



Evaluation of Liver Enzyme Elevation and Its Contributing Factors in Birjand, Iran

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Abstract

Background and Objectives: Abnormal pattern of liver enzymes can provide valuable evidence for the diagnosis of a wide range of diseases. The aim of this study was to evaluate liver enzyme elevation and its contributing factors in Birjand, Iran.

Methods: This descriptive-analytic study was conducted on 5240 residents of Birjand city, Iran. Primarily, liver enzyme test was performed for all participants and then, the test was repeated for all individuals with liver enzyme elevation (i.e. an alanine transaminase of more than 40 IU/L) at the first measurement. After that, individuals with liver enzyme elevation at both measurements were subjected to blood testing for low-density lipoprotein, high-density lipoprotein, fasting blood sugar, hepatitis B surface antigen, hepatitis C virus antibody, and total bilirubin as well as ultrasound assessment for fatty liver disease. The SPSS software (v. 16.0) was employed for data analysis.

Results: Among 5240 individuals, 150 had liver enzyme elevation at both measurements. They aged 41.5 ± 13.1 on average and were mostly male (56.7%). The means of their serum alanine transaminase and aspartate transaminase were 65.4 ± 20.9 (IU/L) and 35.7 ± 15.1 (IU/L), respectively. The prevalence rates of hepatitis B surface antigen positivity, hepatitis C virus antibody positivity, and obesity were 14% (21 cases), 0.2% (4 cases), and 70% (100 cases), respectively. The mean of serum alanine transaminase was significantly higher among males, individuals with hepatitis B surface antigen positivity, and those with grade II and III fatty liver ($P = 0.01$). However, serum aspartate transaminase had no significant correlations with these factors.

Conclusions: Serum alanine transaminase elevation is significantly more common among males as well as individuals with fatty liver disease and hepatitis B. These findings suggest that all individuals with a serum alanine transaminase of more than 40 should be assessed for fatty liver disease and hepatitis B.

Keywords: Liver Enzymes, Birjand, Risk Factors

1. Background

The liver is the largest gland in the body. It is covered with a thick layer of connective tissue named Glisson's capsule. The liver cells have different functions in the body, including protein synthesis, metabolism control, detoxification, bile formation and secretion, and storage of some products (1). Liver enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), catalyze chemical reactions and contribute to the synthesis of essential and semi-essential amino acids in the body (2). ALT and AST are released from parenchymal liver cells (3, 4) and are among the most reliable indicators of serious liver disorders caused by the chronic injuries and the necrosis of the liver cells (5).

AST is found in the cells of the liver, heart, skeletal muscles, adrenal gland, and brain as well as leukocytes, and erythrocytes. When these cells are injured, AST enters the blood flow. For instance, serum AST level increases during myocardial infarction, acute liver diseases, muscle dystrophy, and kidney diseases. On the other hand, ALT is mainly found in the liver and enters the blood flow during the injuries to the liver cells. Thus, ALT is more specific than AST to the liver and liver disorders (2, 3, 5). AST/ALT ratio is also highly important in the diagnosis of liver diseases. For instance, in alcoholic liver disease, serum AST level increases more than ALT, while serum AST and ALT levels are less than 300 and 100, respectively. An AST/ALT ratio of less than 1 is observed in obesity, diabetes mellitus, hyperlipidemia,

and hepatitis, while a ratio of more than 2 is present in alcoholism, hyperthyroidism, hemochromatosis, and Wilson's disease. Most alcoholic patients have elevated liver enzyme levels, however, the elevation is not as high as that in acute viral hepatitis (6).

The causes of serum AST and ALT elevation are grouped into 4 main categories. The 1st is related to uncommon non-hepatic causes, which indirectly involve the liver, including hyperthyroidism, celiac disease, Crohn's disease, and ulcerative colitis. The 2nd includes common systemic causes, which directly affect the liver such as hemochromatosis, Wilson's disease, and antitrypsin deficiency. The 3rd category consists of hepatic causes such as viral hepatitis like hepatitis B and C, which are the main causes of chronic liver diseases (7) and the causes of many deaths each year (8, 9). The 4th category relates to drug-induced symptomatic or asymptomatic hepatitis caused by a wide range of drugs including non-steroid anti-inflammatory drugs (such as acetaminophen, ibuprofen, diclofenac sodium, and naproxen), anticonvulsants (such as carbamazepine and phenytoin), antibiotics (such as cotrimoxazole, isoniazid, sulphonamides, tetracycline, amoxiclav, and macrolides), antihyperlipidemic agents (such as statins), and tricyclic antidepressants (5).

The pattern of liver enzyme elevation provides useful evidence for the diagnosis of hepatic and non-hepatic disorders. Accordingly, severe elevation of serum AST and ALT is observed following the death of a large number of the liver cells, for instance viral hepatitis, while their moderate elevation is observed in conditions such as fatty liver disease (FLD), diabetes mellitus, alcoholism (10, 11), and drug consumption (12). A study showed that the main causes of liver enzyme elevation are drug-induced problems (34%), autoimmune disorders (22.73%), and nonalcoholic FLD (12.5%) (6).

Two studies in Iran showed that ALT elevation was associated with masculinity and high body mass index (BMI). The highest normal ALT value in these studies was set at 34 (IU/L) for non-obese individuals who had a BMI of less than 25 and 40 (IU/L) for obese individuals who had a BMI of more than 25 (13, 14). Another study showed that gender can significantly contribute to FLD and liver enzyme elevation (15). Genetic factors can also cause AST and ALT elevation in 33% - 66% of cases; therefore, AST elevation among black people is 15% more prevalent than white people (16). Given the wide differences among previous studies respecting the causes of liver enzyme elevation, this study was conducted to evaluate liver enzyme elevation and its contributing factors in Birjand, Iran.

2. Methods

This cross-sectional descriptive-analytical study was done in 2 phases on 5240 residents of Birjand city, Iran.

In the 1st phase, 262 clusters were randomly selected via the official software of the Birjand post office. Each cluster had a postal code and a certain address. Then, 2 males and 2 females were recruited from each of the 5 age groups in each cluster-10 males and 10 females in total. Age groups were 15 - 25, 25 - 35, 35 - 45, 45 - 55, and 55 - 65. The total number of individuals recruited from all 262 clusters was 5240. These individuals were informed about the study aim and were asked to complete the informed consent form of the study. Then, liver enzyme tests were performed for all of them.

In the 2nd phase, individuals with an ALT of more than 40 (IU/L) in the 1st phase were identified and liver enzyme tests were repeated for them if they did not suffer from any known liver disease or recent acute cardiac problems and had not received intramuscular injection in the past. These factors are known to elevate liver enzymes. Besides, they were assessed for the potential causes of ALT elevation such as diabetes mellitus, hyperlipidemia, viral hepatitis, and cardiovascular disease. Accordingly, a 5-milliliter blood sample was obtained from each of them and tested for liver enzymes, low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting blood sugar (FBS), hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb), and total bilirubin. Then, a demographic questionnaire was also filled out for those with an ALT level of more than 40 at both measurements. They were also referred to a radiologist for ultrasound assessment respecting FLD. Moreover, individuals with high blood glucose and lipid levels were referred to cardiologists for electrocardiography and echocardiography.

After data collection, the data were entered into the SPSS software (v. 16.0) and described using the measures of descriptive statistics. As the distributions of both AST and ALT were normal, the independent-sample t-test, the one-way analysis of variance, and the Tukey's post hoc test were conducted for data analysis at a significance level of less than 0.05.

This research project was formally approved by the ethics committee of Birjand University of Medical Sciences, Birjand, Iran (with the approval code of IR.BUMS.REC.1395.388).

3. Results

Among 5240 individuals recruited to the study, 150 (2.8%) had a high ALT of more than 40 (IU/L) in both measurements. The age mean of these 150 individuals was

41.5 ± 13.1 and 56.7% of them (85 cases) were male. The means of AST, ALT, and total bilirubin were 35.7 ± 15.1 (IU/L), 65.4 ± 20.9 (IU/L), and 0.67 ± 0.57 (mg/dL), respectively. Around 12% of them were HBsAg-positive, 2.7% were HCVAb-positive, 8.7% had a history of statin use, 12% suffered from diabetes mellitus, 63% had hyperlipidemia, 55% had hypercholesterolemia, 50.5% had hypertriglyceridemia, 42% had both hypercholesterolemia and hypertriglyceridemia, 27% had a BMI of more than 25, and 18% had no comorbid condition.

The prevalence rates of HBsAg positivity, HCVAb positivity, and obesity (i.e. a BMI of more than 25) were 14% (21 cases), 0.2% (4 cases), and 70% (100 cases), respectively.

In total, 129 individuals were referred to radiologists for ultrasound assessment respecting FLD. Around 52.7% of these individuals (i.e. 68 cases) had grade I fatty liver, 34.9% (45 cases) had grade II fatty liver, 9.3% (12 cases) had grade III fatty liver, and only 3.1% (4 cases) had no fatty liver.

The results of the independent-sample t-test and the one-way analysis of variance illustrated that serum ALT level had significant relationships with gender, HBsAg test result, and FLD affliction. In other words, serum ALT level was significantly higher among males, HBsAg-positive individuals, and those with grade II and III fatty liver compared respectively with females, HbSag-negative individuals, and those with no FLD affliction (P = 0.01). However, serum AST level had no significant relationships with gender, HBsAg test result, and FLD affliction (P > 0.05; Table 1).

4. Discussion

Among 5240 selected individuals, 150 had high serum ALT level in both measurements with a 6-month interval. The prevalence rates of grade I, II, and III fatty liver among participants were 52.7%, 34.9%, and 9.3%, respectively. AST had no significant relationships with age and gender. Similarly, ALT had no significant relationship with age. However, its relationship with gender was statistically significant so that male participants had a significantly higher serum ALT level than their female counterparts (93.1 ± 21.9 vs. 34.9 ± 15.1).

In an earlier study on 1939 Iranian blood donors, a significantly higher serum ALT level was observed among male donors and those with a high BMI; however, serum ALT level was not significantly correlated with age. The maximum normal ALT value in that study was set at 34 for females and 40 for males (13). A population-based study on 6823 individuals also reported that the prevalence rates of high serum AST, high serum ALT, and high serum AST-ALT were 8.9%, 4.9%, and 2.8%, respectively (17). Another population-based study in Iran on 5589 individuals revealed that 3.2% of them were HBsAg-positive, less than 1%

Table 1. The Serum Levels of Liver Enzymes According to Participants' Gender, HBsAg Test Results, and FLD Grade^a

Characteristics	Enzymes	
	ALT	AST
Gender		
Male (N = 85)	73.1 ± 21.9	34.9 ± 15.1
Female (N = 65)	58.3 ± 19.3	36.6 ± 15.3
P value	P = 0.01	P = 0.52
HBsAg test result		
Positive (N = 21)	79.7 ± 23.9	34.2 ± 16
Negative (N = 129)	54.7 ± 20.5	35.9 ± 15
P value	P = 0.01	P = 0.64
FLD grade		
Grade I (N = 68)	55.3 ± 17.9	36.1 ± 16.4
Grade II (N = 45)	65.2 ± 24.1	36.8 ± 18.1
Grade III (N = 12)	81.8 ± 12.2	28.2 ± 10.9
Normal (N = 4)	50.5 ± 5.4	30.5 ± 13
P value	P = 0.01 ^b	P = 0.33

^aValues are expressed as mean ± SD.

^bSerum ALT among individuals with grade II and III fatty liver was significantly higher than individuals with no fatty liver.

were HCVAb-positive, and 4% had a serum ALT of more than 40. Moreover, that study showed that the BMI of the individuals with serum ALT elevation was significantly more than those without serum ALT elevation (24.7 vs. 24.9 IU/L). Besides, the prevalence of high serum ALT among male individuals who aged 45 or less was significantly greater than their female counterparts (5.6% vs. 3.1%), while after the age of 45, there was no significant difference between males and females respecting serum ALT elevation (14). In addition, a descriptive-analytical study on 1864 individuals in the United States measured liver enzymes twice with a 170-day interval and reported that respectively, 3% and 0.5% of participants were HBsAg-positive and HCVAb-positive. Moreover, around 23% of individuals with high serum ALT had no risk factor (18). All these findings confirm that high serum ALT is more prevalent among males than females, particularly before their age menopause, probably due to the protective effects of female sex hormones against liver diseases as well as the higher release of ALT from muscle cells in males.

The findings of the present study also showed that although there was no significant relationship between serum AST and FLD, serum ALT among individuals with grade II and III fatty liver was significantly higher than those without FLD. This is in line with the findings of a

previous study, which reported that 33.7% of individuals with high serum ALT had fatty liver at the ultrasonography. Moreover, the prevalence of high serum ALT among people with and without FLD in that study was 23% and 3.4%, respectively (5). Another study on 835 patients with liver enzyme elevation and hepatitis seronegativity indicated that 45% of them had grade I or II fatty liver (19). A study based on ultrasound assessments estimated that the prevalence of FLD in Iran is 32.8% (20). Non-alcoholic FLD is characterized by the accumulation of fat in liver cytosols and can include a wide range of conditions from steatohepatitis to liver fibrosis, cirrhosis, and even liver cancer. Patients with FLD are 2 times more at risk for cardiovascular diseases than those without FLD (20). Therefore, given the significant relationship of high serum ALT with FLD, each individual with high serum ALT needs to undergo an ultrasound liver assessment for the early diagnosis of FLD.

Another finding of the present study was that HBsAg-positive individuals did not significantly differ from HBsAg-negative individuals respecting serum levels of glucose, lipids, and AST. However, their serum ALT was significantly higher than HBsAg-negative individuals (79.7 vs. 54.7). Besides, HCVAb positivity had no significant relationship with the serum levels of liver enzymes and triglycerides, while HCVAb-positive individuals had significantly higher levels of cholesterol and FBS compared to their HCVAb-negative counterparts. Similarly, an earlier study found that 13% - 33% (25%, on average) of patients with chronic hepatitis C also suffered from diabetes mellitus (21). Hepatitis C and B are known risk factors for diabetes mellitus, due to the fact that patients with liver diseases are more at risk for glucose intolerance. On the other hand, diabetes mellitus aggravates hepatitis prognosis, while both diabetes mellitus and hepatitis can increase the risk of FLD (22, 23). A study on 1230 Iranians showed that the prevalence rate of hepatitis in the general population was 7.6% and the prevalence rates of HBsAg positivity in the population and among diabetics were 12.5% and 12.3%, respectively (24). Hyperinsulinemia promotes the replication of hepatitis B and C viruses. Moreover, diabetes mellitus suppresses the immune system, increases serum levels of free fatty acids, and increases the incidence and the severity of steatosis, steatohepatitis, and liver fibrosis (25).

Our findings also showed no significant difference between individuals with high and normal serum ALT respecting FBS. However, the between-group difference was statistically significant in terms of serum cholesterol and triglyceride. These findings are in agreement with the findings reported by Zhou et al. (5).

We also found that a BMI of more than 25 was significantly associated with a higher prevalence of FLD, while

hypercholesterolemia and hyperglycemia had no significant relationships with FLD prevalence. The main reasons behind hepatocellular injury in FLD are elevated intracellular fatty acids, oxidative stress, and mitochondrial dysfunction. Another potential factor may be insulin-related disorders such as insulin resistance (25). In line with our findings, a study on 214 patients with FLD showed that 89% of them had a BMI of more than 25 (26). Similarly, a population-based study on 819 individuals indicated that FLD was significantly correlated with BMI, serum glucose, and serum triglyceride and had no significant correlation with serum cholesterol. The prevalence rates of high liver enzyme and grade I, II, and III fatty liver in that study were 8.8%, 21.5%, 16.4%, and 5.1%, respectively (27).

Around 18% of our participants had no risk factor for high serum ALT. Their high serum ALT can be attributed to their past use of medications, genetic factors, and racial characteristics. Similarly, a study on 149 asymptomatic individuals with serum ALT elevation showed that 20% of them were HCVAb-positive, 11% were alcoholic, 3% suffered from chronic hepatitis, and 2% had no significant risk factor (4). Another study on 100 blood donors with elevated liver enzymes also illustrated that 48% of them were alcoholic, 17% were HCVAb-positive, and 9% had no risk factor for liver enzyme elevation. That study also reported that a mild two-times elevation in serum ALT can be considered as non-problematic (5). Genetic factors were also reported in a study to significantly contribute to serum AST and ALT elevation in 33% - 66%. That study also found that serum AST among black people was 15% more than white people, confirming the effects of race on serum AST level (16).

We asked our participants about their used medications such as statins, antihypertensive agents, glucose-lowering agents, etc. However, most people in Iran do not consider some medications, such as acetaminophen, worthy of noting in their drug history. Due to their wide over-the-counter use, these medications may significantly contribute to liver enzyme elevation. Further studies into the relationships of over-the-counter use of such medications are needed to determine their effects on liver enzymes.

4.1. Conclusion

This study showed that the prevalence of high liver enzyme among a 5240 population-based sample is 3%. Serum ALT elevation is significantly more common among males as well as among individuals with FLD and hepatitis B. The findings of the present study suggest that all individuals with an ALT of more than 40 should be assessed for hepatitis B and FLD.

4.2. Limitations

In this study, we could neither take a comprehensive drug history nor were able to assess blood levels of drugs among individuals with high serum levels of liver enzymes.

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