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Serum Alanine Transaminase Is an Inadequate Nonalcoholic Fatty Liver Screening Test in Adolescents: Results From the National Health and Nutrition Examination Survey 2017-2018

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is common in overweight adolescents, and screening with serum alanine transaminase (ALT) levels is recommended by the American Academy of Pediatrics. We sought to determine if ALT is an accurate adolescent screening measure for NAFLD in a nationally representative sample of overweight adolescents. Diagnosis of NAFLD was determined using vibration-controlled transient elastography. Analyses were performed to calculate the sensitivity, specificity, positive predictive value, negative predictive value, and Youden's index at various serum ALT cutoff levels. Receiver operating curves were generated in order to determine ALT's discrimination capability. Males and females were analyzed separately. While average measures (mean and median) of ALT were higher in subjects with NAFLD, ALT provided only minimal discrimination with AUROC (area under the receiver operating characteristic) values of .66 in males and .67 in females. In a nationally representative sample of overweight and obese adolescents, serum ALT level functioned inadequately as a screening test to detect NAFLD.

Keywords

fatty liver, adolescents, obesity, NAFLD, ALT

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common form of chronic liver illness in the United States affecting an estimated 24% of adolescents.[1] The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Pediatric Guidelines and the American Academy of Pediatrics recommend that all overweight and obese individuals be screened for NAFLD in order to promote changes in diet and physical activity for affected individuals.[2,3] Both interventions are validated approaches to improve and potentially reverse the course of NAFLD.[4,5] More specifically, NASPGHAN Pediatric Guidelines state that serum alanine transaminase (ALT) levels should be used as an initial screening test in overweight and obese adolescents and proposed ALT screening cutoff values of 44 IU/L in girls and 50 IU/L in boys.[2] These recommendations were based on data generated from samples of adolescents under medical evaluation and already deemed to be at high risk for NAFLD. To date, no evaluation of ALT as a screening test has been performed on a nationally representative random sample. In addition, the gold standard for the diagnosis for NAFLD is the histological evaluation of liver biopsy tissue, but for a general population of adolescents, this test would be unethical to perform. The accuracy of ultrasound elastography to detect NAFLD and the simultaneous evaluation of adolescents with both elastography and ALT in the 2017-2018

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Table 1. Demographic and Clinical Characteristics of Sample of Overweight and Obese Adolescents (N = 375).

	No NAFLD (n = 186), % (95% CI)	NAFLD (n = 189), % (95% CI)	*P*
Age (years)			.36
12-15	59.0 (47.7-70.3)	50.6 (40.2-61.0)	
16-19	41.0 (29.7-52.3)	49.4 (39.0-59.8)	
Gender			.004
Male	42.4 (31.1-53.7)	59.9 (52.2-67.6)	
Female	57.6 (46.3-68.9)	40.1 (32.4-47.8)	
Race			.60
White	52.9 (41.6-64.3)	42.3 (29.3-55.3)	
Black	14.9 (7.6-22.2)	11.3 (5.7-16.8)	
Hispanic	24.3 (13.0-35.6)	34.5 (22.1-46.8)	
Other	7.9 (3.6-12.2)	12.0 (5.7-18.2)	
Income			.20
<$20 000	17.7 (10.9-24.5)	20.3 (14.4-26.3)	
$20 000-$100 000	54.8 (44.3-65.3)	61.8 (52.4-71.2)	
>$100 000	27.5 (17.3-37.7)	17.9 (10.5-25.2)	
ALT			.0002
Mean (SE)	16.0 (1.0)	24.9 (1.4)	
Median estimate (95% CI)	13.1 (11.2-15.0)	17.8 (16.8-18.9)	
CAP score			<.0001
Mean (SE)	212.8 (4.0)	304 (3.4)	
Median estimate (95% CI)	221.2 (211.9-230.5)	299.6 (288.3-310.9)	
Clinical abnormalities			
High blood pressure	0.6 (0.0-1.8)	4.6 (1.5-7.8)	.02
High triglyceride	9.6 (1.9-17.3)	26.2 (18.9-33.5)	.0006
Low HDL[a]	18.3 (9.4-27.2)	39.3 (30.7-47.9)	.002
High glucose	0.4 (0.0-1.1)	1.5 (0.0-3.5)	.26
Waist circumference >90%[b]	16.0 (9.1-22.9)	48.2 (38.2-58.2)	.0002

Abbreviations: NAFLD, nonalcoholic fatty liver; CI, confidence interval; ALT, alanine transaminase; SE, standard error; CAP, controlled attenuation parameter; HDL, high-density lipoprotein.
[a]n = 374.
[b]n = 371.

National Health and Nutrition Examination Survey (NHANES) provide an opportunity to examine the usefulness of ALT as a screening tool for NAFLD in a nationally representative sample using elastography as the gold standard. We limited our sample to overweight and obese adolescents, a group for whom screening for NAFLD is appropriate given the high prevalence, the benefits of early intervention, and the potential for the reversal of pathology with appropriate lifestyle changes.

Methods

NHANES is an ongoing, cross-sectional survey of the civilian, noninstitutionalized population.[6] NHANES consists of 3 parts: a health interview survey, a health examination survey, and a nutrition survey. We included 375 individuals in our sample who were between the ages of 12 and 19 years from the 2017-2018 NHANES survey cycle. We excluded any individuals with viral hepatitis B or C and those taking any of the following medications: insulin, prednisone, azathioprine, methotrexate, valproic acid, minocycline, demeclocycline, doxycycline, and tetracycline. Overweight and obesity were determined using CDC (Centers for Disease Control and Prevention) growth for age percentiles, classifying body mass index (BMI) in the 85th to 95th percentile for age as overweight, and BMI >95th percentile for age as obese.[7,8]

NAFLD was determined using vibration-controlled transient elastography (VCTE®; FibroScan 502 V2 Touch) results from the NHANES examination data. VCTE is a noninvasive technique that measures shear wave ultrasonic attenuation, called controlled attenuation parameter (CAP), to detect liver fat with values ranging from 100 dB/m to 400 dB/m. Two probes are available, M-probe and XL-probe, and chosen based on

BMI and skin to liver capsule distance. Adolescents with CAP scores >250 dB/m (M probe) or 263 dB/m (XL probe) were identified as having NAFLD.[10,11]

Laboratory data from NHANES included ALT, high-density lipoprotein, cholesterol, triglyceride, and fasting glucose levels. Analyses were performed in 2020 using SAS Software to calculate the sensitivity, specificity, positive predictive value, and negative predictive value for detecting liver steatosis using incremental ALT cut-off levels. Youden's index and AUROC (area under the receiver operating characteristic) values were derived to determine ALT's discrimination capability and optimal cutoff values for males and females separately.

Results

The overall demographic and clinical characteristics for overweight or obese adolescents with and without NAFLD is shown in Table 1. The prevalence of NAFLD was 50.4% in this cohort and was more common in males. The prevalence of the metabolic parameters, except fasting glucose, was statistically significant higher in subjects with NAFLD. The median and mean ALT levels for subjects with NAFLD were also statistically significantly higher at 17.8 IU/L and 24.9 IU/L as compared with 13.1 IU/L and 16.0 IU/L for subjects without NAFLD ($P < .01$; Table 1).

In general, males had overall higher average levels of ALT than females but only 8.9% of boys and 1.7% of girls had an ALT ≥50 IU/L and ≥44 IU/L, respectively. In males, the ALT cutoff of 50 IU/L produced the greatest level of specificity (.99), but only a sensitivity of .15, equating to a Youden's index of .14. Similarly, the ALT cutoff of 44 IU/L in females produced a specificity of .98 but only a sensitivity of .02, equating to a Youden's index of .00. Using 50 IU/L for males and 44 IU/L for females missed NAFLD detection in >90% of overweight and obese teenagers who were found to have NAFLD by VCTE (Figure 1A and B).

The optimal ALT cutoffs for liver steatosis were 18 IU/L for males and 14 IU/L for females with Youden's index values of .26 and .40, respectively. At the optimal cut value for males, the sensitivity and specificity of ALT were .68 and .58, respectively, with a positive predictive value of .68 and a negative predictive value of .56. At the optimal cut value for females, the sensitivity and specificity of ALT were .75 and .65, respectively, with a positive predictive value of .59 and a negative predictive value of .80. The AUROC (the measure of discrimination and equivalent to the area under the curve) for ALT was .66 in males and in females was .67 (Tables 2 and 3 and Figure 2).

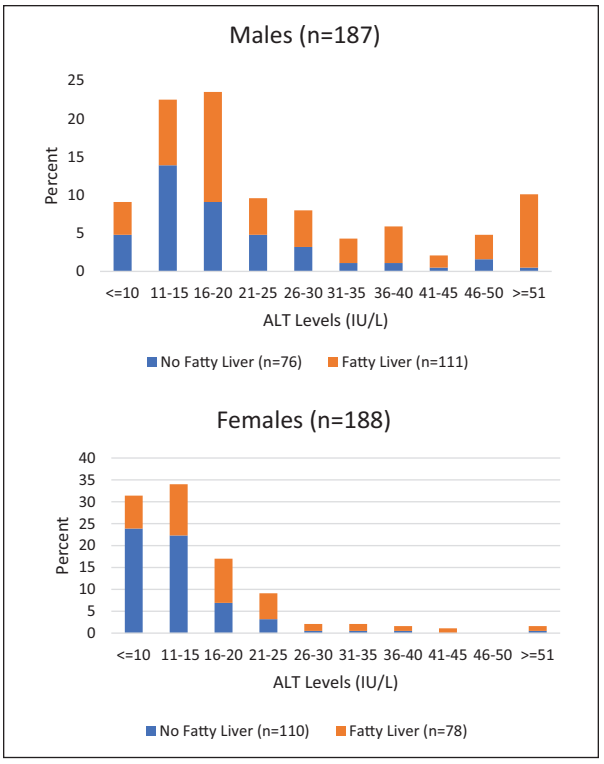

Figure 1. Distribution of alanine transaminase (ALT) values in nonalcoholic fatty liver (NAFLD) and non-NAFLD obese/overweight subjects.

Discussion

We found the average levels of ALT to be higher in overweight and obese adolescents with NAFLD as compared with overweight and obese adolescents without NAFLD, but ALT did not adequately discriminate between these subjects despite the determination of optimal serum ALT cutoff points. ALT failed to provide sufficient sensitivity to detect NAFLD and had poor negative predictive value. Taken together, current ALT guidelines regarding cutoff values miss NAFLD detection in >90% of overweight and obese teenagers who have NAFLD as detected by VCTE. On the other hand, at high levels of ALT, specificity and positive predictive value were excellent in males, and clinicians should suspect NAFLD in these individuals.

Our data do not support the recommendation from the NASPGHAN Pediatric Guidelines that emphasize the need to screen for NAFLD using ALT. This recommendation is based on the assumption that ALT has a high sensitivity and reasonable specificity at 44 IU/L and 50 IU/L for females and males, respectively, which our data do not support.[3] The disparity between their

Table 2. Males' Overweight/Obese Adolescents Fatty Liver Sensitivity and Specificity Cutoffs (n = 187).

ALT cutoff value	Youden's index	Sensitivity	Specificity	Positive predictive value	Negative predictive value
17	.24	.66	.58	.68	.56
25	.16	.37	.79	.69	.48
50	.13	.14	.99	.96	.46

Table 3. Females' Overweight/Obese Adolescents Fatty Liver Sensitivity and Specificity Cutoffs (n = 188).

ALT cutoff value	Youden's index			Sensitivity	Specificity	Positive predictive value	Negative predictive value
13		.40		.75	.65	.59	.80
25	.09	.13	.96	.66	.63		
40	.03	.05	.98	.66	.61		

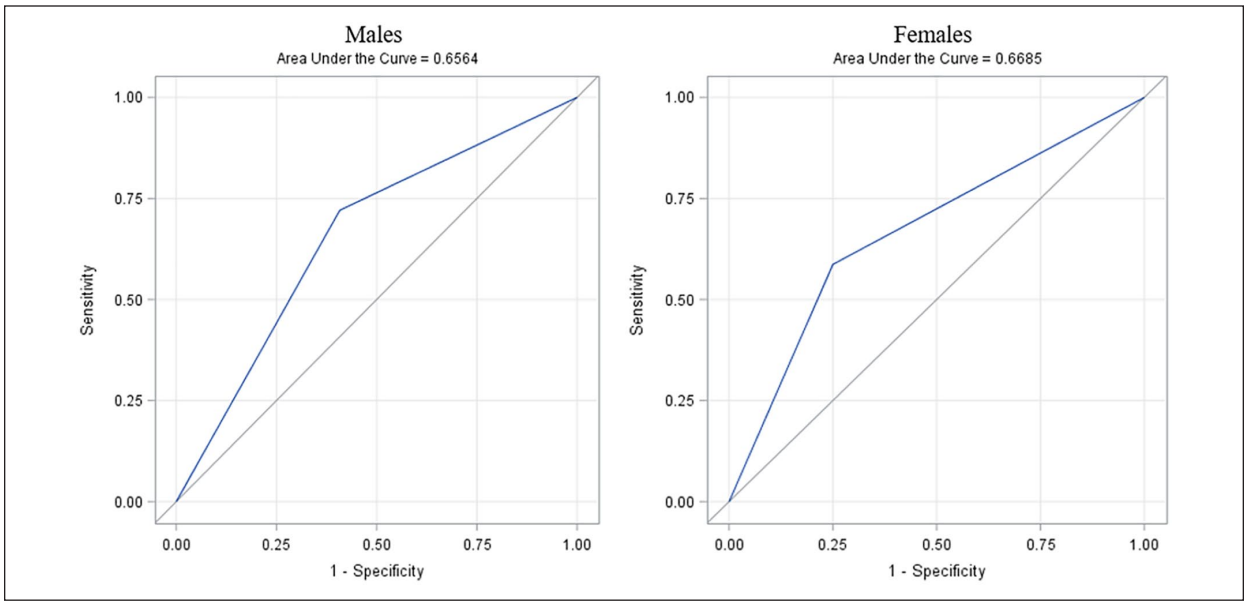

Figure 2. Assessment of diagnostic discrimination for alanine transaminase using receiver operating curves.

findings and ours might be explained by the different populations investigated to establish the ALT cutoff values. The results cited for their recommendation used ALT cutoffs generated from children 10 years of age and older who were referred to a specialist for suspected NAFLD due to elevated ALT.[12] Our results, on the other hand, are representative of the US adolescent population and are consistent with other studies.[13,14]

A limitation of our study is the lack of a liver biopsy to diagnose NAFLD, which was determined using VCTE. While VCTE does not have universal accepted cutoff values to diagnose NAFLD, we chose values of 250 dB/m (M probe) and 263 dB/m (XL probe) to define NAFLD based on prior studies that assessed the validity of this cutoff in children[10] and in adults.[11] Others have suggested CAP scores ranging from 225 dB/m to 288 dB/m to diagnose mild/moderate NAFLD.[15,16] In additional analyses, we found that while changing the CAP score to detect NAFLD did adjust the prevalence of NAFLD, it did not improve the diagnostic sensitivity of ALT (225 dB/m cutoff, AUROC: 0.58; 288 dB/m cutoff, AUROC: 0.62). Finally, subjects in this study were not evaluated by a gastroenterologist or hepatologist and NHANES does not screen for other causes of steatosis such as Wilson's disease.

The strengths of this study rely on high-quality NHANES data collection and subject sampling with extensive quality control measures and by technicians trained and certified in all aspects of data collection. Sampling for NHANES data relies on a probability cluster sampling method and a sampling frame that is representative of the US noninstitutionalized civilian population. This is also the first time VCTE has been used in a representative US population study. Previous studies have used routine abdominal ultrasound, which in children has only an 80% sensitivity to detect a significant degree (20% to 30%) of hepatic steatosis,[17,18] while VCTE is able to detect milder degrees of hepatic steatosis (approximately 5%).

Conclusion

Nonalcoholic fatty liver disease is highly prevalent among obese and overweight adolescents, and the long-term health consequences associated with NAFLD are often attenuated with early lifestyle intervention.[19,20] While these observations form the rationale for NAFLD screening, ALT is an insensitive screening tool, and misses the vast majority of adolescents with NAFLD. NAFLD screening for overweight/obese adolescents might better be performed by VCTE, which is a safe, quick, noninvasive tool that can offer point-of-care assessment to inform patients and their parents. Longitudinal research is needed to establish the cost-effectiveness and clinical usefulness of VCTE screening in overweight or obese adolescents.

Author Contributions

Dr Hecht conceived the research question, contributed to the manuscript, and performed the analyses. Ms Rabil and Ms Williams contributed to the manuscript and performed analyses. Dr Abrams contributed to the development of the research question and contributed to the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

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