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• BRIEF REPORTS •

Healthy ranges of serum alanine aminotransferase levels in Iranian blood donors

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Abstract

AIM: The healthy ranges for serum alanine aminotransferase (ALT) levels are less well studied. The aim of this study was to define the upper limit of normal (ULN) for serum ALT levels, and to assess factors associated with serum ALT activity in apparently healthy blood donors.

METHODS: A total of 1 939 blood donors were included. ALT measurements were performed for all cases using the same laboratory method. Healthy ranges for ALT levels were computed from the population at the lowest risk for liver disease. Univariate and multivariate analyses were performed to evaluate associations between clinical factors and ALT levels.

RESULTS: Serum ALT activity was independently associated with body mass index (BMI) and male gender, but not associated with age. Association of ALT with BMI was more prominent in males than in females. Upper limit of normal for non-overweight women (BMI of less than 25) was 34 U/L, and for non-overweight men was 40 U/L.

CONCLUSION: Serum ALT is strongly associated with sex and BMI. The normal range of ALT should be defined for male and female separately.

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INTRODUCTION

Elevation of aminotransferase level is an important and common finding in different types of parenchymal liver disease. Measurement of serum ALT is one of the most important tests for detection of patients with viral hepatitis or non-alcoholic steatohepatitis (NASH), and the exact definition of upper normal levels of serum ALT activity is an initial and critical step in different screening and follow up studies for chronic liver diseases. Current upper limits of normal for ALT level are set on average, at 40 U/L. This normal range was set in the 1950s and has changed a little since then[1]. Several studies have recently questioned whether previously established values to define normal ALT range are accurate and have suggested that the upper limit of normal should be assessed more accurately and revised accordingly[2,3].

There is no study regarding normal level of ALT in Iranian healthy adults at low risk for chronic liver diseases. This information, in addition to daily clinical practice, is specially important and necessary for different research studies of chronic liver diseases in Iran. The aim of this study was to assess the normal value of ALT in a population at low risk for subclinical chronic liver diseases in the capital city of Tehran and to investigate factors associated with abnormal ALT in this population.

MATERIALS AND METHODS

Study population

From March 2001 through April 2002, 1 959 apparently healthy blood donors at Tehran Blood Donation Center were randomly recruited into the study. The participants were part of a study for identifying the causes of elevated serum ALT level. After explanation about the objectives of the study and possible necessity for further blood test and follow up, a written informed consent was obtained, and a clinical questionnaire with emphasis on psychosocial and medical history to exclude subjects who were considered the high risk group for blood born infections was completed by a physician interviewer, and serum samples were collected from all consenting subjects. Our study was in accordance with the ethical standards for human experimentation and approved by the Ethical Committee of the Digestive Disease Research Center, Tehran University of Medical Sciences. Body weight and height of all subjects were measured and history of alcohol and drug use was taken.

Laboratory methods

Blood samples were centrifuged within 30 minutes of collection. The biochemistry and virologic tests including hepatitis B s antigen (HBsAg), and hepatitis C virus antibody (HCV Ab), and rapid plasma regain test, and HIV Ab were measured. All tests were performed at Digestive Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran. Analyses of serum ALT levels were performed by using the Hitachi 704 autoanalyser, Tokyo, Japan. The upper limit of normal introduced by manufacturer was 40 U/L for both men and women. Body mass index (BMI) was calculated by dividing the weight (in kg) and the squared height (in meter). We considered a BMI of 24.9 kg/m^2 as the upper limit for healthy weight[5].

Definitions of ULN ALT value

Seven methods were used to compare their impact. Method 1: 95th percentile of ALT distribution regardless of the sex. Method 2: 95 th percentile of ALT distribution after separating males and females. Method 3: a common threshold of 40 IU/L for both males and females proposed by the manufacturer. Method 4: 95th percentile after separating subjects with body mass index (BMI) under the median which was 27.12. Method 5: 95th percentile after separating subjects with body mass index (BMI) under 25 -a threshold proposed for separating abnormal and normal weight-[5]. Method 6: 95th percentile of ALT distribution stratified according to BMI (<25) and sex. Method 7: 95th percentile of ALT distribution in each age decade after separating males and females.

Statistical analysis

Statistical analyses were performed by using the SPSS, version 10.1, software package (SPSS, Inc., Chicago, IL). The 50th (median), and 95th percentiles for ALT level were calculated on the basis of the empirical distribution of the data. We set the upper limit for healthy ALT level to the 95 th percentile, as is commonly done for distribution of a continuous variable in the normal population. The univariate associations between factors and ALT expressed in decimal logarithm were assessed by Pearson’s correlation coefficient for quantitative factors and by the Student’s *t* test for qualitative factors. Multivariate analyses were used to identify factors independently associated with ALT: linear regression, and logistic regression. *P* values less than 0.05 were considered statistically significant.

RESULTS

Twenty persons were excluded because of positive HBsAg (10 persons), positive HCV Ab (9 persons), or use of alcohol more than 20 grams daily (1 person). Four persons also consumed less than 20 grams per day of alcohol who were included into the study. Thus a total of 1 939 persons (1 451 males, and 488 females) were included. The characteristics of tested individuals are given in Table 1. Except one subject who took drugs containing female sex hormones, no body had a history of regular drug usage.

Table 1 Characteristics of 1 939 Blood Donors

Factor	Mean	SE
Age (yr)	37.4	0.26
Weight (kg)	79	0.3
Height (cm)	169.96	0.19
BMI (kg/cm^2)	27.35	0.09
ALT (U/L)	19.87	0.27

Abbreviations: SE: Standard error of the mean.

Table 2 Correlation of serum ALT with quantitative clinical factors

Factor	Number	Pearson correlation	*P* value
BMI	1939	0.125	<0.001
Weight	1939	0.17	<0.001
Height	1939	0.096	<0.001
Age	1939	0.027	0.23

Table 3 Serum ALT according to sex, and BMI (lower or higher than 25)

Variable	Count	Mean	SD	*P* Value
Female	488	16.4	8.8	<0.001
Male	1 451	21	12.3	
All subjects with BMI <25	563	17.9	10.4	<0.001
All subjects with BMI ⩾25	1 376	20.7	12.1	
Men with BMI <25	391	19.1	10.8	<0.001
Men with BMI ⩾25	1 060	21.7	12.8	
Women with BMI <25	172	15.2	8.8	0.025
Women with BMI ⩾25	316	17	8.7	

Abbreviation: SD: Standard deviation.

Table 4 Prevalence among blood donors with normal and abnormal ALT according to the six definitions

Subjects	Method 1: 95th percentile of ALT distribution without stratification	Method 2: 95th percentile of ALT distribution stratified according to sex	Method 3: 40 IU/L for both male and female	Method 4: 95th percentile of ALT distribution stratified according to BMI (<27.1)	Method 5: 95th percentile of ALT distribution stratified according to BMI (<25)	Method 6: 95th percentile of ALT distribution stratified according to BMI (<25) and sex
Males	1451	1451	1451	1451	1451	1451
Threshold	40	45	40	39 for BMI⩾27.1	39 for BMI <25	40 for BMI <25
				41/ 721	20/ 391	16/391
				45 for BMI>27.1	43 for BMI ⩾25	46 for BMI⩾25
				40/ 730	65/1060	48/1060
Normal (%)	1 363 (94%)	1378 (95%)	1363 (94%)	1370 (94. 5%)	1366 (94.1%)	1 387 (95. 6%)
Abnormal (%)	88 (6%)	73 (5%)	88 (6%)	81 (5. 5%)	85 (5. 9%)	64 (4.4%)
Females	488	488	488	488	488	488
Threshold	40	34	40	39 for BMI⩾27.1	39 for BMI <25	34 for BMI <25
				6/249	4/ 172	8/172
				45 for BMI >27.1	43 for BMI ⩾25	34 for BMI⩾25
				2/ 239	2/ 316	15/316
Normal (%)	481 (98. 6%)	464 (95%)	481 (98. 6%)	480 (98.4%)	482 (98.8%)	465 (95. 3%)
Abnormal (%)	7 (1.4%)	24 (5%)	7 (1.4%)	8 (1. 6%)	6 (1. 2%)	23 (4.7%)
All donors	1939	1939	1939	1939	1939	1939
Threshold	40	45 for female	40	39 for BMI ⩾27.1	39 for BMI <25	Male: 40 for BMI<25
		34 for male		45 for BMI>27.1	43 for BMI⩾25	46 for BMI⩾25
						Female: 34 for BMI<25
						34 for BMI⩾25

Correlation between factors and ALT

ALT was significantly correlated with BMI, weight, and height, but was not correlated with age (Table 2).

For qualitative factors (Table 3), ALT was higher in males than in females, and ⩾25 than BMI<25 in persons with BMI. Association of ALT with BMI was more prominent in men (P<0.001) than in women (P=0.025).

Linear regression analysis showed that ALT was independently associated with male sex (Regression coefficient: 4.633, 95 % CI: 3.459-5.808, P<0.0001), and BMI (Regression coefficient: 0.362, 95 % CI: 0.237-0.487, P<0.0001), but not with height, weight, and age.

Also, logistic regression analysis showed that men were 4.57 times more likely to have elevated ALT (ALT>40) than women (95 % CI, 2.1-9.96, P=0.0001). BMI was also independently associated with elevated ALT (OR: 1.07, 95 % CI: 1.03-1.13, P=0.004). Age, height, and weight were not found to be related to elevated ALT.

Different definitions of abnormal ALT

The thresholds corresponding to the first six methods to the definition of abnormal ALT are given in Table 4. The threshold to the definition of abnormal ALT according to method 7 is demonstrated in Figure 1.

The threshold for ULN ALT varied from 34 U/L (methods 2 and 6 for females) to 46 U/L (method 6 for males with BMI>25).

The overall median ALT level for the entire study sample was 17 U/L, and the level across the 95th percentile was 40 U/L. In the 1 451 male participants, the median serum ALT level was 18 U/L, and the ALT levels across the 95 th percentile was 45 U/L. The median and 95th percentiles of ALT level in women were 14 U/L and 34 U/L, respectively. When we considered the population at the lowest risk for liver diseases (persons with negative viral markers, use of alcohol less than 20 g/d, normal BMI, and absence of concurrent medication use), the threshold for abnormal ALT was 40 U/L for men, and 34 U/L for women.

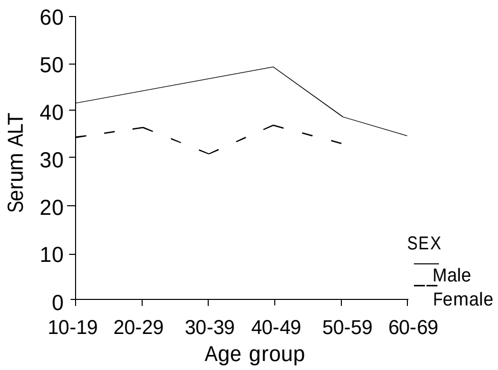

Figure 1 95th percentile of ALT distribution in each age decade after separating males and females. Note that males over age 70 (41 subjects), and females over age 60 (8 subjects) were omitted from the chart, because of a small number of them.

DISCUSSION

This study has identified the factors associated with ALT variability, and determined the thresholds for ALT according to different definitions of ULN ALT. This study further emphasized the findings of previous studies regarding the strong correlation of ALT with sex and BMI[2,3]. This has probably reflected the association between liver steatosis and obesity. The correlation between abnormal ALT and BMI was stronger in men than in women. Additionally, the 95th percentile of ALT in females with BMI <25 was equal to females with BMI ⩾25. This may be due to the fact that the waist to hip ratio (WHR) is higher in men than in women, and non-alcoholic fatty liver disease (NAFLD) is associated with central obesity and higher WHR[5]. WHR was correlated with visceral adipose tissue, which provided a greater supply of potentially hepatotoxic fatty acids to the liver[6].

Our study had some limitations. The study population were apparently healthy blood donors. They could have other unknown factors associated with ALT and they might not exactly reflect the normal general population. Second, the estimation of alcohol consumption was based only on the interview data and might be inaccurate. Third, we could not measure some paraclinical factors associated with ALT such as serum glucose, triglyceride and cholesterol[2,5].

The ULN ALT may differ from different nations and populations and may be influenced by mean BMI and alcohol usage in different societies.

The 95th percentile of ALT in overweight and obese persons may be too high to be defined as the threshold for healthy ranges of ALT. We suggest that even in overweight and obese persons healthy ranges of ALT should be defined as in non-overweight persons (40 U/L and 34 U/L in men and in women respectively). Since higher values may be due to liver steatosis which occurs more frequently in obese persons, and thus may be abnormal. Adjustment of ALT for sex but not for BMI has also been proposed previously[1]. It seems necessary to repeat this type of investigations in a population based sample and in different ethnic and nationals in order to check whether the impact of sex and BMI remain consistent and if it is proved to be so, then the laboratories should set different ranges of ALT for male and female independently.

In conclusion, this study has demonstrated a strong impact of sex and BMI on serum ALT level. Furthermore, if these findings are proved by other studies, then the normal range of ALT according to sex should be defined. This is particularly helpful in follow up and therapy of patients with chronic hepatitis and designing research protocols.

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