Original Article

Normal Ranges of Serum Alanine Aminotransferase Level and Its Modulating Factors in Thai People

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ABSTRACT

Background: Serum alanine aminotransferase (ALT) activity, the variable most commonly measured to assess hepatic function, fails to identify many patients with hepatic injury. Current standards for "normal" ALT level were defined by using populations that included persons with subclinical liver disease. There is no study regarding normal level of ALT and its modulating factors in healthy Thai subjects.

Objective: To define the normal ranges for serum ALT level in Thai subjects.

Design: Cross sectional study

Setting: Phramongkutklao Hospital and Army Institute of Pathology Phramongkutklao Medical center (A.I.P.), Bangkok, Thailand

Participants: 200 first-time blood donors from August through December 2007 who were negative for both antibody to hepatitis C virus (HCV) and hepatitis B antigen (HBsAg), and who had no contraindications to blood donation.

Measurements: Univariate and multivariate analyses were used to examine associations between clinical and laboratory factors and ALT levels. Normal ranges for ALT were computed from the population at lowest risk for liver disease.

Results: In men, serum ALT activity was independently related to body mass index, age, alcoholic consumption, and to laboratory indicators of abnormal lipid or carbohydrate metabolism. The upper limits of normal ranges for serum ALT level in Thai people were 26 U/L for men and 21.67 U/L for women.

Conclusion: Serum ALT is strongly associated with body mass index, age, alcoholic consumption, and to laboratory indicators of abnormal lipid or carbohydrate metabolism. The normal range of ALT should be defined for male and female separately.

Key words : alanine aminotransferase, ALT

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INTRODUCTION

Serum alanine aminotransferase (ALT), a sensitive indicator of liver cell injury, has been used to identify patients with liver disease[1,2,13]. This cytosolic enzyme, which is found in many organs, catalyzes the transfer of the α-ketoglutalic acid[14]. ALT level is particularly high in the liver. For detection of the liver diseases, ALT is thought to be a more specific indicator than aspartate aminotransferase (AST), an enzyme found in cytosal and mitochondria[1]. Normal values of serum ALT range from 10 to 40 U/L in most laboratories; however, normal ranges may vary greatly among laboratories[1,6,11]. Elevated serum ALT levels help identify many types of liver diseases. Nevertheless, ALT measurement often fails to identify patients with minimal necro-inflammatory activity,[3-5] especially in cases of chronic hepatitis C virus (HCV) and fatty deposit in the liver.

Karmen A[13] in 1955 tried to measure the normal range of serum ALT in blood donors and medical students. That study had limitations, as HCV screening and knowledge about NAFLD, were not available at the time. In a study by Prati *et al*, published in Ann Intern Med 2002[6], a support was made to previous studies[8,9,11,16] which had shown a relationship between serum ALT and gender, body mass index ,alcoholic consumption and the laboratory indicators of abnormal lipid or carbohydrate metabolism. All these factors are important regarding NAFLD. This latter study set the normal upper limits for ALT level at 500 nkat/L [30 U/L] for men and 317 nkat/L [19 U/L] for women.[6] There has been no study regarding normal ranges of ALT and its modulating factors in healthy Thai subjects with low risk for chronic liver disease.

We hereby report the results of a 5 month study in first-time blood-donation candidates. To determine the upper normal limit of serum ALT in healthy Thai people, we identified a population at low risk for subclinical liver disease by exploring factors related to enzyme activity in both healthy persons and in those with mild abnormalities of liver function tests.

METHODS

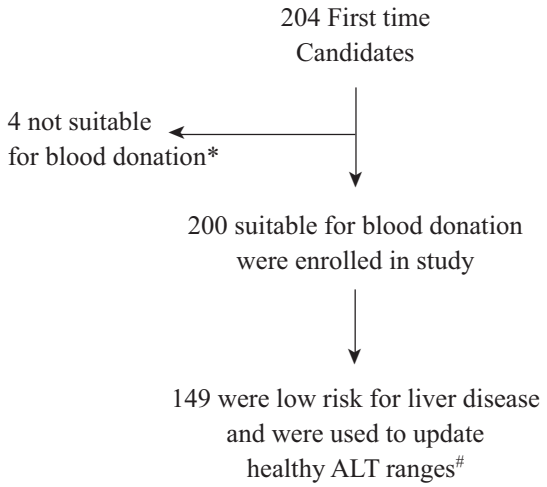
Study population

Figure 1 summarizes the selection of the study participants.

From 1 August through 31 December 2007, 204 blood-donor candidates presenting for first-time donation underwent clinical and laboratory examinations as part of procedures for donor selection of the Army Institute of Pathology Phramongkutklao Medical center (A.I.P.) Bangkok, Thailand. A blood-bank physician 1) administered a psychosocial questionnaire[12], which was aimed at identifying and excluding from donation persons at high risk for blood borne infection; 2) took a medical history; and 3) examined all potential participants and measured body weight and height. Donor candidates had blood drawn for laboratory testing. Clinical data and laboratory-test results were recorded in a relational database management system. We also included in the study donor candidates who had no medical (oral contraceptive pill, statins and oral anti-fungal agent) or behavioral contraindication to blood donation[12] and who tested negative for hepatitis B surface antigen (HBsAg), anti-HCV, anti-HIV and syphilis.

Laboratory Methods

A fasting blood sample was collected in the morning and was centrifuged within 30 minutes of collection. The Laboratory of Biochemistry Division and the Laboratory of Virology Division of the Pathology Phramongkutklao Medical Center (A.I.P.), Bangkok,



* Donor candidates were not suitable for the following reasons: serologic reactivity on screening assays (anti-HIV, HBsAg, anti-HCV) on the sample collected at blood donation (2%).

\# BMI < 23 kg/m^2, FBS < 110 mg/dL, Total triglyceride < 150 mg/dL, Total cholesterol < 200 mg/dL, alcohol < 30 gm/day in men and < 20 gm/day in women, no liver cirrhosis or liver neoplasm, no oral contraceptive pill, statins and oral anti-fungal drug.

Figure 1. Procedures for selection of the study participants.

Thailand, performed all analyses, using consistent methods throughout the study period.

Complete blood counts were performed, using a COULTER LH750 analyzer (USA). Analyses of serum biochemistry were performed by using a Roche COBAS INTEGRA 800(Germany). The upper reference limits for serum biochemistry tests in men and women who were apparently healthy donors with negative viral hepatitis and syphilis tests were as following; 200 mg/dL for total cholesterol level, 150 mg/dL for triglyceride level, 110 mg/dL for blood glucose level, and 40 U/L for ALT level, Virological tests including an hepatitis B surface antigen test, an anti-HIV test ,an anti-HCV test and a syphilis test were performed using an Abbott ARCHITECT i2000 SR (USA). Body mass index (BMI) was calculated by dividing the weight (in kg) by the squared height (in m). On the basis of a recent recommendation (18), we considered a BMI of 23 kg/m^2 the upper limit for healthy weight.

Statistical analysis

Statistical analyses were performed by using the SPSS for window 13.0. The 5th, 25th, 50th (median), 75th, 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 95th percentile, as is commonly held for distribution of a continuous variable in the normal population. Serum ALT values were fitted separately by sex with univariate and multivariate general linear models as a function of qualitative and quantitative variables. Alcohol intake status was categorized as abstainers versus consumers (more than 20 gm/day). Medication usage was classified as none or oral contraceptives pill, statins and oral anti-fungal agent. p-values less than 0.05 were considered statistically significant.

RESULTS

Variables associated with serum ALT levels in the study

Sample

Of the 204 blood-donor candidates, 200 persons met the inclusion criteria. Table 1 summarizes the characteristics of the study participants. Overall, the median ALT level for the entire study sample was 15 U/

Table 1. Baseline characteristics of the study population.

Characteristics	Participants, N (%)	Mean ± SD
Qualitative variables		
Sex		
Male	119 (59.5)	
Female	81 (40.5)	
Alcohol intake		
None (abstainers)	160 (80)	
<20 g/day of ethanol	28 (14)	
≥20 g/d of ethanol	12 (6)	
Smoker		
No	169 (84.5)	
Yes	31 (15.5)	
Use of concomitant medications		
No	189 (94.5)	
Yes	11 (5.5)	
Coffee		
No	138 (69)	
Yes	62 (31)	
Quantitative variables		
Age, yrs		30 ± 12.49
Blood glucose level (mg/dL)		84 ± 9.63
Total cholesterol level (mg/dL)		173 ± 41.65
Triglyceride level (mg/dL)		117.94 ± 77.72
Body mass index (kg/m^2)		22.46 ± 3.21

L, and the levels across the 5th, 25th, 75th, and 95th percentiles were 9, 12, 21.75, 44 U/L respectively. In the 119 male participants, the median serum ALT level was 17 U/L; the distribution of ALT levels across the 5th, 25th, 75th, and 95th percentiles, respectively, were 9, 13, 26, 53 U/L. In the 81 female participants, the median ALT level was 14 U/L; ALT levels among the women were 7.2, 12, 17.50, 34.50 U/L for the 5th, 25th, 75th, and 95th percentiles, respectively.

Because the distribution of serum ALT levels differed between men and women, subsequent analyses were stratified according to sex. Other factors associated with ALT levels in univariate analysis were age; levels of serum total cholesterol, triglycerides, and blood glucose; alcohol consumption; coffee intake and BMI (Table 2). In multivariate analysis, sex specific associations with ALT levels were observed in men for alcohol consumption, BMI, blood glucose, triglyceride, and age, but in women no factors associated with ALT level were noted in this study (Table 3).

Calculation of Healthy Ranges for Serum ALT Level

We selected the population at lowest risk for liver disease by assembling donors who satisfied the following criteria:[17,18] normal BMI, normal serum cholesterol, triglyceride, and glucose levels, and absence of concurrent medication use (statins, oral anti-fungal drug and oral contraceptive pill). In the 149 persons (86 men and 63 women) at lowest risk for liver disease, serum ALT levels were 14 U/L for the median and 8.5, 11, 18 and 25 U/L respectively for the 5th, 25th, 75th, and 95th percentiles. For men, the values for the 5th, 25th, 75th, and 95th percentiles, respectively, were 9, 12, 19.25 and 26 U/L. For women, the corresponding values were 7, 11, 16, and 21.6 U/L. Median ALT

Table 2. Correlation between serum alanine aminotransferase level and qualitative and quantitative factors in male and female blood donors (by univariate analysis).

Variable	Men		Women	
	Participants, Mean ALT Level [95% CI]), Slope [95% CI]		Participants, Mean ALT Level [95% CI], Slope [95% CI]	
	N	U/L	N	U/L
Sex	119	22.19 (19.45-24.94)	81	16 .11 (14.35-17.87)
Alcohol intake				
Abstainers	108	20.36 (17.90-22.82)	81	16.11 (14.35-17.87)
Consumers	12	40.80 (24.67-55.70)	-	
Smoker				
No	88	22.24 (19.43-25.06)	81	16.11 (14.35-17.87)
Yes	31	20.33 (665-34.01)	-	
Medication use				
No	117	22.11 (19.32-24.90)	72	15.56 (13.80-17.85)
Yes (oral contraceptives, Statin, oral anti-fungus)	2	27.00 (36.53-90.53)	9	20.56 (12.40-28.71)
Coffee intake				
No	89	20.38 (17.49-23.28)	49	15.71 (13.58-17.85)
Yes	30	27.57 (20.90-34.24)	32	16.72 (13.54-19.90)
Age		0.37 (0.16, 0.57)		-0.02 (-0.21, 0.171)
Blood glucose level		0.18 (0.12, 0.25)		0.06 (-0.03, 0.15)
Total cholesterol level		0.11 (0.05, 0.17)		0.03 (-0.01, 0.07)
Triglyceride level		0.07 (0.04, 0.10)		0.03 (0.00, 0.06)
Body mass index		2.76(1.96, 3.56)		1.16 (0.73, 1.58)

Table 3. Correlation between serum alanine aminotransferase level and qualitative and quantitative factors in male and female blood donors (by multivariate analysis)

Variable	Men		Women	
	Mean ALT Level [95% CI], Slope [95% CI]	*p-value*	Mean ALT Level [95% CI], Slope [95% CI]	*p-value*
	U/L		U/L	
Alcohol intake				
Abstainers	20.36 (17.90-22.82)		0.011	
Consumers	40.8 (24.67-55.70)			
Medication use				
No	22.11 (19.32-24.90)		0.33	
Yes, (oral contraceptives, Statins, oral anti-fungus)	27.00 (36.53-90.53)			
Age	-0.23 (-0.45, 0.001)	0.049		
Blood glucose level	0.14 (0.08, 0.20)	< 0.001		
Total cholesterol level	0.03 (-0.03, 0.09)	0.270		
Triglyceride level	0.03 (0.01, 0.06)	0.016	0.01 (-0.02, 0.04)	0.559
Body mass index	2.68 (1.27, 4.09)	< 0.001	0.39 (-0.64, 0.66)	0.454

level was 15 U/L for men and 14 U/L for women. We defined healthy serum ALT values as those below the sex-specific 95th percentiles, i.e. 26 U/L for men and 21.60 U/L for women.

DISCUSSION

There are large member of patients in Thailand who suffer from liver diseases, especially, hepatitis B, hepatitis C, alcoholic hepatitis, and NAFLD. This is a major health problem. These patients are also at high risk to develop decompensated liver disease and hepatocellular carcinoma. Accurate treatment planning is important to help reduce risks of liver cancer and liver related death. In this regard, serum ALT is the major indicator for diagnosis and follow-up.

The objective of this study is to evaluate the normal ranges of serum ALT. In 2002, a study in Italy showed the upper limits of normal ALT to be 30 U/L for men and 19 U/L for women.[6] These have been referred to as standards to the present time. However, serum ALT is related to body mass index and alcohol consumption as well as the laboratory indicators of abnormal lipid or carbohydrate metabolism. As the definition of obesity for Asians is BMI > 23 kg/m^2[18], while that for European people is BMI > 25 kg/m^2. The difference may thus cause differing normal limits for serum ALT in Asian and in European populations.

The result from this study indicates that the upper limits of normal for serum ALT is 26 U/L for men and 21.6 U/L for women, similar to in a previous study.[6] In our male participants, the factors influencing serum ALT levels were age, alcoholic consumption, obesity, high level of blood sugar and increased serum triglyceride levels. This is in support of the previous study. However, in female participants, these factors did not show any influence upon serum ALT.

There were some limitations in our study. The number of participants was rather small, and all were blood-donors only. Most participants were young or middle-aged. Thus the study populations may not be representative of the entire population. Further study, to therefore, is needed to achieve a more accurate and more representative normal ALT ranges.

In conclusion, our study has shown the upper normal limits of serum ALT in healthy Thai subjects to be at 26 U/L for men and 21.6 U/L for women. The figures can be used as standard reference for serum ALT in Thai population.

REFERENCES

1. Pratt DS, Kaplan MM. Evaluation of abnormal liver enzyme results in asymptomatic patient. N Engl J Med 2000;342:1266-71.

2. Craxi A, Almasio P. Diagnostic approach to liver enzyme evaluation. J Hepatol 1996;25:47-51.
3. Zanella A, Conte D, Prati D, *et al*. Hepatitis c virus RNA and liver histology in blood donors reactive to a single antigen by second generation recombinant immunoblot assay. Hepatology 1995;21:913-7.
4. Prati D, Capelli C, Zanellar A, *et al*. Influence of different hepatitis C virus genotype on the cause of asymptomatic hepatitis C viral infection. Gastroenterology 1996;110:178-83.
5. Pouti C, Magrini A, Stati T, *et al*. Clinical, histological and virological features of hepatitis c virus carriers with persistently normal or abnormal alanine transferase level. Hepatology 1997;26:1393-8.
6. Prati D, Taioli E, Zanella A, *et al*. Update definition of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137:1-10.
7. Daniel S, Ben-menachem T, Vasudevan G, *et al*. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. Am J Gastroenterol 1999;94:3010-4.
8. Piton A, Poynard T, Imbert-Bimut F, *et al*. Factors associated with serum alanine transminase activity in healthy subjects: consequences for the definition of normal values for selection of blood donors, and for patients with chronic hepatitis c. Hepatology 1998;27:1213-9.
9. Ruhl CE, Everhart JE. Determinants of the associated of overweight with evaluated serum alanine aminotransferase activity in the United states population. Gastroenterology 2003; 124:71-9.
10. Willet WC, Dietz WH, Colditz GA. Guideline for healthy weight. N Engl J Med 1999;341:427-34.
11. Kariv R, Leshno M, Beth-Or, *et al*. Re-evaluation of serum alanine aminotransferase upper normal limit and its modulatimg factors in a large scale population study. Liver International 2006;26:445-50.
12. คู่มือการคัดเลือกผู้บริจาคโลหิต ศูนย์บริจาคโลหิตแห่งชาติ สภากาชาดไทย พ.ศ. 2546.
13. Karmen A, wroblewski F, LaDu JS. Transminase activity in human blood. J clinical Invest 1955;34:126-33.
14. Awapara J, Seale B. Distribution of transminases in rat organ. J Biol Chem 1952;194:497-502.
15. Rej R, Aspartate aminotransferase activity and isoenzyme proportion in human liver tissue. Clin Chem 1971;24:24-9.
16. Annie P, Thierry P, Francoise I, *et al*. Factors associated with serum alanine transferase activity in healthy subjects: consequences for the definitive of normal values, for selection of blood donors, and for patients with chronic hepatis C. Hepatology 1998;27:5.
17. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Circulation 2002;106:3143.
18. Inoue S, Zimmet P, *et al*. Assessment and diagnosis. The Asia-Pacific perspective: redefining obesity and its treatment 2000:15-21.
19. Satyajit D, Tamir BM, Gopikrishnan V. *et al*. Prospective evaluation of unexplained chronic liver transminase abnormalities in asymptomatic and symptomatic patients. AJG 1999;94:3010-4.