

## Causes of Persistently Elevated Alanine Aminotransferase Levels in Patients who Presented to Two Referral Hospitals in Mashhad, Iran during 2011

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### ABSTRACT

#### BACKGROUND

Worldwide, chronic liver disease is a major cause of morbidity and mortality. Causes of elevated serum alanine aminotransferase (ALT) levels vary depending on the population under study. The aim of this study is to evaluate the frequency and causes of persistently elevated ALT levels in patients of the Gastroenterology (GI) Clinics in Ghaem and Emam Reza Hospitals in Mashhad, Iran.

#### METHODS

A total of 100 consecutive patients with persistently elevated ALT levels that referred to the GI Clinics at Ghaem and Emam Reza Hospitals in 2011 were studied. Elevated levels were defined as ALT  $\geq 40$  U/L at least twice within six months. A comprehensive history that included previous surgeries, transfusion, alcohol consumption and medications was obtained. Patients underwent physical examinations, laboratory analyses and ultrasonography studies. When necessary, liver biopsies were performed.

#### RESULTS

Patients' mean age was  $44.4 \pm 11.83$  years. Females comprised 62% of cases. Patients presented with the following conditions: non-alcoholic fatty liver disease (NAFLD, 55%), hepatitis B (17%), autoimmune hepatitis (13%), hepatitis C (4%), autoimmune hepatitis and hepatitis C (2%), overlapping autoimmune disease (2%), Wilson disease (1%), celiac disease (1%), alcoholic hepatitis (1%), primary biliary cirrhosis (PBC, 1%), primary sclerosing cholangitis (PSC, 1%), and cryptogenic (2%).

#### CONCLUSION

NAFLD was the most common cause of persistently elevated serum ALT levels in this study.

#### KEYWORDS

Alanine aminotransferase; Non-alcoholic fatty liver disease; Viral hepatitis; Chronic liver disease; Iran

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## INTRODUCTION

Worldwide, chronic liver diseases are among the common causes of morbidity and mortality in adults over the age of 15.<sup>1</sup> They are characterized by a long pre-clinical course and may take more than two decades to develop to cirrhosis. Early detection of liver diseases, appropriate treatment and life style modification may cause regression in liver fibrosis.<sup>2</sup> Serum alanine aminotransferase (ALT) is an enzyme that transfers an amino group from alanine to ketoglutarate and catalyzes the formation of acid pyruvic and glutamate. It is a sensitive marker for hepatocellular damage and the most common marker used to assess hepatocellular injury.<sup>3-6</sup> This study assesses the causes for elevated ALT levels in 100 consecutive patients who presented to clinics in two hospitals in Northeastern Iran.

## MATERIALS AND METHODS

This is a one year cross-sectional study on 100 consecutive patients over the age of 14 years that referred to the Gastroenterology (GI) Clinics of Ghaem and Imam Reza Hospitals at Mashhad University of Medical Sciences. All patients whose ALT levels were above normal ( $\geq 40$  U/L), at least twice, during at least six months were enrolled. A full history that included demographics, history of alcohol consumption (amount and duration), history of drug use particularly over the previous three months prior to study entry, transfusion of blood products, tattoos, suspected sexual activity, jaundice, traveling, surgery, and any dental procedures, previous history of liver disease, diabetes, hyperlipidemia, thyroid disease, and family history of liver diseases were recorded for all patients. A complete physical examination and measurement of height and weight were performed. Body mass index (BMI) was calculated by dividing the patient's weight (kg) by height ( $m^2$ ) and classified according to the National Institute of Heart, Lung and Blood in the United States of America as follows:  $<18.5$  kg/ $m^2$  (underweight),  $18.5-24.9$  kg/ $m^2$  (normal weight),  $25-29.9$  kg/ $m^2$  (overweight) and  $\geq 30$  kg/ $m^2$  (obese).

Initial lab tests included fasting blood sugar (FBS), partial thrombin time (PTT), prothrombin time-international normalized ratio [PT (INR)], CBC (diff), cholesterol [low density lipoprotein (LDL) and high density lipoprotein (HDL), triglycerides], markers of viral hepatitis C and B (HBsAg, anti-HBc, anti-HCV) and liver ultrasound. Tests for other liver diseases were performed when necessary and included the following: autoimmune hepatitis [anti-nuclear antibody (ANA), smooth muscle antibody (SMA), serum protein electrophoresis, anti-liver kidney mitochondrial antibody (anti-LKM)]; primary biliary cirrhosis (PBC) [anti-mitochondrial antibody (AMA)]; hemochromatosis (serum iron, total iron binding capacity, iron saturation, ferritin); Wilson in patients  $<40$  years of age (serum ceruloplasmin, 24-hour urine copper); and  $\alpha 1$ -antitrypsin deficiency [serum protein electrophoresis (phenotype)].

Causes for non-hepatic increases in ALT levels such as celiac disease [anti-tissue transglutaminase antibody or anti-tTG (IgA)] were assessed. When positive, a biopsy of the second part of the duodenum was performed. Thyroid disorders (TSH) and muscle diseases (creatinase) were also analyzed.

If necessary, according to the results of the initial tests, additional studies were requested. In cases of positive HBsAg, patients were also tested for HBeAg, anti-HBe, and HBV-DNA. For cases of positive HCV-RNA, anti-HCV and HCV genotype analyses were performed.

NAFLD was diagnosed based on ultrasound findings of fatty liver, evidence of metabolic syndrome and/or diabetes, and dyslipidemia if other studies were negative. Liver biopsy and histopathologic examination of liver tissue required for definitive diagnosis was performed on 12 patients after obtaining their consent. In the other cases, diagnosis was based according to patient history, physical examination and clinical laboratory analyses. For increased accuracy all tests were conducted in one laboratory affiliated with the School of Medicine with the use of one kit. Ultrasonography was performed by a skilled sonographer and histological slides were reviewed by one pathologist.

## RESULTS

Of the 100 participants, there were 38 males and 62 females. Mean age of patients was  $44.4 \pm 11.83$  years. NAFLD was the cause of persistent ALT elevation in 52% of patients. Hepatitis B and autoimmune hepatitis were the second and third causes, respectively. Other causes for elevated ALT levels are shown in Figure 1.

Tables 1-3 show demographic characteristics, laboratory analyses and BMI of the study patients.

There were 42.1% of female patients and 58.1% of male patients who had NAFLD. The chi square test showed a significant relationship between causes of ALT elevation and gender ( $p < 0.001$ ).

NAFLD was present in 62.2% of patients less than 40 years of age, in 44.8% of patients between the ages of 40–60 years and in 60% of patients over the age of 60 years. The chi square test showed no significant difference between age groups ( $p = 0.890$ ).

NAFLD was found in 71.4% of patients whose BMI was over 30, 69.7% of those whose BMI ranged from 25–29.9, and in 24.3% of patients with BMI of 18.5–24.9. None of the patients with BMI  $< 18.5$  had NAFLD.

## DISCUSSION

This study determined that NAFLD was the leading cause for persistently elevated ALT levels in our patients. Several studies reported an association with fatty liver and increased serum ALT levels, even within the normal range.<sup>3,4,7</sup> Jamali et al. reported persistently increased serum ALT levels in 43.5% (64 out of 147) of participants. In their study, elevated serum ALT levels were detected in 9.3% of patients with hepatitis B, 6.2% who had hepatitis C, and in 4.6% of patients with alcoholic hepatitis.<sup>8</sup> In a study by Pourshams, NAFLD was the most common cause for the persistent increase in serum ALT levels among blood donors in Tehran.<sup>9</sup> Clark et al. found that aminotransferase elevation was more frequent in males (9.3%) compared to females (6.6%). Excessive alcohol consumption,

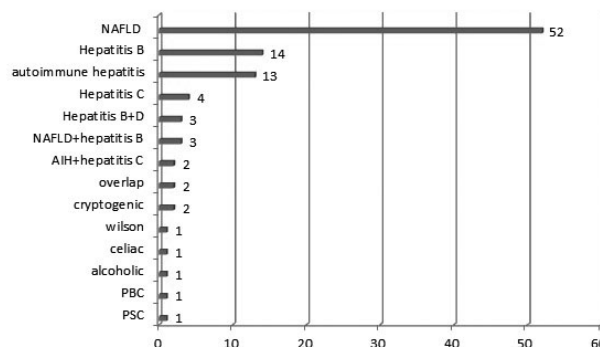


Fig. 1: Frequency (%) of causes for elevated ALT levels in Mashhad, Iran.

\*\*For figure one, please capitalize the following: autoimmune; overlap; cryptogenic; Wilson; celiac; alcoholic. Please define "PBC; PSC and AIH".

hepatitis B, C and transferrin saturation above 31% were the causes for elevated ALT levels. However the cause for increased ALT was not detected in 69% of cases. There were significantly higher ALT levels in males and females with increased BMI, increased triglycerides and fasting insulin, and lower HDL, particularly in females with type II diabetes and hypertension. A recent study showed that the most common cause of cryptogenic cirrhosis was NAFLD.<sup>10</sup> In a study conducted by Zhang et al. the most important risk factor for increased ALT was non-alcoholic fatty liver disease (NAFLD) (10.79%), followed by metabolic syndrome (16.25%) or both (20.31%). NAFLD was more frequent in females with increased age and BMI, fasting plasma glucose, triglycerides, and LDL levels, as well as lower HDL levels. Elevated ALT levels were more common in individuals from a low socioeconomic level and in males with increased triglyceride levels, with higher BMI and metabolic syndrome.<sup>11</sup> In another study, Chen et al. observed that 11.4% of the study population had increased ALT levels. Possible reasons for this increase included excessive alcohol consumption (0.8%), hepatitis B virus (HBV) (28.5%), hepatitis C virus (HCV) (13.2%), HCV and HBV (2.2%), NAFLD (33.6%), and unknown etiology (21.8%). Although etiologically the ALT increase was similar in both sexes, more males (17.3%) had evidence of increased ALT levels than females (6.1%). The preva-

**Table 1:** Frequencies for causes of persistent elevations in ALT levels according to gender.

Etiology	Gender				p-value
	Female		Male		
	Number	Percent	Number	Percent	
(Non Alcoholic Fatty Liver Disease) NAFLD	16	42.1	36	58.1	
NAFLD+ Hepatitis B	0	0	3	4.8	
Hepatitis B	1	2.6	13	21	
Hepatitis B+D	0	0	3	4.8	
Hepatitis C	2	5.3	2	3.2	
Autoimmune Hepatitis (AIH)	12	31.6	1	1.6	
AIH+ Hepatitis C	0	0	2	3.2	
Overlap	2	5.3	0	0	< 0.001
Wilson	1	2.6	0	0	
Celiac	0	0	1	1.6	
Alcoholic	0	0	1	1.6	
Primary biliary cirrhosis	1	2.6	0	0	
Primary sclerosing cholangitis	1	2.6	0	0	
Cryptogenic	2	5.3	0	0	
Total	38	100	62	100	

**Table2:** Causes of ALT elevation according to age groups.

Etiology	Age groups						p-value
	<40 years		40-60 years		>60 years		
	Number	Percent	Number	Percent	Number	Percent	
NAFLD	23	62.2	26	44.8	3	60	
NAFLD+ Hepatitis B	1	2.7	2	3.7	0	0	
Hepatitis B	5	13.5	8	13.8	1	20	
Hepatitis B+D	0	0	3	5.2	0	0	
Hepatitis C	0	0	4	6.9	0	0	
Autoimmune hepatitis	6	12.6	6	10.3	1	20	
AIH+ Hepatitis C	0	0	2	3.4	0	0	
Overlap	0	0	2	3.4	0	0	0.890
Wilson	1	2.7	0	0	0	0	
Celiac	0	0	1	1.7	0	0	
Alcoholic	0	0	1	1.7	0	0	
PBC	0	0	1	1.7	0	0	
PSC	0	0	1	1.7	0	0	
Cryptogenic	1	2.7	1	1.7	0	0	
Total	37	100	58	100	5	100	

lence of higher ALT levels in NAFLD patients was 18.1% with a positive predictive value of 33.6. The study reported NAFLD as the most common cause for increased ALT levels in Taiwan and was associ-

ated with numerous metabolic disorders.<sup>12</sup>

The results of our study showed that NAFLD, hepatitis B and autoimmune hepatitis were the most common causes for persistently elevated ALT levels.

**Table3:** Frequencies of causes of ALT elevation according to body mass index (BMI).

Etiology	BMI							
	<18.5		18.5-24.9		25-29.9		>30	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
NAFLD	0	0	9	24.3	23	69.7	20	71.4
NAFLD+ Hepatitis B	0	0	1	2.7	0	0	2	7.1
Hepatitis B	0	0	9	24.3	4	12.1	1	3.6
Hepatitis B+D	0	0	3	8.1	0	0	0	0
Hepatitis C	0	0	2	5.4	1	3	1	3.6
Autoimmune Hepatitis	0	0	6	16.2	3	9.1	4	14.3
AIH+ Hepatitis C	0	0	2	5.4	0	0	0	0
Overlap	1	50	0	0	1	3	0	0
Wilson	0	0	1	2.7	0	0	0	0
Celiac	0	0	1	2.7	0	0	0	0
Alcoholic	0	0	1	2.7	0	0	0	0
PBC	0	0	1	2.7	0	0	0	0
PSC	0	0	0	0	1	3	0	0
Cryptogenic	1	50	1	2.7	0	0	0	0
Total	2	100	37	100	33	100	28	100

#### CONFLICT OF INTEREST

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

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