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Estimation of the Normal Upper Limits for Serum Alanine Aminotransferase in a Population-Based Study from Southeast of Iran

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Abstract

Background: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are two accessible indices for liver evaluation. Upper limit of normal (ULN) of these tests are important for starting further investigations for persons with high values. In recent years, cut off points for ULN of these tests have been disputed. This study aimed to determine the ULN of ALT and AST in a population-based study.

Methods: This cross-sectional study was performed on a randomized clustered sample of people of Kerman city. Demographic, anthropometric, and laboratory data were collected and analyzed. After excluding the recognized risk factors for liver function tests in another group (group 2), data were analyzed in this subgroup.

Results: Of 2748 subjects included in this study, 1172 (42.4%) were men, with an age range of 15-85 years. The mean (± SE), median, mode, and 95th percentile were 23.74 ± 0.18, 22, 19, and 37 for AST and 22.37 ± 0.27, 18, 15, and 46 for ALT, respectively. The levels of AST and ALT were higher in men and middle age group (P<0.0001). Similar results were obtained for gender but the association of AST and ALT with age was disappeared in another group.

Conclusion: According to the results of the present study, it is recommended to measure the ULN of AST and ALT periodically in different regions concerning age and gender.

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Introduction

Alanine Aminotransferase (ALT) and aspartate aminotransferase (AST) are two accessible and relatively reliable tests for evaluating liver tissue health. For many last years, the upper limit normal (ULN) of these enzymes had set at 40 IU/L (1). In recent years, these thresholds have been disputed between researchers, especially because of changing lifestyle and increasing the prevalence of fatty liver disease as its complication. In recent years, some investigators have tested the ULN of these enzymes in different populations. The results of some of these studies are similar to those of past studies (2). Comparing the past and recent studies (3), the diversity of causes of liver diseases and condition of lifestyle have changed during recent years. So, it is expected that the ULN of the AST and ALT could be changed accordingly.

As these studies have been conducted in past years on different population groups with different ethnic and lifestyles. The aim of this study was to determine the ULN of AST and ALT in a general population and healthy adult subjects in Kerman, the main city located in the Southeast of Iran.

Materials and Methods

This population-based, cross-sectional study was designed on adults (15-85 years old) in urban area of Kerman city, in the Southeast of Iran, from 2011 to 2012. After approving the survey by the Ethics Committee of Kerman University of Medical Sciences, the subjects were selected according to their postal code in family clusters randomly. Those subjects with severe morbidity, major psychiatric and vital organ disorders, who refused to enter the study, patients with known or suspected hepatobiliary disease, including viral hepatitis, autoimmune problems, and those taking medications with potential effect of liver injury were excluded. A total of 2748 subjects were enrolled in the survey after endorsement of informed written consent. Data collection was performed by a trained general practitioner through face to face interview and physical examination. Body mass index (BMI) was calculated by dividing the body weight by the square height (kg/m^2). Venous blood samples were obtained from participants after a 12-hour fasting. These samples were analyzed for AST, ALT, fasting blood sugar (FBS), triglyceride (TG), cholesterol, blood urea nitrogen, and creatinine.

In the first step, mean ± SE, the 95^{th} percentile of AST and ALT were calculated in the 2748 enrolled subjects (group 1). Meanwhile in the second step, after excluding the subjects with confounding factors including history of diabetes mellitus or FBS ≥ 126 mg/dl, TG ≥ 150 mg/dl, cholesterol ≥ 200 mg/dl, history of alcohol consumption, and BMI ≥ 25; above-mentioned measures were calculated in 666 subjects (group 2). Regarding age and gender, subgroup analysis was also performed. By this method, the ULN of both enzymes was set in the 95^{TH} percentile in the second and third group as healthy population.

Statistical analysis

Data analysis was performed using independent t-test and one-way ANOVA test for continuous variables by SPSS version 16 (SPSS Inc, Chicago, IL, USA). A two tailed $P<0.05$ was considered statistically significant.

Results

A total of 2748 subjects, 1169 (42.5%) men, citizens of Kerman city, were included. The means ± SE of ALT and AST were 23.74 ± 0.18 and 22.37 ± 0.27 IU/L, respectively. Distribution of the mean of AST and ALT according to gender is shown in Table 1.

Table 1. Mean of AST and ALT in a subset of general population according to gender difference

	N (%)	Mean	SE	Percentile 95th	P-value
AST (IU/L) total	2748(100)	23.74	0.18	37	
Men	1169 (42.5)	26.04	0.32	42	<0.0001
Women	1579 (57.5)	22.05	0.19	33	
ALT (IU/L) total	2748(100)	22.37	0.27	46	
Men	1169 (42.5)	25.97	0.49	55	<0.0001
Women	1579 (57.5)	19.71	0.29	35	

There was a significant difference between two genders for both AST and ALT levels (P<0.0001). In terms of age, distribution of the mean of AST and ALT is shown in Figures 1 and 2. The peak level of AST was in the age range of 55-64 years while it was in the range of 35-44 years for ALT. The means of both AST and ALT were lower at higher ages. As shown in Figure 1, the mean of AST and ALT followed a similar pattern in three different groups.

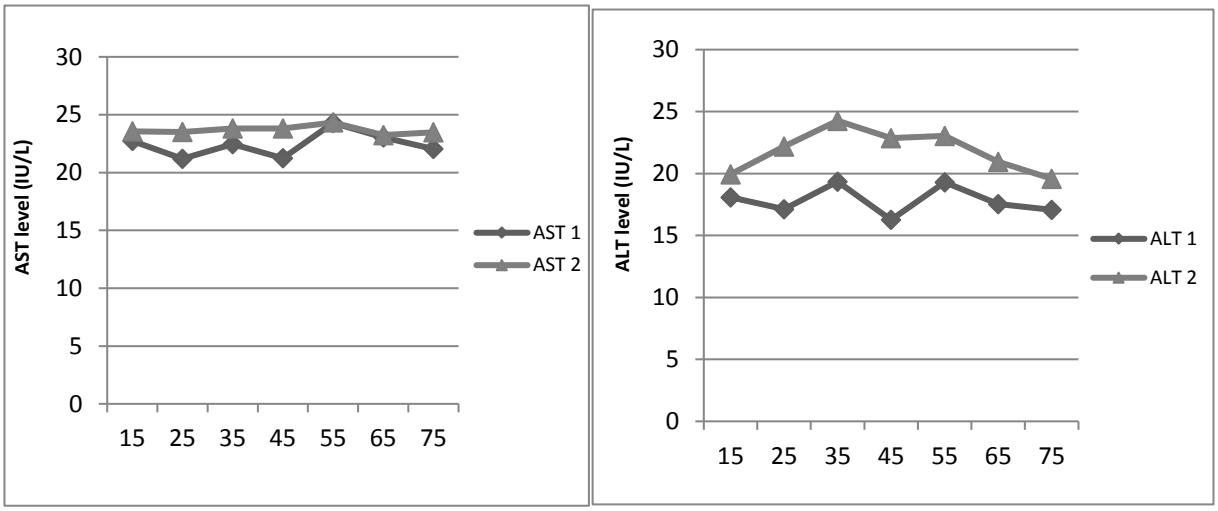

Figure 1. Mean of AST and ALT according to age in three groups.

The association of some risk factors affecting AST and ALT levels, namely alcohol consumption, BMI, triglyceride, cholesterol, blood pressure, and diabetes mellitus is shown in Table 2.

Table 2. Association of risk factors with AST and ALT levels

	Number (%)	AST (IU/L)			ALT (IU/L)		
		Mean	**SD**	**P-value**	**Mean**	**SD**	**P-value**
Alcohol consumption							
No	2695 (99)	23.68	9.39	0.013	22.36	14.39	0.003
Yes	37 (1)	28.02	10.09		32.97	20.29	
BMI							
<18.5	174 (6)	21.47	5.95	<0.0001	21.47	4.64	<0.0001
18.5-24.9	1036 (38)	20.29	13.21		22.98	8.28	
>25	1491 (55)	24.57	15.21		24.50	9.91	
TG (mg/dl)							
<150	1737 (63.2)	22.93	8.88		20.65	13.75	
150-199	478 (17.4)	24.74	9.24	<0.0001	24.56	13.96	<0.0001
200- 499	502 (18.3)	25.05	10.36		25.72	15.68	
>500	31 (1.1)	33.13	17.14		31.26	15.25	
Cholesterol (mg/dl)							
< 200	1546 (56.3)	22.91	8.59	<0.0001	20.99	14.47	<0.0001
200-239	757 (27.5)	24.21	9.10		23.57	13.64	
≥240	445 (16.2)	25.84	11.88		25.14	14.62	
Sys BP (mmHg)							
<130	1944 (71.5)	23.40	8.69	0.007	21.90	13.99	0.005
≥ 130	774 (28.5)	24.59	10.95		23.63	15.33	
DIA BP (mmHg)							
<85	2199 (80.9)	23.30	8.91	<0.0001	21.60	13.55	<0.0001
≥85	518 (19.1)	25.59	11.07		25.76	17.20	
Diabetes Mellitus							
No	2297 (83.6)	23.52	8.26	0.041	21.78	13.64	<0.0001
Yes	450 (16.4)	24.89	13.75		25.42	17.32	

In group 2, after excluding the risk factors affecting AST and ALT levels, a total of 666 cases remained that their statistical parameters are shown in Table 3. As in other groups, there was a significant statistical difference between gender and AST, ALT parameters for both mean (SE) and 95th percentile (P<0.0001).

Table 3. Parameters of AST and ALT in healthy adult population

	N (%)	Mean	SE	95th Percentile	P-value
AST (IU/L)	666 (100)	22.05	0.297	32	
Men	306 (45.9)	24.30	0.56	39	<0.0001
Women	360 (54.1)	20.14	0.23	27	
ALT (IU/L)	666 (100)	17.78	0.46	32	
Men	306 (45.9)	20.31	0.73	42	<0.0001
Women	360 (54.1)	15.63	0.57	24	

Discussion

In this population-based study, the 95th percentile of AST and ALT was 37 and 46 IU/L, respectively. These results are consistent with the findings of some other studies on general population with similar design; i.e. Kariv et al. reported 50.1 IU/L as 95th percentile for ALT in general population in a large survey in Israel (2).

In the present study, men had higher levels of AST and ALT in either two groups, similar to almost all other surveys. In a German study on 1953 cases, the 95th percentile of AST for men and women was 33 and 25 IU/L while it was 60 and 34 IU/L for ALT (4). Kariv et al. reported 60.8 and 40.6 IU/L as the 95th percentile of ALT in men and women, respectively (2). A Korean study reported 67 and 46.6 IU/L in men and women, respectively, for ALT before excluding the risk factors (5).

In the present study, after excluding the risk factors affecting the level of AST and ALT (group 2), the 95th percentile of both enzymes was 32 IU/L in all subjects; it was 39 and 27 IU/L for AST and 42 and 24 IU/L for ALT in men and women, respectively. These results, which were lower than those obtained from group 1, were close to the recommended values for men, but were lower than those previously scheduled values in women. Similar results were seen in the study of Zheng et al. (2012) for ALT (35.2 and 23.4 IU/L for men and women, respectively) (5). However, the 95th percentile of ALT was lower in some other studies. It was reported 21 and 17 IU/L for men and women in a study in Taiwan (6); while in a study by Prati et al. (2002), it was reported 30 and 19 IU/L for men and women, respectively (7). Compared to the results of the present study, the findings of Kariv survey showed higher results, as ALT was 37.5, 44.9, and 31.8 IU/L in total studied population, men, and women, respectively (2).

The levels of AST and ALT were higher in men in the present study and many other surveys. This finding was compatible with the results of studies on either youth or old population (7). The cause of difference between two genders is not clear, but might be related to physical activity (8), muscle mass or sex hormones.

Regarding age, the maximum values for both enzymes were in the range of 35-44 years in both genders in general population. These results are comparable to the results of studies by Elinav (9) and Grossi (10). In the study of Kariv et al., this pattern was observed just in men in the fourth decade (2); while such a difference was not seen in group 2 in the present study. It could be explained by the presence of multiple risk factors in middle age groups and their influence on liver enzymes.

The results of the present study showed significant high levels of AST and ALT in subjects with higher BMI, diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, blood

hypertension, and alcohol consumption. Kang et al. in a study on the Korean population reported a relationship between all above-mentioned factors and increasing level of ALT (11) whilst Kabir et al. showed higher levels of ALT in subjects with triglyceride levels more than 150 mg/dl (12). As in the present study, some other surveys also pointed out to the effect of BMI as an important factor with liver enzymes levels (3, 13-15). In addition, hypercholesterolemia was also identified as a risk factor for increased AST and ALT levels in some studies (16). Some of them found it to be effective just in men (13). Although many authors believe that diabetes mellitus can act as a risk factor for inducing liver steatosis and elevation of liver enzymes (11, 17-19), but this relationship was observed just in women in Pacifico et al survey (20). In a study on apparently healthy Iranian old population, such a relationship was not reported (12).

As mentioned in the above surveys, there was no complete consistency between different studies to set point a unique numerical value for AST and/or ALT generally. On the other hand, the clinical significance of a new set point value for AST and ALT is not elucidated at the present time. However, the main question that should be answered is that "Is it time to replace the previous defined levels of AST and ALT with new ones? It is worrying that setting a lower level of AST and ALT, could motivate the healthcare personnel to perform undue costly paraclinical procedures resulting in resource wastes, especially in developing countries. Nevertheless, according to the most recent studies, it seems logical to have a settled lower levels of AST and ALT in healthy adult population without risk factors. Now it is time to answer this question by performing a systematic meta-analysis review.

Limitations

Despite of a relatively large sample size, this study was a cross-sectional designed survey and implementation of objective tools such as liver ultrasound and paraclinical assessment of liver injury was not feasible to be used in a general population.

Conclusion

According to the results of the present study, it is recommended to measure the ULN of AST and ALT periodically in different regions concerning age and gender. However, in clinical point of view, the impact of the new lower levels of AST and ALT does not seem to have an impressive practical effect. Therefore, performing a systematic meta-analysis review is highly recommended.

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Declaration of conflicting interests

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