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Upper Normal Limit of Serum Alanine Aminotransferase and Its Association with Metabolic Risk Factors in Pars Cohort Study

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ABSTRACT

BACKGROUND

The range of serum alanine aminotransferase (ALT) varies in different sub-populations or countries. Its population-specific cut-off points may provide a more effective screening tool for non-alcoholic fatty liver disease (NAFLD).

Objectives

To investigate the upper normal level (UNL) of ALT and its association with metabolic syndrome (MS) in a semi-urban population in southern Iran.

METHODS

The baseline data of Pars Cohort Study was used. A total of 9264 subjects aged 40-75 years were enrolled. UNL of ALT was estimated based on 95 percentile of ALT in participants who had body mass index (BMI) < 25. Multivariable logistic regression was applied and adjusted odds ratio (OR) and its 95% confidence interval (CI) were estimated.

RESULTS

95 percentile of ALT was 41.71 U/L and 32.9 U/L in men and women, respectively. Abnormal waist circumference (OR: 1.72, 95%CI: 1.34, 2.21), triglyceride (OR: 1.63, 95%CI: 1.25, 2.13), fasting blood sugar (OR: 1.69, 95%CI: 1.32, 2.16), cholesterol level (OR: 1.06, 95%CI: 1.03, 1.09) and systolic blood pressure (OR: 1.08, 95%CI: 1.01, 1.16) were independently associated with ALT.

CONCLUSION

UNL of ALT in southern Iranian women is lower than the current recommended level, while these are almost the same for men. MS components are highly common in southern Iran and are associated with elevated serum ALT. Further studies are recommended to estimate the UNL of serum ALT among the Iranian population with NAFLD.

KEYWORDS:
Alanine aminotransferase, Metabolic syndrome, Upper normal limit, Pars Cohort Study, Iran

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INTRODUCTION

Serum alanine aminotransferase (ALT), as a hepatic-predictive value for chronic metabolic diseases, is an important factor for screening non-alcoholic fatty liver disease (NAFLD).[1,2] However, its range varies in different populations

based on age, sex, ethnicity, body mass index (BMI), the prevalence of NAFLD, serum levels of low-density lipoprotein (LDL), and components of metabolic syndrome (MS).[3-6] Therefore, population-specific cut-offs for ALT may provide a more effective screening tool for NAFLD in each population.[7,8]

The current UNL of serum ALT for the screening of liver diseases is 40 U/L (ranging from 30-50). However, this is not very accurate for the diagnosis of NAFLD, and considering this range of ALT for all populations may lead to misdiagnosis of some subjects.[9-11]

There are controversies on the cut-off point of ALT in Iranian adults and the correlation of available cut-offs with NAFLD, MS, or other chronic diseases.[2,12,13]

We analyzed the baseline data of the participants of Pars Cohort Study to investigate the normal range of ALT and its association with MS in a semi-urban population in southern Iran.

MATERIALS AND METHODS

Study subjects and setting:

The baseline data of Pars Cohort Study was used. In brief, in the PCS, inhabitants of Valashahr city, with an age range of 40-75 years (totally 9721) were invited to participate in the study. They were introduced to the aims and phases of PCS. The participants who gave informed consent were interviewed and underwent physical examinations and blood sampling. A total of 9264 subjects (95%) participated in the PCS. Both ethical review committees of Shiraz University of Medical Sciences (SUMS) and Digestive Disease Research Institute of Tehran University of Medical Sciences (DDRI) approved the PCS protocol. All participants completed and signed informed consent before their participation in the PCS. Further details are presented in the PCS profile.[14]

Exclusion criteria:

PCS participants who had a history of diagnosed liver disease, renal failure, cancer, ischemic heart disease, stroke, chronic hemolysis, acute infection, viral hepatitis (subjects who had positive viral markers), those who took hepatotoxic drugs,[15,16] as well as alcohol drinkers (with an intake of more than 20 grams alcohol per day) were excluded from the study.

Variables measurement:

More than 200 socio-demographic, medical history, and biochemical and biomedical variables were collected in the PCS at the baseline.[14] Data on demographic characteristics (age, sex, ethnicity, weight, height, body waist circumference (WC), blood pressure (BP), history of physical activity, medication history, history of chronic diseases, alcohol consumption (the number and type of drinks per day), cigarette smoking, opium usage, fasting blood sugar (FBS), lipid profile, and ALT level were selected for this study.

Data collection:

Biochemical parameters including the serum ALT were measured by using the auto-analyzer, model Bt1500, and the kits were made by Parse Azmoon Company.

We defined MS based on the definition of the We defined MS based on the definition of the Azizi et al (as follows: any three of the following five factors: WC $\geq$ 90 cm, triglyceride (TG) $\geq$ 150 mg/dL, FBS $\geq$ 100 mg/dL, or previously diagnosed type 2 DM, high-density lipoprotein (HDL) < 40 mg/dL in men, and < 50 mg/dL in women, systolic blood pressure (SBP) $\geq$ 130 mm Hg or diastolic blood pressure (DBP) $\geq$ 85 mm Hg, or treatment of previously diagnosed HTN).[17]

Body mass index (BMI) was categorized into three groups (< 25 kg/m^2, $\geq$ 25-30 < kg/m^2 and $\geq$30 kg/m^2). Also, age was categorized into four groups (40-49, 50-59, 60-69, and $\geq$ 70 years). By applying a recommended method for analysis of the International Physical Activity Questionnaire (IPAQ), the value of Metabolic Equivalent of Task (MET) scores was calculated as a measure of physical activity and then categorized into its tertiles (low, medium, and high physical activity). To estimate the prevalence of abnormal metabolic factors in association with the serum ALT level, we defined four categories for the ALT level (< mean, mean to mean + SD, mean + SD to mean + 2SD and $\geq$ mean + 2SD) in men and women separately.

Statistical Analysis:

We estimated the proportions and means ± standard deviations (SD) to describe the data. 95% confidence interval of prevalence was estimated. Two-sided independent sample t test and Chi-square test were used. UNL of ALT

was estimated based on 95 percentage of ALT distribution in participants who had BMI < 25 kg/m^2. The effect of confounding variables was controlled using multivariable logistic regression. Two logistic regression models were fitted to assess the correlates of "current UNL of serum ALT" (what was identified in this study) and "past UNL of serum ALT" (ALT > 40). The significance level was set at 0.05. Stata software version11.2 (StataCorp. LP) was used for data analysis.

RESULTS

6459 out of 9264 subjects were included in this study. Female/male ratio was 1:1.01 (3217/3242). MS was significantly more prevalent in women than men (n = 862; prevalence = 26.9%, 95%CI: 25.36-28.46 vs. n = 542; prevalence = 16.7%, 95%CI: 15.42-18.03; $p < 0.001$). For 1.1% (n = 73) of participants, including: 1.6% (n = 52) of female participants and 0.6% (n = 21) of male ones, all of the MS components were abnormal (table 1).

Mean ALT was significantly higher in men than women (23.78 ± 15.08 vs. 18.65 ± 12.24; $p < 0.001$). In participants with normal BMI, 95 percentile of ALT was 41.71 U/L and 32.9 U/L in men and women, respectively (table2). In women with a history of DM, the mean of ALT was significantly higher than non-diabetics (22.07 ± 14.97 vs. 18.32 ± 11.88; $p < 0.001$), but there was no statistically significant difference between diabetic and non-diabetic men (24.88 ± 17.34 vs. 23.73 ± 14.97; $p = 0.364$).

Abnormal WC was found to be a risk factor for increasing the serum ALT in both current UNL and in ALT > 40 U/L (OR: 1.72, 95%CI: 1.34, 2.21 vs. OR: 1.42, 95%CI: 1.09, 1.86), according to multivariable analyses (table 3).

The prevalence of high BP increased due to the increase in the serum ALT in men but not in women (table 4).

DISCUSSION

The UNL of serum ALT level is about 40 U/L in laboratory references, but according to different studies in different regions, the cut-off point of serum ALT needs to be revised.[1,8,18] In the current study, among the inhabitants in southern Iran, in those with normal BMI, 95 percentile of serum ALT was 41.71 and 32.9 in male and female subjects, respectively. The upper limit of the serum ALT level was significantly higher in subjects who had at least one abnormality in their metabolic syndrome components.

In our previous study in northern Iran, UNL of the serum ALT was 37.5 in men and 36 in women, which were different in comparison with our current estimates. This difference may be due to the difference in our sampling population, one from the north and another from the south of Iran.[12]

Our estimation for UNL is considerably higher than some previous reports.[4,7,9,12,18] It may be due to the difference in the studied population or methodological considerations such as statistical methods applied for the estimation of UNL and inclusion of participants with NAFLD. Lack of any information about participants with NAFLD was another point that must be considered.[2,11] In addition, differences between laboratories and various detection kits of ALT may cause test heterogeneity in different studies and regions.[10]

All MS components were positively correlated with an increase in the serum ALT. These findings were consistent with those of the previous studies showing that higher levels of serum ALT were associated with MS components and the development of MS.[19,20] In 2012 in China, the cut-off point for the serum ALT level, which causes metabolic disorder affecting the liver, was 21-25 IU/L for men and 17-22 IU/L for women.[8] In recent studies, NAFLD has been a prerequisite for the development of metabolic diseases.[21] By an increase in the level of liver enzyme, the risk of the presence of NAFLD will increase, even in normal population. It seems to be necessary to investigate people whose ALT level is even in the upper normal range.[8]

Overall, in subjects who have high physical activity in our study, UNL of ALT was lower in comparison to people with low and moderate activity. Previous reports have shown a significant decrease in the liver enzyme by an aerobic exercise.[22-24] These results may be influenced by the effect of exercise on MS components, especially in the distribution of visceral fat and insulin resistance that affects the serum ALT.[25] More studies are recommended to evaluate the direct effect of physical activity on serum ALT.[22,24,26]

According to multivariable analysis, age had a negative correlation with elevated serum ALT. This finding was in the same line with that of the study published by Dong and his collaborators in 2011. In Dong's study, by analyzing two cohorts of individuals who participated in the Rancho Bernardo's study, with an increase in age, the

Table 1: The participants' characteristics

Variables	Total = 6459 n(Prevalence) 95% CI	Male = 3242 n(Prevalence) 95% CI	Female = 3217 n(Prevalence) 95% CI	*p* value
Age (mean ± SD in years)	51.66 ± 9.25	51.73 ± 9.5	51.6 ± 9.0	0.59
BMI (mean ± SD, kg/m^2)	25.54 ± 4.63	24.21 ± 4.04	26.88 ± 4.8	< 0.001
BMI < 25 kg/m^2	3035(47.2) 46.0, 48.4	1901(58.9) 57.2, 60.6	1134(35.4) 33.7, 37.1	< 0.001
25 ≤ BMI < 30 kg/m^2	2344(36.5) 35.3, 37.7	1055(32.7) 31.1, 34.3	1289(40.3) 38.5, 42.0	< 0.001
BMI ≥ 30 kg/m^2	1049(16.3) 15.4, 17.2	271(8.4) 8.3, 8.5	778(24.3) 22.8, 25.8	< 0.001
WC ≥ 95 cm	2331(36.3) 35.13, 37.49	946(29.3) 27.74, 30.9	1385(43.3) 41.58, 45.03	< 0.001
FBS ≥ 100 mg/dL	2455(38) 36.8, 39.2	1186(36.6) 34.9, 38.3	1269(39.4) 37.7, 41.1	0.018
Low HDL**	886(13.7) 12.9, 14.6	256 (7.9) 7.7, 8.0	630(19.6) 18.2, 21.0	< 0.001
TG ≥ 150 mg/dL	2430(37.6) 36.4, 38.8	1179(36.4) 34.7, 38.1	1251(38.9) 37.2, 40.6	0.037
High BP***	1315(20.4) 19.4, 21.4	617(19.0) 17.7, 20.4	698(21.7) 20.3, 23.1	0.008
MS	1404(21.8) 20.8, 22.83	542(16.7) 15.42, 18.03	862(26.9) 25.36, 28.46	< 0.001
History of HTN	643(10) 9.3, 10.7	176(5.4) 5.2, 5.6	467(14.5) 13.3, 15.7	< 0.001
History of T^2 DM	438(6.8) 6.7, 6.9	150(4.6) 4.4, 4.8	288(9.0) 8.9, 9.1	< 0.001
History of opium use	514(8) 7.9, 8.1	496(15.3) 14.1, 16.6	18(0.6) 0.58, 0.62	< 0.001
Current cigarette smoking	977(15.2) 14.3, 16.1	959(29.6) 28.0, 31.2	18(0.6) 0.58, 0.62	< 0.001
Physical activity				
Low	1805(28) 26.9, 29.1	666(20.6) 19.2, 22.0	1139(35.4) 33.7, 37.1	< 0.001
Moderate	2203(34.1) 32.9, 35.2	942(29.1) 27.5, 30.7	1261(39.2) 37.5, 40.9	< 0.001
High	2445(37.9) 36.7, 9.1	1631(50.4) 48.7, 52.1	814(25.3) 23.8, 26.8	< 0.001

n, number of participants; BMI, body mass index; WC, waist circumference; FBS, fasting blood sugar; HDL, high-density lipoprotein; TG, triglyceride; BP, blood pressure; MS, metabolic syndrome; HTN, hypertension; T2DM, diabetes mellitus type 2

**HDL < 40 in men, HDL < 50 mg/dL in women

***Systolic blood pressure ≥ 130 and/ or diastolic blood pressure ≥ 85 mm Hg

serum level of ALT decreased, especially in old ages.[27] By an increase in age, the function of the liver decreases and it may cause a decrease in the level of liver enzymes.[28] It seems to be necessary to define the UNL of serum ALT in different age groups in laboratory reference values.

Although this is a cross-sectional study on 40-75 years old adults of a semi-rural population, one of the most important strengths of the current study was its adequacy of the sample size which enabled us to do an in-depth stratified analysis. We also used baseline data of the Pars Cohort Study, which has been collected in a valid and standardized way.

Lack of any data about the subjects who were diagnosed with NAFLD (by sonography or liver biopsy) was an important limitation in our study and further investigation is required to determine an exact cut-off point for the

Table 2: ALT features in different subgroups

ALT U/L	Sex	Subgroups	N (%)	Median U/L	MIN, MAX	Mean ± SD	95th	*p* value
ALT U/L overall	M		3242	19.94	1.81, 137.86	23.78 ± 15.08	51.68	< 0.001
	F		3217	15.65	1.1, 153.64	18.65 ± 12.24	37.94	
BMI	M	< 25 kg/m^2	1901 (58.9)	17.05	1.81, 137.86	20.34 ± 12.96	41.71	< 0.001
		≥ 25-30 < kg/m^2	1055 (32.7)	24.03	5.62, 126.77	27.97 ± 16.13	57.29	
		≥ 30kg/m^2	271 (8.4)	26.1	7.47, 107.33	31.7 ± 17.53	66.74	
	F	< 25 kg/m^2	1134 (35.4)	14.03	1.1, 147.4	16.34 ± 10.49	32.9	< 0.001
		≥ 25-30 < kg/m^2	1289 (40.3)	16.41	1.81, 153.64	19.53 ± 13.0	40.01	
		≥ 30 kg/m^2	778 (24.3)	16.91	1.31, 124.4	20.63 ± 12.86	41.41	
TG	M	≥ 150 mg/dL	1179 (36.4)	24.02	4.25, 135.8	28.21 ± 16.77	61.55	< 0.001
		< 150 mg/dL	2063 (63.6)	18.0	1.81, 137.86	21.26 ± 13.39	44.21	
	F	≥ 150 mg/dL	1251 (38.9)	17.37	1.5, 151.46	20.65 ± 12.38	43.04	< 0.001
		< 150 mg/dL	1966 (61.1)	14.76	1.1, 153.64	17.39 ± 11.98	34.33	
FBS	M	≥ 100 mg/dL	1186 (36.6)	21.34	2.7, 125.05	25.49 ± 16.26	56.32	< 0.001
		< 100 mg/dL	2056 (63.4)	19.09	1.81, 137.86	22.8 ± 14.27	47.83	
	F	≥ 100 mg/dL	1269 (39.4)	16.98	1.5, 151.46	20. 3 ± 12.82	42.58	< 0.001
		< 100 mg/dL	1948 (60.6)	14.82	1.1, 153.64	17.58 ± 11.72	35.35	
HDL	M	< 40 mg/dL	256 (7.9)	23.05	2.7, 125.05	27.27 ± 17.69	62.25	0.001
		≥ 40 mg/dL	2986 (92.1)	19.72	1.81, 137.86	23.49 ± 14.8	50.73	
	F	< 50 mg/dL	630 (19.6)	16.26	4.32, 147.41	20.1 ± 14.33	43.31	0.004
		≥50 mg/dL	2587 (80.4)	15.52	1.1, 153.64	18.3 ± 11.64	36.7	
High* BP	M	High	617 (19.0)	21.56	3.32, 135.8	25.61 ± 16.38	54.94	0.001
		Normal	2622 (81.0)	19.57	1.81, 137.86	23.36 ± 14.74	50.86	
	F	High	698 (21.7)	16.01	1.31, 116.28	18.73 ± 10.98	38.94	0.833
		Normal	2516 (78.3)	15.57	1.1, 153.64	18.62 ± 12.56	37.75	
WC	M	≥ 95 cm	946 (29.3)	24.79	7.21, 126.77	24.79 ± 16.85	64.81	<0.001
		< 95 cm	2281 (70.7)	18.09	1.81, 137.86	21.55 ± 13.5	45.5	
	F	≥ 95 cm	1385 (43.3)	17.06	1.31, 153.64	20.62 ± 13.45	41.38	< 0.001
		< 95 cm	1816 (56.7)	14.69	1. 1, 151.46	17.18 ± 11.04	34.92	

ALT U/L	Sex	Sub-groups	N (%)	Median U/L	MIN, MAX	Mean ± SD	95th	*p* value
MS	M	Yes	542 (16.7)	25.1	8.13, 125.05	30.61 ± 18.5	67.09	< 0.001
		No	2629 (83.3)	18.73	1.81, 137.86	22.41 ± 13.91	46.68	
	F	Yes	862 (26.9)	17.83	1.81, 120.2	21.3 ± 12.59	44.55	< 0.001
		No	2345 (71.4)	14.96	1.1, 153.64	17.69 ± 11.98	35.61	
Physical Activity	M	Low	666 (20.6)	20.36	2.7, 135.2	25.01 ± 17.39	56.87	< 0.001**
		Moderate	942 (29.1)	20.69	1.81, 135.8	24.99 ± 16.2	54.73	
		High	1631 (50.4)	19.29	3.32, 137.86	22.59 ± 13.2	45.59	
	F	Low	1139 (35.4)	15.71	1.1, 151.46	18.27 ± 11.17	37.42	0.491**
		Moderate	1261 (39.2)	15.68	1.31, 153.64	19.17 ± 13.45	38.9	
		High	814 (25.3)	15.49	1.7, 147.41	18.41 ± 11.66	37.28	
Age	M	(40-49)	1597 (49.3)	22.64	3.33, 137.86	27.01 ± 16.75	60.15	< 0.001***
		(50-59)	1017 (31.4)	19.39	3.56, 122.91	21.74 ± 12.23	43.15	
		(60-69)	432 (13.3)	17.27	3.25, 135.8	20.15 ± 4.44	35.89	
		≥ 70	196 (6)	14.5	1.81, 47.35	16.11 ± 7.07	31.25	
	F	(40-49)	1593 (49.5)	15.31	1.1, 147.41	18.35 ± 12.34	38.17	< 0.001***
		(50-59)	944 (29.3)	16.99	2.04, 151.46	19.83 ± 12.1	39.93	
		(60-69)	548 (17)	15.67	1.81, 153.64	18.48 ± 12.82	36.02	
		≥ 70	132 (4.1)	12.94	4.5, 58.29	14.73 ±7.63	31.49	

ALT, alanine aminotransferase; N, number of participants; M, male; F, female; BMI, body mass index; TG, triglyceride; FBS, fasting blood sugar; HDL, high-density lipoprotein; BP, blood pressure; WC, waist circumference; MS, metabolic syndrome.

*Systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 85 mm Hg

**Mean of high physical activity group compared with two other groups overall

***Mean of age > 70 compared with three other age groups overall

Table 3: Serum ALT correlates in the Pars cohort study, southern Iran, 2014

Variables	Current UNL of serum ALT		Past UNL of serum ALT	
	Crude. OR	Adj. OR	Crude. OR	Adj. OR
Age (year)	0.95 (0.94, 0.96)	0.94 (0.92, 0.95)	0.94 (0.93, 0.95)	0.93 (0.92, 0.95)
WC ≥ 95cm	2.29 (1.8, 2.92)	1.72 (1.34, 2.21)	2.12 (1.75, 2.57)	1.42 (1.09,1.86)
BMI > 25 kg/m^2	-	-	2.19 (1.78, 2.68)	1.65 (1.24, 2.21)
Cholesterol mg/dL	1.08 (1.05, 1.1)	1.06 (1.03, 1.09)	1.06 (1.04, 1.09)	1.07 (1.04, 1.09)
Male sex	-	-	2.54 (2.07, 3.13)	3.39 (2.71, 4.22)
TG ≥ 150 mg/dL	2.38 (2.0, 3.85)	1.63 (1.25, 2.13)	2.48 (2.04, 3.0)	1.59 (1.28, 1.98)
FBS ≥ 100 mg/dL	1.6 (1.34, 1.9)	1.69 (1.32, 2.16)	1.63 (1.35, 1.98)	1.52 (1.24, 1.86)
SBP mm Hg	1.09 (1.02, 1.16)	1.08 (1.01, 1.16)	1.07 (1.02, 1.12)	1.07 (1.0, 1.13)

[a]Abbreviations: adj, adjusted; OR, odds ratio; WC, waist circumference; BMI, body mass index; TG, triglyceride; FBS, fasting blood sugar; SBP; systolic blood pressure

Table 4: **Percentage of abnormality in metabolic syndrome components by serum ALT levels**

		ALT,U/L				
Variables	**N**	**< Mean**	**Mean to Mean + 1SD**	**Mean + 1SD to Mean + 2SD**	**≥ Mean + 2SD**	***p****
			Male			
Overall	3242	2068	820	214	140	-
High BP mm Hg	617	17.3	22.6	19.6	22.9	0.007
FBS ≥ 100 mg/dL	1186	33.9	39.9	42.5	47.9	< 0.001
TG ≥ 150 mg/dL	1179	27.9	48.8	55.1	60.0	< 0.001
HDL < 40 mg/dL	256	6.5	10.2	9.3	12.9	0.001
WC ≥ 95cm	946	18.7	35.6	41.7	50.8	< 0.001
			Female			
Overall	3217	2094	825	192	106	-
High BP mm Hg	698	21.0	22.8	25.1	20.8	0.467
FBS ≥ 100 mg/dL	1269	35.1	46.3	49.0	55.7	< 0.001
TG ≥ 150 mg/dL	1251	32.9	48.4	53.6	56.6	< 0.001
HDL < 50 mg/dL	630	18.5	20.0	24.0	30.2	0.009
WC ≥ 95 cm	1385	38.9	51.4	56.6	59.3	< 0.001

Abbreviations: BP, blood pressure; FBS, fasting blood sugar; TG, triglyceride; HDL, high-density lipoprotein; WC, waist circumference

*p-value for trend

serum ALT in normal population. Information about the use of herbal drugs was also limited in our survey.

In conclusion, the UNL of ALT in southern Iranian women is lower than the current recommended level (i.e. > 40), while these are almost the same for men. MS components are highly common in southern Iran and are associated with elevated serum ALT. Further studies are required to estimate the UNL of the serum ALT among the Iranian population with NAFLD.

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ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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