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RAPID COMMUNICATION

Persistent alanine aminotransferase elevation among the general Iranian population: Prevalence and causes

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Abstract

AIM: To determine the prevalence and causes of persistently elevated alanine aminotransferase (ALT) levels among the general population in northern Iran.

METHODS: A total of 2292 (1376 female, aged 18-75 year), were selected by systematic clustered random sampling from the cities and villages of Gonbad and Kalaleh in Golestan Province and invited to participate in the study. A comprehensive history regarding alcohol drinking and medication was taken. Body mass index (BMI), viral markers and ALT levels were measured. If ALT level was ⩾ 40 U/L, it was rechecked twice within 6 mo. Those with ⩾ 2 times elevation of ALT were considered as having persistently elevated ALT level. Non-alcoholic fatty liver disease (NAFLD) was diagnosed based on evidence of fatty liver upon sonography and excluding other etiology.

RESULTS: A total of 2049 (1351 female) patients participated in the study, 162 (7.9%) had elevated ALT level at the first measurement. Persistently elevated ALT level was detected in 64 (3.1%) participants, with 51 (79.6%) with no obvious etiology, six (9.3%) with Hepatitis B, four (6.2%) with Hepatitis C virus (HCV) infection and three (4.6%) with alcoholic hepatitis. The prevalence of NAFLD and alcoholic hepatitis was 2.04% (42 patients) and 0.1% (three), respectively. There was correlation between NAFLD and male gender, overweight, diabetes and living in an urban area [odds ratio = 3.03 (95% CI: 1.6-5.72), 4.21 (95% CI: 1.83-9.68), 2.86 (95% CI: 1.05-7.79) and 2.04 (95% CI: 1.00-4.16) respectively].

CONCLUSION: NAFLD is the most common cause of persistently elevated serum ALT level among the general population of Iran.

Key words: Alanine aminotransferase; Iran; Non-alcoholic fatty liver disease; Viral hepatitis

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INTRODUCTION

End-stage liver disease is among the top ten common causes of morbidity and mortality in adults older than 15 years, worldwide[1]. The World Health Organization (WHO) estimates that in 2002, cirrhosis caused 382 000 deaths worldwide[1]. According to the 2002 mortality report of the Ministry of Health of Iran, chronic liver diseases accounted for 1% of mortality of inhabitants aged > 15 years across the whole country[2]. Liver cirrhosis was the third and first leading cause of mortality and

hospitalization, respectively, in an Iranian gastrointestinal and hepatology ward[3]. Recognition of the relative contribution of various etiologies to a disease burden is important for setting public health priorities and prevention guidelines. Iran, a Middle East developing country, has an average prevalence of Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection, 3%-5% and 0.5% respectively[4-9]. HBV has been reported as the most common cause of chronic liver disease in the last decade in Iran[10,11]. The etiology of chronic liver disease changes by health concerns, national prevention programs, and people's lifestyle. The prevalence of HBV infection among healthy Iranian blood donors has declined; this may be due to better donor selection programs and an increasing number of repeat donors[12]. Rapidly increasing metabolic syndrome manifestations, including non-alcoholic fatty liver disease (NAFLD), are reported in Iran[13]. Information regarding the causes of chronic liver disease in the general population is rare in Middle-east countries. Alanine aminotransferase (ALT) is a sensitive indicator of liver cell injury and has been used to identify patients with liver disease for almost 50 years[14]. Currently, determination of serum ALT level constitutes the most frequently applied test for the identification of patients suffering from liver disease. The aim of this study was to determine the causes of chronic liver disease in the general population in Iran, using ALT as a surrogate marker of liver disease.

MATERIALS AND METHODS

Our study was carried out according to the ethical standards for human experimentation and was approved by the ethics committee of the Digestive Disease Research Center, Tehran University of Medical Sciences. After explaining the aim of the study and the possible need for further blood tests and follow up, written informed consent was obtained.

Subjects

Golestan province is located in North East Iran and has 1 614 376 inhabitants. Gonbad and Kalaleh are located in the North east of Golestan province. Gonbad has a population of 43 960, Kalaleh has a population of 154 349. In 2006, a total of 2292 (1376 females) 18-79 year old inhabitants of the villages and cities of Gonbad and Kalaleh were selected by systematic clustering random sampling, according to the data from family registry in health care centers, and were invited to take part in this study. Among the invited subjects, 698 of 916 males and 1351 of 1376 females participated in the study (participation rate: 76.2% and 98.1% for men and women, respectively). General parameters including age, gender, weight, height, drug history, especially during the past 3 mo, alcohol consumption (the number and type of drinks per day), hypertension and diabetes mellitus were ascertained and recorded by a trained general physician. An alcohol drinker was defined as a subject with an alcohol intake of > 20 g/d. Diabetes mellitus and hypertension were diagnosed according to previous diagnosis of these diseases by a physician or the use of drugs to control them. BMI of 25-30 kg/m^2 is defined as overweight and BMI $\geqslant$ 30 kg/m^2 is obese[15]. Morning serum was obtained for measuring ALT and detection of Hepatitis B surface antigen (HBsAg) and HCV antibody (HCV Ab). HCV Ab was detected using ELISA. HCV recombinant immunoblot assay Ⅲ was carried out on positive samples of HCV by ELISA. Those with a positive test result were considered positive for anti-HCV and exposed to HCV.

The normal range for the kit, as recommended by the manufacturer, for serum ALT level was 0-40 U/L. ALT levels $\geqslant$ 40 U/L were considered elevated. In step 2 of the study, all participants with serum ALT level $\geqslant$ 40 U/L in the first blood sampling were invited again and reassessed for alcohol consumption and medication. In step 3 of the study, participants with elevated serum ALT in the second step were considered as having persistently elevated serum ALT level, and were excluded. Those with normal ALT value in the second step were checked again in 3 mo, and if elevated, were considered to have persistently elevated serum ALT. Participants with persistently elevated ALT levels were examined by liver sonography to detect fatty liver. Participants with persistently elevated ALT levels and a negative test result for viral Hepatitis B and C, non-alcohol drinkers, and a negative history of medication intake, along with evidence of fatty infiltration of the liver upon sonography, were presumed to have NAFLD.

Laboratory assessments

Serum was tested for ALT level using Hitachi autoanalyser 704 (Roche, Switzerland) with Pars Azmoon reagents kit (Tehran, Iran). HBsAg was measured by Enzygnost HBs Ag 5.0 kit (Dade Behring, Germany). HCV Ab was checked by ELISA using the Anti-HCV-EIA-Avicenna kit (Moscow, Russia), and confirmed with recombinant immunoblot assay Ⅲ using INNOLIA™ HCV-Score kit (Innogenetics, Ghent, Belgium). All sonography was carried out by an expert sonographer using a 3.5-MHz probe (Logiq 200 PRO, Tokyo, Japan). Fatty infiltration of the liver was graded from 1 to 3, based on the echogenicity of the liver. In grade 1, echogenicity was slightly increased, with normal visualization of the diaphragm and the intrahepatic vessel borders. In grade 2, echogenicity was moderately increased, with slightly impaired visualization of the diaphragm or intrahepatic vessels. In grade 3, echogenicity was markedly increased, with poor or no visualization of the diaphragm, intrahepatic vessels, and posterior portion of the right lobe. Liver size was also assessed. If the liver was > 15 cm in length in the mid-clavicular line in the sagittal view, a diagnosis of hepatomegaly was made[16].

Statistical analysis

Statistical analysis was performed using SPSS, version 10.1 (SPSS, Chicago, IL, USA). Continuous variables were analyzed with the *t* test and categorical variables with χ^2. $P < 0.05$ was considered statistically significant. Logistic regression analysis (multivariate analysis) was performed to identify factors independently associated with NAFLD.

RESULTS

A total of 2049 participants (1351 females and 1073

Table 1 Relative frequency of the participants according to demographic characteristics, laboratory test results, BMI and gender *n* (%)

Characteristic	Male (698)	Female (1351)	*P* -value	Total (2049)
Mean age ± SD (yr)	43.91 ± 15.52	38.88 ± 13.94	0.000	40.59 ± 14.69
Mean BMI ± SD (kg/m^2)	25.02 ± 4.29	26.70 ± 5.34	0.000	26.13 ± 5.07
Median BMI (kg/m^2)	24.91	25.94		25.56
BMI (kg/m^2)				
< 18.5	40 (5.9)	43 (3.3)		83 (4.2)
18.5-24.9	308 (45.3)	509 (38.8)		817 (41)
25-29.9	240 (35.3)	418 (31.8)		650 (33)
30-34.9	82 (12.1)	248 (18.9)		330 (16.6)
35-39.9	9 (1.3)	73 (5.6)		82 (4.1)
⩾ 40	1 (0.1)	22 (1.7)		23 (1.2)
Mean ALT ± SD (U/L)	24.01 ± 15.67	19.38 ± 12.56	0.000	20.96 ± 13.87
HBsAg positive	38 (5.4)	64 (4.7)	0.340	102 (5)
HCV Ab positive	8 (1.1)	12 (0.8)	0.360	20 (1)
Diabetes mellitus	28 (4)	59 (4.3)	0.400	87 (4.2)
Hypertension	64 (9.1)	155 (11.4)	0.060	219 (10.6)

Table 2 Demographic characteristics, laboratory test results, and sonography findings of presumed non-alcoholic steatohepatitis subjects *n* (%)

Characteristics	Male (24)	Female (18)	Total (42)
Mean age ± SD (yr)	41.04 ± 12.32	44.33 ± 9.12	42.45 ± 11.06
Mean BMI ± SD (kg/m^2)	29.65 ± 4.07	31.62 ± 7.41	30.47 ± 5.7
BMI (kg/m^2)			
< 18.5	0 (0)	0 (0)	0 (0)
18.5-24.9	3 (12.5)	4 (23.5)	7 (17.1)
25-29.9	9 (37.5)	3 (17.6)	12 (29.3)
30-34.9	9 (37.5)	5 (29.4)	14 (34.1)
35-39.9	3 (12.5)	2 (11.8)	5 (12.2)
⩾ 40	0 (0)	3 (17.6)	3 (7.3)
First mean ALT ± SD (U/L)	62.58 ± 21.51	61.11 ± 24.20	61.95 ± 22.42
Second mean ALT ± SD (U/L)	51.42 ± 15.16	45.18 ± 12.28	48.83 ± 14.22
Third mean ALT ± SD (U/L)	62.50 ± 20.46	54.00 ± 27.99	56.83 ± 25.10
Liver texture at sonography			
Grade 1	17 (70.8)	11 (61.1)	28 (66.7)
Grade 2	7 (29.2)	7 (38.9)	14 (33.3)
Grade 3	0 (0)	0 (0)	0 (0)
Liver span > 15 cm in sonography	0 (0)	0 (0)	0 (0)
Diabetes mellitus	1 (4.1)	4 (22)	5 (11.9)
Hypertension	1 (4.1)	2 (11)	3 (7.1)

urban) were included in the study. Relative frequency of the participants according to demographic characteristics, laboratory tests, BMI and sex is shown in Table 1.

A total of 162 participants (7.9%) had elevated serum ALT level at the first measurement. Among the 147 of 162 participants who were invited for further evaluation, 64 were considered to have persistently elevated ALT level. In this group 51 (79.6%) had no obvious etiology, six (9.3%) had Hepatitis B, four (6.2%) had Hepatitis C, and three (4.6%) had alcoholic hepatitis. Drug history was unremarkable. Liver sonography was performed for 51 participants with persistently elevated ALT level with no obvious cause, in which 42 (2.04%) showed fatty liver and were presumed to have NAFLD. Demographic characteristics, laboratory test results, and sonography findings in participants with persistently elevated ALT level and fatty liver are shown in Table 2.

The mean BMI of NAFLD participants was 30.47 ± 5.07 kg/m^2 compared with 26.04 ± 5.02 kg/m^2 of those without NAFLD (P = 0.001). In participants with NAFLD, there were 34 who were overweight and obese, and seven who were normal weight (P = 0.001). In this study, 34/1095 (3.1%) of the overweight and 22/435 (5%) of the obese participants had NAFLD.

The mean BMI in urban participants (26.52 ± 5.32 kg/m^2) was greater than that in their rural counterparts (25.69 ± 4.74 kg/m^2) (P = 0.035). The prevalence of overweight and obese participants was greater in urban (626) than rural (469) participants (P = 0.001). NAFLD was more common in urban (31) than rural (11) participants, and also in men (24) than in women (18) (P = 0.005 and 0.001, respectively). There was a correlation between NAFLD and male gender, overweight and obese, diabetes and living in an urban area [odds ratio = 3.03 (95% CI: 1.6-5.72), 4.21 (95% CI: 1.83-9.68), 2.86 (95% CI: 1.05-7.79) and 2.04 (95% CI: 1.00-4.16), respectively].

DISCUSSION

The prevalence of once-only elevated ALT levels, after excluding individuals with viral hepatitis, alcohol and drug etiology, was 2.1%, which was nearly half of the previously reported prevalence of 5.7% in healthy blood donors in Iran[7]. This may have been due to the greater prevalence of overweight and obese participants and male predominance (70.9% and 74.7%, respectively) in the previous study compared with the present study (54.8% and 34%, respectively). It has already been shown that serum ALT level is associated with male gender and obesity[17-19]. This value is near the prevalence reported in the Third National Health and Nutrition study in the United States (2.8%)[18].

The prevalence of persistently elevated serum ALT levels (3.1%) in our study is comparable with that in previous studies from Western countries and the study of healthy blood donors in Iran[7,20]. The prevalence of HBsAg positivity was 5% in the present study, which is comparable to previous studies in the general population of Hamadan (2.49%), Nahavand (2.3%) and Golestan (9.7%)[4-6]. There are no published data about HCV prevalence in the general population in Iran for comparison. According to previous studies performed in healthy blood donors in Tehran, the prevalence of HBsAg positivity has declined sharply during the past 20 years, which is mainly due to better donor selection and an increasing number of repeat donors[12].

NAFLD is a diagnosis of exclusion when clinical and laboratory examination fail to reveal a cause of liver disease. It is suggested when an imaging study shows fatty liver. Liver sonography is non-invasive, safe, widely available and highly sensitive for the detection of fatty liver. In one study that compared the sensitivity of MRI, CT and liver sonography to detect fatty liver, sonography and CT had sensitivity of 100% and 93%, respectively, in detecting fatty changes that involved > 33% of the liver, with a positive predictive value of 62% and 76%, respectively[21]. We did not perform liver biopsy for diagnosis of NAFLD, and we used criteria similar to those

of previous epidemiological studies of NAFLD[18,22]. Large epidemiological studies on the prevalence of NAFLD in the general population are lacking, but prevalence of 2.8%-24% has been reported[18,23,24]. In the present study, the prevalence of NAFLD was 2.04%, which is comparable to that reported previously in healthy blood donors (2.35%) and autopsies (2.1%) in Iran[7,25]. Although the participation rate in men was less than in women, mainly due to work constraints in men, NAFLD was three times more prevalent in men, which accords with previous studies in Asia, including the study of healthy blood donors in Iran[7,26,27]. Previously, it was thought NAFLD is more prevalent in women, but recent data suggest there is no significant difference between the sexes. Women are overrepresented in studies of NAFLD, but it is unclear if gender is an independent risk factor for the disease[22]. The frequency of overweight (54.9%) and obesity (21.9%) in the present study was close to the frequencies reported previously in northern Iran, which showed 62.2% were overweight and 28% were obese[28]. The frequency of NAFLD reaches 80% in obese persons; NASH is reported in 9%-30% of obese adults[29,30]. In the present study, 34/1095 (3.1%) overweight and 22/435 (5%) obese participants had NAFLD. There is a correlation between BMI and steatosis in several studies[22]. We showed that overweight and obesity were associated with a 4.21-fold increased risk in NAFLD participants, and mean BMI was also greater in NAFLD than non-NAFLD participants.

This study showed that living in an urban area is associated with a 2.04-fold increase in NAFLD, and this may be due to daily physical activity, lifestyle and greater prevalence of overweight and obesity in urban participants. NAFLD is associated with type 2 diabetes mellitus and glucose intolerance with or without superimposed obesity. Type 2 diabetes has been described in 20%-75% of NAFLD patients, and may increase the risk of NAFLD more than two-fold compared with that in non-diabetics. In the present study, prevalence of diabetes was 11.9% in NAFLD, and diabetes was associated with a 2.86-fold increase in NAFLD compared with non-diabetics[30]. NAFLD is now recognized as the hepatic manifestation of the metabolic syndrome, which includes hyperlipidemia, hypertension, glucose intolerance and obesity. The risk and severity of NAFLD increase with the number of components of the metabolic syndrome[31]. According to previous studies in the general population of Iran, metabolic syndrome has a prevalence of 33%, which is more common than the rate of 22% reported by the Third National Health and Nutrition Examination Survey for the USA[13,32]. We did not test for uncommon liver diseases such as Wilson's disease, α1-antitrypsin deficiency, primary biliary cirrhosis and primary sclerosing cholangitis, which can also be responsible for elevated ALT levels; as they are too infrequent to have had a major impact on our results. There are two studies that show that self-reported use of alcohol and opium are reliable and valid in this population[27,33].

NAFLD was the most common cause of persistently elevated serum ALT levels in our study. The importance of NAFLD and ALT elevation is their impact on mortality as a component of the metabolic syndrome. NAFLD is not a western disease, and is the most frequent cause of persistently elevated serum ALT level in the Asia-Pacific region[26]. Identifying its risk factors and therapeutic strategies to control this public health problem seems reasonable.

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COMMENTS

Background

End-stage liver disease is among the top ten common causes of mortality in adults worldwide. Recognition of the risk factors for chronic liver disease is important for establishing prevention guidelines.

Research frontiers

Non-alcoholic fatty liver disease (NAFLD) has been recognized as the main cause of chronic liver injury in both western and developing countries.

Innovations and breakthroughs

Prevalence of NAFLD in Iranian populations is comparable to that in western countries. Obesity and other manifestations of the metabolic syndrome, in addition to urban lifestyle, are the main risk factors for NAFLD.

Applications

National planning to increase knowledge regarding NAFLD and control of its risk factors are recommended.

Terminology

NAFLD is the hepatic manifestation of the metabolic syndrome that includes insulin resistance, obesity, hyperlipidemia and hypertension. NAFLD is recognized by fat infiltration of hepatocytes and inflammatory reaction in the liver.

Peer review

This is a good and interesting study. It is a very descriptive report about persistently elevated ALT levels in the Iranian population. The authors screened almost 3200 patients in a north eastern part of Iran for elevated ALT.

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