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CLINICAL RESEARCH

Serum γ-glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase activity in Iranian healthy blood donor men

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Abstract

AIM: To determine serum γ-glutamyltransferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) activity, and to assess their correlation with demographic and clinical findings in healthy blood donors.

METHODS: This cross-sectional study was performed in 934 male blood donors, aged 18 to 68 years, who consecutively attended Tehran blood transfusion service in 2006. All participants were seronegative for HBV or HCV infections, non alcohol users, and all underwent a standard interview and anthropometric tests. Clinical and biochemical parameters including AST, ALT, and GGT activities were determined. Patients taking drugs known to cause hepatic fat deposition were excluded. For AST, ALT, and GGT variables, we used 33.33 and 66.66 percentiles, so that each of them was divided into three tertiles.

RESULTS: Mean AST, ALT, and GGT activities were 25.26 ± 12.58 U/L (normal range 5-35 U/L), 33.13 ± 22.98 (normal range 5-35 U/L), and 25.11 ± 18.32 (normal range 6-37 U/L), respectively. By univariate analyses, there were significant associations between increasing AST, ALT, or GGT tertiles and age, body weight, body mass index, and waist and hip circumferences ($P < 0.05$). By multiple linear regression analyses, ALT was found to be positively correlated with dyslipidemia (B = 6.988, $P = 0.038$), whereas ALT and AST were negatively correlated with age. AST, ALT, and GGT levels had positive correlation with family history of liver disease (B = 15.763, $P < 0.001$), (B = 32.345, $P < 0.001$), (B = 24.415, $P < 0.001$), respectively.

CONCLUSION: Although we did not determine the cutoffs of the upper normal limits for AST, ALT, and GGT levels, we would suggest screening asymptomatic patients with dyslipidemia and also subjects with a family history of liver disease.

Key words: γ-glutamyltransferase; Alanine aminotransferase; Aspartate aminotransferase; Blood donor

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INTRODUCTION

The level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT) elevation that is considered abnormal varies widely and has recently been brought into question[1]. There is also debate as to whether or not different cutoffs are indicated for normal ranges of liver enzymes. Several studies have shown that variation in serum AST ALT or GGT in the population is associated with risk of development of cardiovascular disease, type 2 diabetes, stroke, or hypertension[2,3]. Nonalcoholic fatty liver disease (NAFLD) is a common explanation for abnormal liver-test results in blood donors, and it is the cause of asymptomatic elevation of aminotransferase levels in up to 90 percent of cases once other causes of liver disease are excluded[4]. Associations between abnormal values and also the prevalence and the risk factors for fatty liver have not undergone a formal evaluation in a representative sample of the general population. NAFLD is emerging as a component of the metabolic syndrome, although it is not known whether markers of NAFLD, including elevated concentrations of AST, and ALT, predict the development

of metabolic syndrome. The third report of the National Cholesterol Education Program expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP Ⅲ) defines metabolic syndrome as involving three or more of the following criteria[5]:

- Central/abdominal obesity as measured by waist circumference: for men > 40 inches (102 cm) and for women > 35 inches (88 cm).
- Fasting plasma triglycerides ⩾ 150 mg/dL (1.69 mmol/L)
- HDL cholesterol for men < 40 mg/dL (1.04 mmol/L), and for women < 50 mg/dL (1.29 mmol/L)
- Blood pressure ⩾ 130/85 mmHg
- Fasting plasma glucose ⩾ 110 mg/dL (6.1 mmol/L)

Also frequently seen with metabolic syndrome but not included in the ATP Ⅲ criteria are prothrombotic and proinflammatory tendencies. All of the factors associated with metabolic syndrome are interrelated. Obesity and lack of exercise tend to lead to insulin resistance. Insulin resistance has a negative effect on lipid production, increasing VLDL (very low-density lipoprotein), LDL and triglyceride levels in the bloodstream and decreasing HDL (high-density lipoprotein). This can lead to fatty plaque deposits in the arteries enhancing the risks for cardiovascular disease, blood clots, and strokes. Excess insulin increases renal sodium retention, which increases blood pressure and can lead to hypertension.

Our aim was to determine serum γ-glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase activity and to investigate their relationship with several components of the metabolic syndrome in 934 healthy male blood donors in Tehran blood transfusion center from 15 February to 22 March 2006.

MATERIALS AND METHODS

Clinical and laboratory assessment

Nine hundred thirty four apparently healthy Iranian men, who attended to Tehran blood transfusion center for blood donation during a 37-d period from 15 February to 22 March 2006, were consecutively enrolled in the cross-sectional study. A standard interview, anthropometrics, and biochemical analyses were conducted for each participant. Samples from all donations were tested according to the recognized screening test algorithms for hepatitis B surface antigen, anti-HCV, anti-HIV1/2, syphilis, and for AST, ALT and GGT levels. Samples repeatedly reactive or indeterminate for HBsAg were further analyzed with a second independent HBsAg enzyme immunoassay (EIA), and if further reactive, were tested by a neutralization assay. Samples repeatedly reactive or indeterminate for anti-HCV were confirmed with an additional independent anti-HCV EIA and with a HCV-RIBA assay. Samples repeatedly reactive or indeterminate for HIV were confirmed with a second independent anti-HIV1/2 test, a p24 Ag assay and a HIV western blot. Samples reactive to venereal disease research laboratory (VDRL) were tested by fluorescent Treponemal antibody absorbed (FTA-ABS) as confirmatory test for syphilis infection.

The following conditions were excluded: seropositivity for hepatitis B surface antigen, and or antibody to hepatitis C virus, approved by confirmatory tests of hepatitis B and C viruses, alcohol consumption, use of drugs which may produce fatty liver as asparaginase, tetracycline, warfarin, amiodarone, tamoxifen, estrogens, bleomycin, diltiazem, nifedipine, methotrexate, corticosteroids, and salicylates. Cigarette smoking was not considered a criterion for exclusion. As number of female blood donors were limited (56 subjects), their data were not included. Personal and family history of hypertension, ischemic heart disease, stroke, dyslipidemia, diabetes mellitus, chronic liver disease according to diagnosis of physician, cigarette smoking, medication history, demographic findings such as body weight, height, body mass index, waist and hip circumferences, waist to hip ratio, and blood pressure were recorded. All anthropometric measurements were made by the same physician. Former and present smokers were defined as ever smokers. Established diagnosis of diabetes was considered if random blood sugar > 200 mg/dL (⩾ 11.1 mmol/L) plus symptoms of diabetes or the patient was a known case of diabetes by a physician. Dyslipidemia was diagnosed in the case of documented use of anti-lipemic medication, or the fasting levels of total cholesterol above 200 mg/dL or triglycerides above 170 mg/dL. The diagnosis of hypertension was based on the following criteria: systolic blood pressure ⩾ 140 mmHg and or diastolic blood pressure ⩾ 90 mmHg measured within 30 min in the sitting position using a brachial sphygmomanometer or ongoing use of antihypertensive treatment. Personal history of ischemic heart disease, stroke, family history of diabetes, family history of chronic liver disease in first relatives were recorded if the diagnoses were approved by a physician.

Venous blood was drawn from antecubital vein. AST, ALT and GGT levels were detected by auto-analyzer. AST, ALT and GGT in serum were determined by ELISA method. Furthermore, to eliminate effect of freeze-thawing of samples that may lower enzyme activity values, ALT, AST, and GGT testing was conducted on samples which were immediately carried to the laboratory. We did not exclude people with known diabetes that is likely to be affected more commonly with fatty liver disease, to avoid bias in conclusions. The study proposal and the protocol were approved by the ethics committee of Baqiyatallah University of Medical Sciences, and a written informed consent was obtained from each participant.

Statistical analysis

Analysis was performed using SPSS software version 13.0. For numerical variables we used mean value, standard deviation, median, 5^{th} and 95^{th} percentiles, maximum and minimum. For categorical variables we used number and percent. Since AST, ALT, and GGT values were not gaussian distributed, the levels of these variables were logarithm neperian (Ln) transformed. For measurement of their mean, we changed the amounts to normal Log and then we used exponential of mean and used that as mean of variables.

We used 33.33 and 66.66 percentiles and each variable was divided into three groups. For associations of them with numerical variables variance analyses, and for analyzing statistical difference among categorical variables in relation to AST, ALT, and GGT levels, chi-square tests

Table 1 AST tertiles according to characteristics of the study population

Variable	AST			*P*
	< 21	21-25	> 25	
Age (mean ± SD), yr	42.1 ± 11.4	40.9 ± 11.2	39.5 ± 10.2	0.020 (group 1 *vs* group 3)
Body weight (mean ± SD), km	80.6 ± 11.9	82.1 ± 12.8	85.7 ± 13.4	0.000 (group 1, 2 *vs* group 3)
Height (mean ± SD), cm	174.4 ± 6.9	174.9 ± 6.4	175.3 ± 6.8	0.232
Body mass index (BMI) (mean ± SD)	26.6 ± 3.7	26.9 ± 3.9	27.9 ± 4.3	0.000 (group 1, 2 *vs* group 3)
Waist circumference (mean ± SD), cm	94.3 ± 8.6	95.5 ± 9.7	97.3 ± 9.7	0.000 (group 1, 2 *vs* group 3)
Hip circumference (mean ± SD), cm	100.7 ± 8.2	101.5 ± 9.4	103 ± 9.1	0.001 (group 1, 2 *vs* group 3)
Waist to hip ratio (WHR) (mean ± SD)	0.94 ± 0.04	0.94 ± 0.05	0.94 ± 0.05	0.449
Diabetes mellitus (% positive)	2.7	1.3	1.0	0.226
Family history of diabetes (% positive)	23.3	18.8	18.6	0.271
Family history of liver disease (% positive)	0.3	1.6	1.3	0.276
Hypertension (% positive)	3.7	2.6	2.3	0.574
Dyslipidemia (% positive)	6.3	4.9	8.1	0.262
Smoking habit (% positive)	24.0	21.7	19.7	0.435

Table 2 ALT tertiles according to characteristics of the study population

Variable	ALT			*P*
	< 22	22-34	> 34	
Age (mean ± SD), yr	42.1 ± 11.9	41.5 ± 10.9	38.9 ± 9.9	0.001 (group 1, 2 *vs* group 3)
Body weight (mean ± SD), kg	79.0 ± 11.5	83.0 ± 11.4	86.5 ± 14.4	0.000 (all of groups)
Height (mean ± SD), cm	174.45 ± 6.76	174.67 ± 6.69	175.4 ± 6.6	0.173
Body mass index (BMI) (mean ± SD)	25.94 ± 3.4	27.29 ± 3.6	28.1 ± 4.6	0.000 (all of groups)
Waist circumference (mean ± SD), cm	93.2 ± 9.5	95.7 ± 8.6	98.1 ± 9.5	0.000 (all of groups)
Hip circumference (mean ± SD), cm	99.5 ± 9.0	102.0 ± 8.2	104.1 ± 9.2	0.001 (all of groups)
Waist to hip ratio (WHR) (mean ± SD)	0.94 ± 0.04	0.94 ± 0.05	0.94 ± 0.05	0.152
Diabetes mellitus (% positive)	2.0	1.0	1.9	0.571
Family history of diabetes (% positive)	20.6	21.8	18.2	0.538
Family history of liver disease (% positive)	0.3	1.3	1.6	0.268
Hypertension (% positive)	3.6	2.4	2.6	0.621
Dyslipidemia (% positive)	4.9	7.4	7.1	0.402
Smoking habit (% positive)	21.64	23.57	20.2	0.602

were performed. If it was a difference between groups, in analysis variance, we used LSD test for showing the group that had significant difference. All reported *P* values are two tailed, and those < 0.05 were considered statistically significant. Multiple linear regression analyses were conducted to assess variables that are associated with increased AST, ALT, or GGT levels, and all the variables entered the model and then those that had a *P* value less than 0.1 were maintained in the equation.

RESULTS

The mean age of 934 participants was 40.83 ± 10.96 (range of 18.00 to 68.00) years. The mean body mass index, waist circumference, and waist to hip ratio (WHR) were 27.09 ± 3.98, 95.62 ± 9.41 centimeter, and 0.93 ± 0.04, respectively. Mean AST, ALT, and GGT activities were 25.26 ± 12.58 U/L (normal range 5-35 U/L), 33.13 ± 22.98 U/L (normal range 5-35 U/L), and 25.11 ± 18.32 U/L (normal range 6-37 U/L), respectively. Mean (Transformation Ln) of AST, ALT, and GGT were 23.76, 28.45, and 20.52, respectively. Considering 5th and 95th percentiles of AST (16, 42), ALT (13, 70), or GGT (8, 58) U/L, the 95th percentiles values were high in the population studied. Subjects were divided into three groups according to liver enzyme tertiles. In AST tertiles, AST level was < 21, 21-25 U/L, and AST > 25 U/L in groups 1, 2, and 3, respectively. In ALT tertiles, ALT level was < 22, 22-34, and > 34 U/L in groups 1, 2, and 3, respectively. In GGT tertiles, GGT level was < 15 U/L, 15-25 U/L, and > 25 U/L in groups 1, 2, and 3, respectively.

Comparative demographic, clinical and biochemical characteristics of our study population in AST, ALT, and GGT tertile groups by univariate analyses are shown in Tables 1, 2, and 3. Univariate analyses show significant associations between increasing AST, ALT, or GGT tertiles and age, body weight, body mass index, central adiposity, waist and hip circumferences ($P < 0.05$). Moreover, evidence that increasing ALT, AST, and GGT tertiles are associated with demographic parameters of the metabolic syndrome (body weight, body mass index, waist circumference and hip circumference), support the conclusion that most of the abnormalities are probably due to NAFLD. The mean body mass index in our study population of 27.09 ± 3.98 could implicate a potentially important public health attention.

Table 4 shows correlation of our study characteristics with AST, ALT, or GGT levels in multiple linear regression.

In multiple linear regression analysis, AST was found

Table 3 GGT tertiles according to characteristics of the study population

Variable	GGT			*P*
	< 15	15-25	> 25	
Age (mean ± SD), yr	38.8 ± 11.4	42.4 ± 11.2	41.3 ± 10.1	0.000 (group 1 *vs* group 2, 3)
Body weight (mean ± SD), kg	79.1 ± 11.2	83.8 ± 12.6	85.7 ± 13.9	0.000 (group 1 *vs* group 2, 3)
Height (mean ±SD), cm	174.6 ± 6.5	174.9 ± 7.0	175.1 ± 6.6	0.675
Body mass index (BMI) (mean ± SD)	25.9 ± 3.3	27.6 ± 4.3	27.9 ± 4.0	0.000 (group 1 *vs* group 2, 3)
Waist circumference (mean ± SD), cm	92.9 ± 9.1	96.5 ± 9.5	97.8 ± 8.9	0.000 (group 1 *vs* group 2, 3)
Hip circumference (mean ± SD), cm	99.2 ± 8.9	102.8 ± 9.0	103.7 ± 8.5	0.001 (group 1 *vs* group 2, 3)
Waist to hip ratio (WHR) (mean ± SD)	0.94 ± 0.04	0.94 ± 0.04	0.94 ± 0.05	0.103
Diabetes mellitus (% positive)	0.6	2.0	2.3	0.217
Family history of diabetes (% positive)	19.1	22.1	19.5	0.608
Family history of liver disease (% positive)	0.0	1.0	2.3	0.023
Hypertension (% positive)	2.2	2.7	3.6	0.582
Dyslipidemia (% positive)	5.1	7.1	7.2	0.486
Smoking habit (% positive)	19.49	23.29	22.7	0.471

to be inversely related with age and smoking habit (B = -0.125, $P = 0.002$; B = -1.874, $P = 0.076$, respectively).

ALT was negatively correlated with age (B = -0.317, $P = 0.000$), and positively with a personal history of dyslipidemia (B = 6.988, $P = 0.038$). For AST, ALT, and GGT levels positive associations were found with a family history of liver disease (B = 15.763, $P < 0.001$; B = 32.345, $P < 0.001$; and B = 24.415, $P < 0.001$, respectively).

Table 4 Correlation of the study population characteristics with AST, ALT, and GGT levels

Dependent variable	Independent variable	Coefficients		*P*
		B	Std. Error	
AST	Age	-0.125	0.039	0.002
	Family history of liver disease	15.763	4.029	0.000
	Smoking habit	-1.874	1.056	0.076
ALT	Age	-0.317	0.071	0.000
	Family history of liver disease	32.345	7.258	0.000
	Dyslipidemia	6.988	3.363	0.038
GGT	Family history of liver disease	24.415	5.791	0.000

DISCUSSION

In the general population, the estimated NAFLD prevalence ranges from 3% to 24%, with most estimates in the 6% to 14% range. NAFLD appears to be most strongly associated with obesity. It appears to be more common in men, and it increases with increasing age and after menopause. More advanced stages of NAFLD are associated with older age and higher body mass index[6]. In Ruhl *et al*[7] study, elevated ALT was associated with younger age corresponding to our study in which increasing ALT and AST tertiles were inversely related to age.

NAFLD is the major cause of elevation of ALT and it is in fact considered the hepatic manifestation of metabolic syndrome[8]. In a study of 10368 adults aged 20 years and over, participating in the Tehran Lipid and Glucose Study[9], the age-standardized prevalence of the metabolic syndrome was 33.7%.

Several studies have shown that variation in serum GGT in the population is associated with risk of death or development of cardiovascular disease, type 2 diabetes, stroke, or hypertension. Whitfield JB *et al*[2] estimated the relative importance of genetic and environmental sources of variation in GGT. There were highly significant correlations between GGT and body mass index, serum lipids, lipoproteins, glucose, insulin, and blood pressure. These correlations were more attributable to genes that affect both GGT and known cardiovascular risk factors than to environmental factors.

Nakanishi N *et al*[3] investigated the association between serum GGT and risk of metabolic syndrome and type 2 diabetes mellitus. The results of the article indicate that serum GGT may be an important predictor for developing metabolic syndrome and type 2 diabetes mellitus. Kim HC, *et al*[10] showed that the serum ALT and GGT levels were significantly associated with metabolic syndrome in men but not in women.

In the present study, correlation between family history of liver disease and increased liver enzymes may be attributable to genes that affect AST, ALT, and GGT and also known metabolic syndrome risk factors and environmental factors. Although we did not exclude other etiologies of hepatitis in families of blood donors, the association of family history of hepatitis with increasing AST, ALT, or GGT levels may show a genetic predisposition. As fatty liver is the most common cause of liver function test abnormality, further investigation is needed for genetic and dietary habits as predisposing factors for liver abnormality. Interaction of genetic and environmental factors might be the trigger of inflammatory cascades leading to metabolic syndrome. Rising liver enzymes activity may be the hepatic manifestation of ongoing inflammation and metabolic syndrome. The liver plays an important role in maintaining normal glucose concentration. It is also a major site of insulin clearance[11]. Type 2 diabetes mellitus is a public health problem of epidemic dimension and its prevalence is on the rise. Many risk factors, including the metabolic syndrome, have been implicated in its development[12].

There are controversies about normal ranges of liver enzymes in the general population. Furthermore, the level of elevation that is considered abnormal varies widely and has recently been brought into question. There is also a

debate as to whether or not different cutoffs are indicated for normal ranges of liver enzymes in men and women. Given all the controversy, it is clear that more acceptable and accurate means of noninvasive diagnostic approach to NAFLD as the most common cause of liver function test abnormality is needed. In addition, the use of higher cutoff values for normal ALT, AST, or GGT would lower the estimated prevalence of occult liver disease in the population.

Mohammadnejad M *et al*[13] showed that serum ALT activity was independently associated with body mass index and male gender, but not with age. The upper normal limit for non-overweight women (BMI of less than 25) was 34 U/L, and for non-overweight men 40 U/L. This article suggested that the normal range of ALT should be defined for male and female separately. Using this level of upper limit value for ALT activity, the authors of this paper may lose some men with NAFLD who need screenings. Our study corresponds with their data with respect to the association of liver enzymes and body mass index but we also noted liver enzyme correlation with age, body weight, and waist and hip circumferences.

Ruhl and Everhart[7] reviewed data from the third US National Health and Nutrition Examination Survey (1988-1994) in which adult participants underwent anthropometric measurements. Abnormal ALT was defined as ALT > 43 U/L for men or women. Serum ALT levels as a surrogate marker for NAFLD were elevated in 2.8% of the study population. Moreover, using recently suggested lower normal values for ALT (> 30 U/L for men and > 19 U/L for women), they found elevated levels in 12.4% of men and 13.9% of women. Clark JM and Diehl AM[1] in their editorial comment on Ruhl C *et al*[7] acknowledged that occult liver disease may be more common than previously suspected. They agreed that the association of ALT abnormalities with the metabolic syndrome supports the conclusion that the ALT elevations are due to NAFLD. The conditions associated with fatty liver disease presenting with normal liver enzymes and the mechanism involved in its development remain to be fully elucidated.

The hypothesis that fatty liver with normal liver enzymes occurs more frequently in arterial hypertensive patients was tested by Donati G *et al*[14] and they found that the condition is associated with insulin resistance. Essential hypertension is considered an insulin resistant state[15], and approximately 50% of patients with arterial hypertension are reported to be insulin resistant with hyperinsulinemia[16], a value much higher than that is found in the general population.

Our study population was consisted of healthy blood donors who are a better sample to indicate the burden of occult liver disease and NAFLD in the general population compared to the sampling from gastroenterology clinics or referred patients with metabolic syndrome. History of personal hypertension had no statistically significant association with increasing liver enzyme levels. It is noteworthy that hypertensive patients are not good candidates for blood donation and, because most of them have already been excluded from our study, interpretation of our findings in this regard is limited.

Our study has some limitations. The vast majority of our participants were male; and the volunteer blood donors are healthier than general population. In this study, all the biochemical and clinical variables predicting the presence of metabolic syndrome were not examined. We did not consider the racial, ethnicity, genetic and environmental sources of variation in AST, ALT, and GGT; amount of regular physical activity, eating habits, and biochemical characteristics of metabolic syndrome. We did not determine cutoffs of liver enzymes for estimation of non-alcoholic fatty liver disease, although NAFLD is reported even in normal range of liver enzymes. A better understanding of the factors that modulate liver disease progression is critical, so that we can target selected patients for more aggressive monitoring, lifestyle interventions, and pharmacotherapy.

In conclusion, variation within the normal ranges of AST, ALT, and GGT in healthy subjects is associated with some components of metabolic syndrome. In adult healthy men, those in the highest AST, ALT, and GGT levels, present with family history of liver disease; and those in the highest ALT levels, present with dyslipidemia. It is reasonable to recommend screening those with dyslipidemia that is also a risk factor for atherosclerosis and premature cardiovascular disease. Moreover, screening subjects with evidence of abdominal obesity and family history of liver disease is necessary.

The follow-up of these individuals would determine if certain amounts of AST, ALT, and GGT values might be considered as early predictors of subsequent fatty liver and the metabolic syndrome. In this way, the health-related outcomes of AST, ALT, and GGT values and the needed optimal frequency of their visiting would be determined. The health benefits of screening for fatty liver and other components of metabolic syndrome seems as necessary as performing tests for evidence of viral hepatitis B and C infections.

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