Indian Journal of Gastroenterology (December 2020) 39(6):608–613
https://doi.org/10.1007/s12664-020-01091-2

SHORT REPORT

Prevalence of elevated alanine aminotransferase levels in adult participants from a community-based study from northern part of India

Nishant Aggarwal[1] · Alka Singh[1] · Ashish Agarwal[1] · Vignesh Dwarakanathan[2] · Anil K. Verma[1] · Ritvik Amarchand[2] · Shyam Prakash[3] · Anand Krishnan[2] · Vishnubhatla Sreenivas[4] · Shalimar[1] · Vineet Ahuja[1] · Govind K. Makharia[1]

Received: 31 March 2020 / Accepted: 1 September 2020 / Published online: 24 October 2020

Abstract

Alanine aminotransferase (ALT) is a cytosolic enzyme specific to hepatocytes, and its elevated level in the peripheral blood denotes liver cell injury. Detection of persistently elevated ALT levels during routine health check-up in asymptomatic or symptomatic individuals provides a window of opportunity to explore the causes of liver cell damage and for the timely institution of appropriate treatment. This was a retrospective study using a subset of the data from a previous community-based prospective study done for the estimation of the prevalence of celiac disease (CD) in India, during which estimation of ALT levels in the blood samples of participants was also carried out. Of the 11,053 individuals (4399 [39.8%] males; mean age 37.9 ± 13.3 years) screened, 6209 consented to provide blood samples for testing for CD. Of these, assessment of serum ALT levels was done in 6083 (2235 [36.7%] males) patients. ALT was elevated above the upper limit of normal (ULN) (> 40 IU/L) in 1246 (20.5%) of the participants and > 1.5 times (> 60 IU/L) in 329 (5.4%) participants. The ALT levels were elevated more frequently in men as compared to women (29.4% vs. 15.3%, $p < 0.001$). There was a significant positive correlation (Pearson correlation coefficient [r] = 0.25, $p < 0.0001$) between ALT levels and body mass index (BMI). With increasing age, there was a significant decrease in the proportion of subjects with ALT ≥ 1.5× ULN ($p < 0.001$). Our results suggest that a high proportion (20.5%) of individuals otherwise considered healthy have values of ALT level in the serum above the "normal" range/cut-off suggesting likely ongoing underlying liver damage. There is a need for measures to evaluate and, if found, treat the underlying cause for the same.

Keywords Alanine transaminase · Body mass index · Celiac disease · Hepatocytes · Metabolic syndrome · Non-alcoholic fatty liver disease · Obesity · Prevalence · Public health · Tissue transglutaminase

Introduction

Alanine aminotransferase (ALT) is a cytosolic enzyme specific to hepatocytes, and its elevated level in the peripheral blood denotes liver cell injury [1]. While the determination of the serum levels of ALT is currently the most commonly applied test for screening for liver diseases, its level in blood also acts as a surrogate marker of the severity of liver disease [2]. Elevated serum ALT levels have been shown to be associated with age, gender, obesity, metabolic syndrome, ingestion of hepatotoxic drugs, and various forms of acute and chronic hepatitis including viral, alcoholic, and non-alcoholic fatty liver disease (NAFLD) [3–5]. Detection of persistently elevated ALT levels during routine health check-up in asymptomatic or symptomatic individuals provides a window of opportunity to explore the causes of liver cell damage and for the timely institution of appropriate treatment [6]. In a single

✉ Govind K. Makharia
govindmakharia@gmail.com

[1] Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India

[2] Department of Community Medicine, All India Institute of Medical Sciences, New Delhi 110 029, India

[3] Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi 110 029, India

[4] Department of Biostatistics, All India Institute of Medical Sciences, New Delhi 110 029, India

Bullet points of the study highlights

What is already known?

- Elevated level of a lanine aminotransferase (ALT) in the peripheral blood denotes liver cell injury.

What is new in this study?

- ALT was elevated above the upper limit of normal (>40 IU/L) in 20.5% of the participants, and >1.5 times (>60 IU/L) in 5.4% participants.

What are the future clinical and research implications of the study findings?

- A substantial number of people in community likely have an ongoing liver injury, and this knowledge provide an opportunity to evaluate and treat them.

community-based study from the southern part of India including 10,765 healthy subjects, Annasamy et al. showed that 18% of healthy subjects had elevated ALT [7]. There is a lack of data on the community prevalence of high ALT in northern India.

Methods

This was a retrospective analysis using a subset of data from a previous Indian Council of Medical Research–supported community-based prospective study done to determine the prevalence of celiac disease (CD) in India, the results of which have been published earlier [8]. As a part of the incentive for participation in the above-mentioned study, we also assessed the levels of ALT, random blood sugar, and hemoglobin in the blood samples drawn for the screening for CD by estimation of anti-tissue transglutaminase antibody (anti-tTG Ab). The study protocol was approved by the Institutional Ethics Committee (IEC reference no. IEC/NP-45/2011), and an informed and written consent was taken from each participant. The results of serum ALT levels of participants from northern India from a total of 33 villages and 27 urban wards are being presented here. In total, 11,053 individuals (4399 [39.8%] males; mean age 37.9 ± 13.3 years) were screened, of whom 6209 consented to provide blood samples for testing for CD. Assessment of serum ALT levels was done in 6083 (2235 [36.7%] males) patients on the same day of blood collection using a semi-automated bio-analyzer (Mindray BA-88 A, Shenzhen, China). A serum ALT level of 40 IU/L was considered as a cut-off for the upper limit of normal (ULN) for the ALT level. All the blood samples were screened for anti-tTG Ab by Aeskulisa CELICHEK tTG-A New Generation kits (Catalog No. 3503, Aesku Diagnostics Gmbh, Wendelsheim, Germany). The samples that tested positive in the first assay were subjected

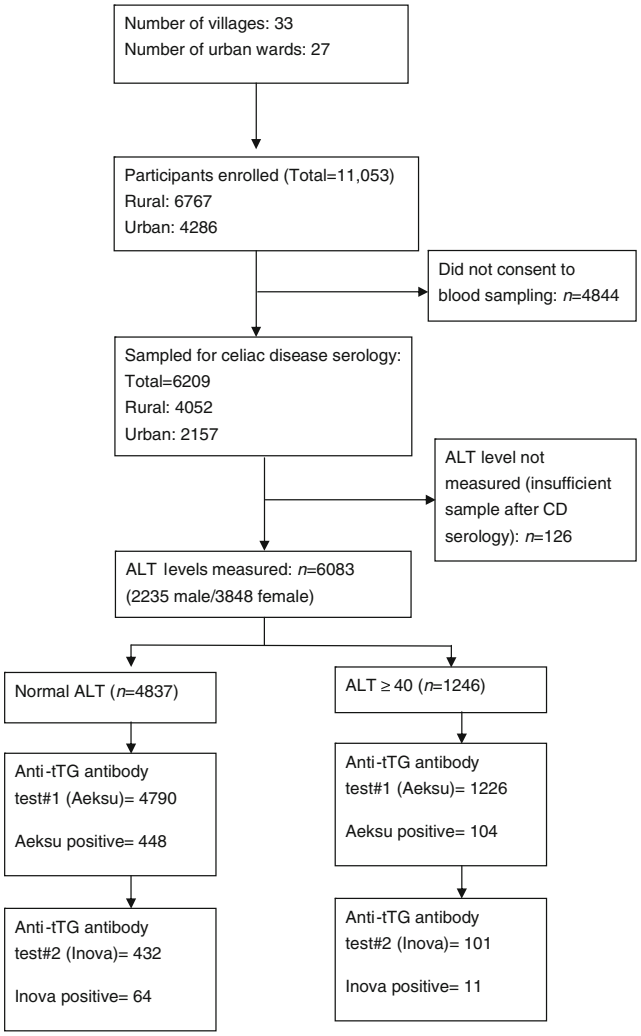

Fig. 1 Flow of participants through the study. *ALT* alanine aminotransferase, *CD* celiac disease, *tTG* tissue transglutaminase

to a more specific test, an enzyme-linked immunosorbent assay (ELISA; QUANTA Lite h-tTG IgA ELISA, Catalog No. 708760, Inova Diagnostics, San Diego, CA, USA) that used purified human erythrocyte tTG to capture and measure anti-tTG Ab. Seropositivity for CD was defined as the presence of anti-tTG Ab with positive Aesku ELISA with titer > 18 U/mL with a subsequent positive Inova ELISA > 30 U/mL.

Statistical analysis

Data were analyzed in STATA version 15 (StataCorp, College Station, TX, USA). Baseline clinical characteristics were described as mean (SD) for age and ALT, and percentage for body mass index (BMI) categories and gender. The proportion of subjects with ALT more than 40 IU/L and 60 IU/L were estimated across categories like age, BMI, and sex. The *p*-value for trend was calculated for age and BMI to test for trend. The Chi-square test was applied to look for the difference between the two sexes. We used analysis of variance (ANOVA) with post-hoc Bonferroni for testing significant differences across age groups and BMI. We used a multivariable linear regression model to look for the association of age, BMI, and sex with ALT levels. Pearson coefficient was calculated to assess the correlation between ALT levels and BMI. Chi-square test was used to compare the differences in proportion of patients with normal and elevated ALT who had serological evidence of CD.

Results

The flow of participants in our study is depicted in Fig. 1. The ALT levels in the serum were elevated above the ULN cut-off (≥ 40 IU/L) in 1246 (20.5%) participants, and it was elevated to more than 1.5 times (> 60 IU/L) in 329 (5.4%) participants (Table 1). The elevation of ALT levels above the cut-off was more frequent in men compared to women (29.4% vs. 15.3%, $p < 0.001$). The distribution of ALT levels in our study participants is shown in Fig. 2. There was a significant positive correlation (Pearson correlation coefficient [r] = 0.25, $p < 0.0001$) between ALT levels and BMI (Table 2; Fig. 3), with a higher proportion of patients displaying elevated ALT levels with increasing BMI. With increasing age, there was a statistically significant decrease in the proportion of subjects with ALT ≥ 1.5× ULN (Table 1). The proportion of patients having serological evidence of CD was not significantly different between the groups with normal and elevated ALT levels (1.32% vs. 0.88%, $p = 0.209$).

Table 1 Table showing mean alanine aminotransferase (ALT) levels and derangements in various subgroups. *SD* standard deviation, *IU* international unit, *L* litre, *BMI* body mass index

	Mean (± S.D.) ALT levels (IU/L)	% of patients with elevated ALT (≥ 40 IU/L)	% of patients with elevated ALT (≥ 60 IU/L)
Age categories, years ($n = 6083$)		($n = 1246$)	($n = 329$)
< 20 ($n = 114$)	28.7 (17.2)	18 (15.8%)	8 (7.0%)
20–29 ($n = 1597$)	31.5 (17.2)	303 (19.0%)	97 (6.1%)
30–39 ($n = 1756$)	32.8 (17.5)	427 (24.3%)	109 (6.2%)
40–49 ($n = 1230$)	32.2 (15.9)	268 (21.8%)	67 (5.5%)
50–59 ($n = 718$)	31.5 (16.0)	144 (20.1%)	31 (4.3%)
≥ 60 ($n = 668$)	27.5 (14.0)	86 (12.9%)	17 (2.5%)
p-value	< 0.0001[a]	0.01[b]	< 0.001[b]
BMI categories ($n = 4116$)			
< 18.5 kg/m^2 ($n = 505$)	23.7 (8.8)	27 (5.4%)	2 (0.4%)
18.5–22.9 kg/m^2 ($n = 1723$)	28.7 (14.4)	256 (14.9%)	56 (3.2%)
23–24.9 kg/m^2 ($n = 866$)	32.9 (16.5)	220 (25.4%)	46 (5.3%)
25–29.9 kg/m^2 ($n = 837$)	35.7 (18.8)	242 (28.9%)	74 (8.8%)
≥ 30 kg/m^2 ($n = 185$)	38.4 (20.0)	63 (34.0%)	19 (10.3%)
p-value	< 0.0001[a]	< 0.001[b]	< 0.001[b]
Sex ($n = 6083$)			
Males ($n = 2235$)	35.7 (20.3)	657 (29.4%)	214 (9.6%)
Females ($n = 3848$)	29.1 (13.5)	589 (15.3%)	115 (3.0%)
p-value	< 0.0001[c]	< 0.001[d]	< 0.001[d]
Total ($n = 6083$)	31.5 (16.6)	1246 (20.5%)	329 (5.4%)

[a] *p*-value calculated by ANOVA

[b] *p*-value calculated for trend

[c] *p*-value calculated by *t* test

[d] *p*-value calculated by Chi-square test

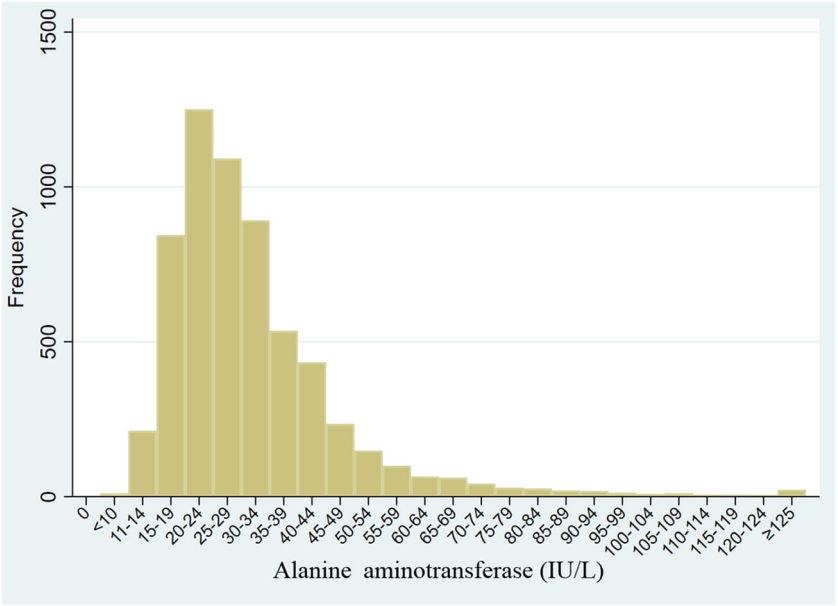

Fig. 2 Distribution of alanine aminotransferase values (IU/L) in the study community

Discussion

Our study suggests a high prevalence of elevated ALT levels in apparently healthy community dwellers in the northern part of India, similar to a previous study from southern India. Our study also shows a higher prevalence of elevated ALT levels in men compared to women and a significant increase in the proportion of patients with elevated ALT levels with an increase in the BMI, which could possibly be related to a higher prevalence of NAFLD and metabolic syndrome in patients with higher BMI, as seen in previous studies [9, 10].

In our study, we have used the ULN for ALT as 40 IU/L as described previously [1]. Using this cut-off, we found that 20% of the healthy individuals in our study had elevated level of ALT and it was estimated to be more than 1.5 times (> 60 IU/L) in 5.4% participants. However, recent studies have shown that the ULN for ALT in healthy Indian individuals is much lower (28–37 IU/L in males, 24 IU/L in females), which would make the findings even more significant, suggesting high levels of ongoing liver cell injury in these individuals [11, 12]. While the inclusion of a large number of subjects is a major strength of the study, such data should be interpreted with caution. We have estimated ALT at a single point of time and there is no follow-up data. Furthermore, we have not assessed any subject with elevated ALT for its etiology and thus the underlying cause for this abnormality cannot be ascertained from this study. Although there was no difference in the proportion of patients with CD between the two groups, the evidence is not conclusive and CD as one of the causes for the elevation of ALT cannot be ruled out. Many of these

Table 2 Association of alanine aminotransferase (ALT) with clinical characteristics (age, body mass index [BMI], and sex). CI confidence interval

Variable	Adjusted beta coefficient (95% CI)	*p*-value[a]
Age ($n = 6083$)	− 0.11 (− 0.15 to − 0.07)	< 0.001
BMI categories ($n = 4116$)		
18.5–22.9 kg/m^2 ($n = 1723$)	Reference	
< 18.5 kg/m^2 ($n = 505$)	− 4.92 (− 6.44 to − 3.41)	< 0.001
23–24.9 kg/m^2 ($n = 866$)	4.04 (2.79 to 5.29)	< 0.001
25–29.9 kg/m^2 ($n = 837$)	7.14 (5.87 to 8.41)	< 0.001
≥ 30 kg/m^2 ($n = 185$)	10.64 (8.31 to 12.97)	< 0.001
Sex ($n = 6083$)		
Males ($n = 2235$)	Reference	< 0.001
Females ($n = 3848$)	− 6.45 (− 7.45 to − 5.46)	< 0.001

[a] *p*-value calculated by multivariable linear regression

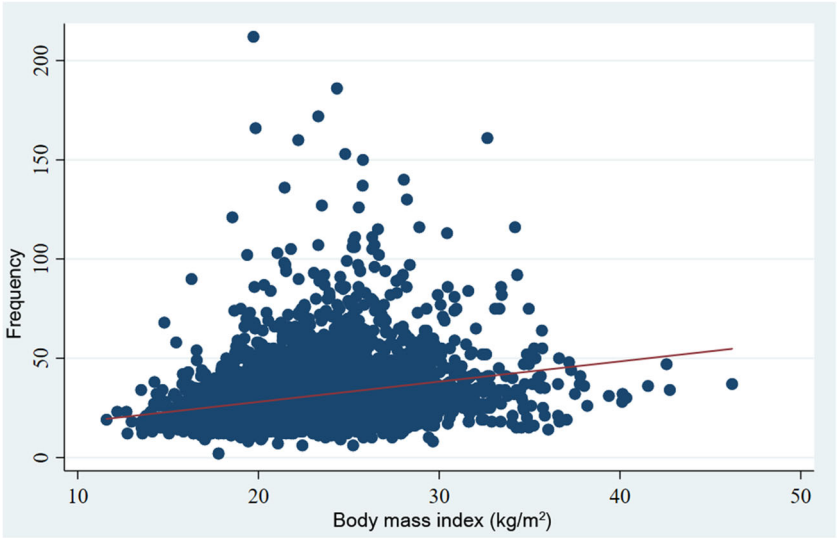

Fig. 3 Graph depicting correlation of alanine aminotransferase values with body mass index (Pearson correlation coefficient [r] = 0.25, $p < 0.0001$)

subjects might have non-alcoholic fatty liver disease, alcohol-related liver disease, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, or some other cause for the elevated transaminase levels, and our study suggest that there is a significant need for public health efforts to evaluate the underlying disease and treat these apparently healthy individuals before the disease has advanced [13].

To conclude, the study suggests a high prevalence of elevated ALT levels in asymptomatic healthy community dwellers, possibly indicating ongoing underlying liver damage. There is a higher prevalence in males and in individuals with higher BMI, which needs to be appropriately investigated and managed accordingly. Public health initiatives should focus on the evaluation for possible reasons of these derangements and appropriate preventive studies should be initiated.

Acknowledgments We acknowledge the support of the Indian Council of Medical Research for providing funding for the conduct of Pan India prevalence of celiac disease. This study was using the clinical data and blood samples collected during the above-mentioned study.

Authors' contribution Conceptualization: Vineet Ahuja, Govind K. Makharia. Methodology: Anil K. Verma, Ritvik Amarchand, Shyam Prakash, Anand Krishnan, Govind K. Makharia. Formal analysis: Nishant Aggarwal, Vishnubhatla Sreenivas, Govind K. Makharia. Funding acquisition: Govind K. Makharia. Project administration: Govind K. Makharia. Visualization: Alka Singh. Writing - original draft: Nishant Aggarwal. Writing - review and editing: Nishant Aggarwal, Alka Singh, Ashish Agarwal, Vignesh Dwarakanathan, Shalimar, Govind K. Makharia. Approval of final manuscript: all authors.

Compliance with ethical standards The study protocol was approved by the Institutional Ethics committee (IEC reference no. IEC/NP-45/2011) and an informed and written consent was taken from each participant.

Conflict of interest NA, AS, AA, VD, AKV, RA, SP, AK, VS, S, VA, and GKV declare that they have no conflict of interest.

Ethics statement The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

Disclaimer The authors are solely responsible for the data and the contents of the paper. In no way, the Honorary Editor-in-Chief, Editorial Board Members, the Indian Society of Gastroenterology or the printer/publishers are responsible for the results/findings and content of this article.

References

1. Kaplan MM. Alanine aminotransferase levels: what's normal? Ann Intern Med. 2002;137:49–51.
2. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med. 2000;342:1266–71.
3. Tsai JF, Jeng JE, Ho MS, et al. Serum alanine aminotransferase level in relation to hepatitis B and C virus infections among blood donors. Liver. 1997;17:24–9.
4. Piton A, Poynard T, Imbert-Bismut F, et al. Factors associated with serum alanine transaminase activity in healthy subjects: consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C. MULTIVIRC Group Hepatol. 1998;27:1213–9.
5. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterology. 2003;124:71–9.
6. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003;98:960–7.

7. Annasamy C, Narayanasamy K, Karthick R. Prevalence of elevated serum aminotransferases among asymptomatic population of Tamil Nadu, India. Biomed Pharmacol J. 2017;10:1249–57.
8. Ramakrishna BS, Makharia GK, Chetri K, et al. Prevalence of adult celiac disease in India: regional variations and associations. Am J Gastroenterol. 2016;111:115–23.
9. Loomis AK, Kabadi S, Preiss D, et al. Body mass index and risk of nonalcoholic fatty liver disease: two electronic health record prospective studies. J Clin Endocrinol Metab. 2016;101:945–52.
10. Kumar S, Amarapurkar A, Amarapurkar D. Serum aminotransferase levels in healthy population from western India. Indian J Med Res. 2013;138:894–9.
11. Mohan P, Sundar V, Bhaskar E, Anthony S. Estimation of upper limit of normal for serum alanine transaminase in healthy south Indian population. Indian J Clin Biochem. 2017;32:337–42.
12. Najmy S, Duseja A, Pal A, et al. Redefining the normal values of serum aminotransferases in healthy Indian males. J Clin Exp Hepatol. 2019;9:191–9.
13. Majumdar A, Misra P, Sharma S, et al. Prevalence of nonalcoholic fatty liver disease in an adult population in a rural community of Haryana, India. Indian J Public Health. 2016;60:26–33.