have some population-based limitations. Additional factors such as gender and ethnicity may also play a role in the screening of NAFLD in pediatric population studies.



**Key words:** Nonalcoholic fatty liver disease; Children; Alanine aminotransferase; Ethnicity; Gender; Detection methods

**Peer reviewers:** Stephanie Abrams, MD, Texas Children's Hospital, 6621 Fannin, Suite 1010.00, Houston, TX 77030, United States; Jean Molleston, MD, Riley Hospital for Children, 702 Barnhill Drive, ROC 4210, Indianapolis, IN 46202, United States

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## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has emerged as the most common cause of liver disease among children, paralleling the rise in obesity over the past few decades. Fatty liver disease has a spectrum of clinical manifestations, ranging from simple steatosis to steatosis with inflammation and fibrosis nonalcoholic steatohepatitis (NASH)[1]. NAFLD was first described by Zelman[2] in 1952 among an inpatient population of thirty obese men with liver disease. In 1983, Moran *et al*[3] reported 3 children less than 14 years of age with severe hepatitis and fibrosis. Population studies also seem to suggest racial and gender variability regarding NAFLD[4,5]. Factors including obesity, gender and ethnicity may influence the development of NAFLD.

Development of safe and cost-effective methods for screening and detection of NAFLD is critical given the large number of patients. Frequently used screening methods for NAFLD include aminotransferases and ultrasonography. NAFLD is the most common etiology for transaminase elevation among adults[6]. Although the gold standard for diagnosis is a liver biopsy, the invasiveness and expense of the procedure limits the feasibility of this option in children. Available imaging modalities, including ultrasound, computed axial tomography and magnetic resonance imaging, have some limitations for broad use, including cost, radiation exposure, as well

as technical limitations due to body habitus. A literature search was performed, through PubMed, using the following and combination of the following terms: NAFLD, NASH, nonalcoholic fatty liver, steatohepatitis, infant, child and adolescent. The results were limited to human studies, and infant, child, adolescent and the English language. The utility of current screening methods for the detection of pediatric NAFLD will be reviewed.

## ALANINE AMINOTRANSFERASE AS A SURROGATE OF NAFLD

Unexplained alanine aminotransferase (ALT) elevation is a frequently used surrogate for the presence of NAFLD in children and adults. ALT elevation (> 30 U/L) was reported in 6% of overweight adolescents and 10% of obese adolescents among 2450 children enrolled in the NHANES Ⅲ survey (National Health and Examination Survey cycle Ⅲ) by Strauss *et al*[7]. ALT elevation (>30 U/L) was an independent predictor for NAFLD among an Italian pediatric sample of 268 children between the ages of 6 and 20 years with a body mess index (BMI) of >90th percentile[8]. ALT elevation was present in 76 children with NAFLD (81% sensitivity of ALT for NAFLD prediction); in 49 children ALT values were > 40 U/L (89% sensitivity of ALT for NAFLD prediction)[8]. Louthan *et al*[5] noted that elevated ALT (ALT > 40 U/L) was four times more likely in obese children.

In several studies, ALT elevation has correlated with the presence of hepatic fat on imaging. Fishbein *et al*[9] reported a retrospective review of hepatic magnetic resonance imaging (MRI) findings of 39 obese Caucasian children, noting hepatic fat fraction correlated with serum ALT (ALT > 35; $r = 0.44$; $P < 0.05$) and age ($r = 0.54$; $P < 0.005$) but not with BMI z-score. In a prior study of obese children with hepatomegaly, he reported 21 of 22 (95%) subjects had elevated fat fraction on hepatic MRI and 12 of 20 (60%) had elevated serum ALT (ALT > 35)[10]. Correlation between ALT elevation (ALT > 58) and fatty liver on ultrasound ($P < 0.001$) was reported in a prospective study of 84 Chinese children seen in the obesity and lipid disorder clinic (ages 9.5-14 years); gamma-glutamyl-transpeptidase (GGT, abnormal GGT > 40) also correlated with fatty liver on imaging ($P < 0.001$)[11]. Tazawa *et al*[12] reported sensitivity, specificity and positive predictive values of 0.92, 0.62 and 0.83 respectively for ALT elevation (ALT > 30 U/L) and detection of evidence of fatty liver on ultrasound for a school-aged population in Japan.

## PITFALLS OF ALT

There can be shortcomings with utilizing ALT as a screening method for NAFLD. Aminotransferase elevation is not universally encountered among patients with NAFLD. The Dallas Heart study conducted in Dallas County on 2287 adult subjects revealed that abnormal ALT was not a useful diagnosis of NAFLD as 79% of subjects with hepatic steatosis (determined by elevated hepatic triglycerides on imaging) had normal ALT levels[13]. In the study conducted by Franzese *et al*[14], 26 out of 38 (68%) obese children with fatty liver on imaging had normal aminotransaminases. Similar concerns were raised by Fishbein *et al*[10] upon demonstration that ALT (ALT > 35) did not detect low levels of hepatic fat fraction. In the study by Tazawa *et al*[12], 18% of Japanese schoolchildren with normal ALT levels (ALT < 30) had ultrasound findings of a fatty fibrotic pattern suggestive of nonalcoholic steatohepatitis. A study by Burgert *et al*[15] demonstrated that only 48% of obese children (42% Caucasian/25% African American/33% Hispanic) with intrahepatic fat accumulation on MRI had abnormal ALT levels (ALT > 35), concluding that use of serum ALT as a screening tool may not be effective. Of note, children with an absence of abnormal ALT levels are rarely investigated for NAFLD; evidence of insulin resistance and diabetes should heighten concern for possible NAFLD as it has been associated with liver disease in adults and children[16]. Upcoming imaging methods may enhance capacities for non-invasive detection and staging of NAFLD and NASH in children. Preliminary adult data suggest the FibroScan® probe as a potential noninvasive technique due to its non-specificity and potential to compensate for larger size. FibroScan® measures liver stiffness by transient elastography as a surrogate for fibrosis[17]. FibroScan® has been studied in adult mixed populations, including hepatitis and NAFLD. Prior probes were unable to measure liver stiffness in 2%-10% of patients due to inflammation and body size[18]. The XL® FibroScan probe has improved detection of NAFLD and fibrosis among adults through improved transducer sensitivity with greater measurement depth but still has suboptimal reliability among morbidly obese adults (BMI > 40) and diabetics[18-20]. However, the reproducibility of results is a drawback as well as concerns regarding specificity of findings.

## GENDER IN NAFLD

Several studies have indicated a potential relationship between gender and the presence of NAFLD. In general, it has been noted that NAFLD is more prevalent in males than females. Several imaging studies using ultrasound and hepatic MRI have suggested male predominance[8,15]. In addition, a retrospective review, published in 2006 of pediatric autopsies by Schwimmer *et al*[4] in San Diego County, observed that children with fatty liver were older and more likely to be male with a higher BMI. An earlier study published by Schwimmer *et al*[21] published in 2003 observed that age and sex did not differ in patients with liver fibrosis, although the majority of patients in the study with NAFLD were male (70%). Similarly, male dominance was reported in a Japanese study by Tominaga *et al*[22] but the values were not statistically significant. In an Australian study of 500 adolescents, the prevalence of

transaminase elevation was increased in obese boys (40% in boys and 20% in girls), but there was no screening for the presence of underlying liver disease[16]. Likewise, in a study done in Taiwan (which included screening for hepatitis B and C), there was a higher prevalence of transaminase elevation in obese boys over girls[23]. A higher prevalence of transaminase elevation among obese boys has also been reported by Chan *et al*[11] and Schwimmer *et al*[24] (defined as ALT > 40 U/L), as well as Strauss *et al*[7], but with a note of caution as there was alcohol consumption reported among adolescent males. Using subjects from the ages of 12-19 years from the NHANES study (1999-2002) with exclusion of those with ethanol consumption, Graham *et al*[25] reported an interaction with male sex upon ALT elevation (ALT > 40).

Gender influences upon the prevalence of NAFLD in children have not been consistently substantiated by other investigators. Louthan *et al*[5] did not report an influence of gender upon ALT (ALT > 40) in her pediatric study population. Similarly, Fishbein *et al*[9] did not detect differences in ALT based upon gender.

## ETHNICITY AND NAFLD

There has been a correlation between ethnicity and ALT levels. Normal ALT ranges vary between different ethnicities and differing ALT levels will have to be regarded for different ethnic groups.

In particular, African Americans have been noted to have the lowest percentage of elevated ALT levels, while those of Hispanic origin have been observed to have the highest. The prevalence of ALT elevation (ALT > 30) was 7.4% in Caucasian adolescents, 11.5% in Mexican Americans and 6.0% in African American adolescents in one study conducted utilizing the NHANES survey (1999-2004)[26]. Louthan *et al*[5] also observed that elevated ALT was four times less likely in African Americans than Caucasians, despite increased obesity and insulin resistance suggestive of potential ethnic differences in ALT norms[5].

Several studies have noticed the effect of ALT on the Hispanic population. A recent multicenter pediatric cross-sectional study by Schwimmer *et al*[24] reported a prevalence of elevated ALT (ALT > 40) levels as 36%, 22% and 14% among Hispanic, Caucasian and African American adolescents, respectively; other studies have reported similar findings[27]. Discrepancies may also exist among Asian subpopulations as children of Filipino descent had a prevalence of 20%, but only 4% in those of Vietnamese or Cambodian origin[4].

Similar ethnic influences upon NAFLD/NASH have been reported among adults, although higher percentages of African American patients were encountered. Likewise, out of 151 adults cared for at Brooke Army Medical Center and diagnosed with NAFLD (46% of cohort), the prevalence of NAFLD/NASH confirmed by biopsy was 58.3% among Hispanics, 44% among Caucasians and 35.1% among African Americans[28].

## CONCLUSION

Paralleling the rise of obesity in children and adolescents has been a rise in the incidence of NAFLD in pediatric populations. Optimal methods for population-based screening for pediatric NAFLD remain undefined to date. As demographic factors such as gender and ethnicity may play a role in the prevalence of NAFLD/NASH, use of targeted screening methods may be feasible but consideration for ethnicity norms on markers, including ALT, may be necessary to enhance sensitivity. Data on influences of gender upon NAFLD/NASH prevalence/detection in children has been inconsistent to date, warranting additional investigation.

Utilizing ALT as a determinant of NAFLD may not be effective. Studies using ultrasonography indicated fibrotic patterns, yet subjects had normal ALT. Also, hepatic steatosis was noted in subjects with normal ALT in the Dallas Heart study. Therefore, further studies are needed to determine surrogate markers of NAFLD in varying pediatric populations.

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