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Elevated alanine aminotransferase activity is not associated with dyslipidemias, but related to insulin resistance and higher disease grades in non-diabetic non-alcoholic fatty liver disease

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ABSTRACT

Objective: To explore demographic and metabolic factors associated with increased alanine aminotransferase (ALT) activity in non-diabetic non-alcoholic fatty liver disease (NAFLD) patients. **Methods:** Overall 372 patients who consecutively attended to Gastroenterology Clinic of Baqiyatallah University of Medical Sciences, Tehran, Iran awere diagnosed as NAFLD entered into analysis. Exclusion criteria were having diabetes mellitus and fasting blood glucose over 126 mg/dL, active hepatitis B virus infection, having hepatitis C virus positive serology, and to be under corticosteroid therapy. ALT levels were considered pathologically high when it was over 30 IU/L for men and over 19 IU/L for women. **Results:** Bivariate analyses using *t* test and *chi*-square test showed that patients with pathologically augmented ALT levels had significantly higher NAFLD grades in their ultrasonographic evaluations (P=0.003). Moreover, these patients represented significantly higher homeostatic model assessment levels (P=0.003), levels of serum insulin (P=0.002), fasting blood glucose (P<0.001), and uric acid (P=0.02). The prevalence of insulin resistance was also higher in patients with increased serum ALT concentrations. Multifactorial logistic regression models showed that ultrasonographic grading of NAFLD (P=0.027) and insulin resistance (P=0.013) were the only variables significantly associated with abnormal ALT levels. **Conclusions:** This study shows that the associations of increased ALT serum levels in NAFLD patients are different from what are supposed before. By excluding diabetic patients from our population, we find that increased ALT levels are not associated with dyslipidemias but are independently associated with insulin resistance and NAFLD grading on ultrasonographic evaluations. Further studies are needed to confirm our results.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a term with a wide spectrum of disorders from non-evaluative simple steatosis to progressive nonalcoholic steatohepatitis and cirrhosis[1,2], an emerging state in the community especially after control of hepatitis B virus infection with vaccination, and a very important public health dilemma owing to its increasing financial and health burden to the patients and the society. The health burden of NAFLD is mostly related to the risk of its progression into cirrhosis, liver failure and hepatocellular carcinoma[3]. It is also associated with a large amount of heath care cost[4]. NAFLD represents the most frequent chronic liver disease in the general population and is anticipated to become even more prevalent with time, due to the elevating proportion of people of both younger and older age, obesity and diabetes[5-9]. Putting together, NAFLD is emerging as a serious and global health problem which needs to be more precisely and critically addressed.

Addressing modification of the natural history and outcome of NAFLD, one should concentrate on attempts potentially which can amend or improve the clinical conditions known to promote the disease development. Thereby, at the first step, we need to know hypothesis on the pathogenesis of NAFLD and factors playing major roles in this process, to be able to adjust these factors in a way

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that best fits prevention of disease progression.

The pathogenesis of NAFLD is believed to result from two physiologic events[10]. The first event is insulin resistance, a metabolic state in which normal biologic serum concentrations of insulin induce a lower-than-normal response, or to obtain a normal blood glucose level, we need a higher-than normal insulin concentration. Insulin resistance has been suggested to produce an accumulation of triglycerides in hepatocytes, and lead to subsequent lipid peroxidation. The second event is thought to be the increased oxidative stress, cytokine release and other inflammatory processes. Serum alanine aminotransferase (ALT) level is a well-recognized clinical marker of liver injury and may represent a consequence of the second event in the pathogenesis of NAFLD[11]. On the other hand, it has been demonstrated that augmented ALT activities can be a predictor of the development of insulin resistance, diabetes mellitus, cardiovascular diseases, and metabolic syndrome in NAFLD patients[12-16].

Diabetes mellitus is highly prevalent in patients with NAFLD patients, and this disease substantially affects all laboratorial and pathological measures. Although some previous studies have focused on the associations of ALT increase in NAFLD patients, the associations of increased ALT activity, insulin resistance and/or NAFLD ultrasonografic grading have not been widely investigated; and there is data scarcity on the issue for non-diabetic NAFLD patients. In this cross-sectional study, we aimed to explore demographic and metabolic factors associated with increased ALT activity in non-diabetic NAFLD patients.

2. Materials and methods

The study was performed longitudinally in the outpatients visiting Gastroenterology Clinic of Baqiyatallah University of Medical Sciences, Tehran, Iran. Overall 372 patients consecutively attended to our clinic, were diagnosed as NAFLD and entered into analysis. Exclusion criteria were having diabetes mellitus and fasting blood glucose over 126 mg/dL, active hepatitis B virus infection, having hepatitis C virus positive serology, and to be under corticosteroid therapy. The study participants comprised a full range of socioeconomic levels. The study was approved by the local Ethics Committee of the Baqiyatallah University of Medical Sciences and written informed consent for participation was obtained from all the participants.

2.1. Anthropometrical measures

Anthropometrical measurements (height, weight, blood pressure, and waist/hip diameter) were collected by trained fieldworkers while patients wore light clothing and no shoes. Waist circumference was measured with the subject standing and wearing only underwear, at the level midway between the lower rib margin and iliac crest.

Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Overweight and obesity were defined as follows: Overweight (BMI$\geqslant$25.0); pre-obese (BMI 25.0-29.9), class I obesity (BMI 30.0-34.9), class II obesity (BMI 35.0-39.9), and class III obesity (BMI$\geqslant$40.0).

2.2. Blood samples

Blood samples were taken in 1 g/L EDTA in morning and after 12 h fast. Blood tubes were immediately stored at 41 °C and shielded from light. Blood tubes were centrifuged within 6 h at 2 500 rpm for 20 min to separate plasma. Serum concentrations of total cholesterol, fasting triglycerides, glucose, low-density lipoprotein- and high-density lipoprotein-cholesterol (LDL-C, HDL-C plus 2nd generation, direct quantification) were determined by using enzymatic kits from Roche Diagnostics with an autoanalyzer. Cholesterol measurements were standardized according to the program specified by the Centers for Disease Control and the National Heart, Lung and Blood Institute.

Homeostatic model assessment (HOMA) was calculated with the following formula: insulin (mIU/L)$\times$glucose (mM/L)/22.5. ALT levels were considered pathologically high when it was over 30 IU/L for men and over 19 IU/L for women.

2.3. Metabolic syndrome

As detailed in the third report of the Adult Treatment Panel (ATP III), subjects having three or more of the following criteria were defined as having the metabolic syndrome[17]: (i) abdominal girth: waist girth over 102 cm in men or 88 cm in women; (ii) hypertriglyceridemia: serum triglycerides over 150 mg/dL; (iii) low HDL-C: serum HDL cholesterol below 40 mg/dL in men or 50 mg/dL in women; (iv) high blood pressure: blood pressure over 130/85 mmHg; (v) high fasting glucose: blood glucose levels exceeding 100 mg/dL. Subjects using antihypertensive medication were considered to meet the criteria for high blood pressure.

2.4. Data analysis

For descriptive data, student's *t* test was used. *Chi* square test was used for categorical analysis. Likelihood estimates (Odds ratio) and 95% confidence intervals were obtained by use of logistic regression. A value of $P<0.05$ on the two-tail test was considered statistically significant. Statistical analyses were performed using SPSS 17.0 (SPSS Corp.; Chicago, IL, USA) for Windows.

3. Results

A total of 372 patients were entered into analysis. There were 237 (63.7%) males and 135 (36.3%) females. In the study, the age of population was (43.9$\pm$12.9) years. Self-rated socioeconomic levels were 362 (97.3%) intermediate, 6 (1.6%) low and 4 (1.1%) high. Educational levels of the study participants were 207 (55.9%) high school diploma, 108 (29.2%) under diploma, 1 (0.3%) illiterate, and 54 (14.6%) bachelor of science or more. Thirty four (9.1%) were smokers and 7 (1.9%) reported alcohol consumers.

Table 1 summarizes associations of different variables with

Table 1
Demographic and laboratorial measures of our non-diabetic NAFLD population regarding their serum ALT level.

Variables	Population with elevated ALT	Population with normal ALT	*P* value
Gender [male (%)]	172 (65.6)	50 (60.2)	0.430
BMI (kg/m^2)	29.7±3.9	29.7±4.9	0.960
BMI categorized			0.647
Normal weight	11 (4.9)	5 (7.5)	–
Overweight	126 (55.8)	36 (53.7)	–
Obese class I	62 (27.4)	19 (28.4)	–
Obese class II	22 (9.7)	4 (6.0)	–
Obese class III	5 (2.2)	3 (4.5)	–
Ultrasonography NAFLD grading			0.003
Grade 1	125 (47.7)	54 (65.1)	–
Grade 2	90 (34.4)	25 (30.1)	–
Grade 3	47 (17.9)	4 (4.8)	–
Waist circumstance (cm)	104±11	102±13	0.272
Waist>102 cm (male), >88 cm (female)	155 (68.0)	44 (59.5)	0.205
Systolic blood pressure (mmHg)	123±14	125±16	0.379
Diastolic blood pressure (mmHg)	80±8	81±8	0.499
Total cholesterol (mg/dL)	198±43	204±38	0.275
LDL-cholesterol (mg/dL)	114.1±36.8	116.4±30.7	0.087
HDL-cholesterol (mg/dL)	45.7±10.4	48.1±11.4	0.625
Triglyceride (mg/dL)	206±136	218±120	0.486
Fasting insulin (mIU/L)	12.8±5.8	10.4±5.5	0.002
Insulin resistance (HOMA>2.5)	142 (62.3)	34 (42.5)	0.003
Uric acid (mg/dL)	6.2±1.5	5.8±1.1	0.023
Alkaline phosphatase (IU/mL)	193.2±67.9	178.8±68.1	0.093
Metabolic syndrome	69 (28.2)	22 (28.6)	1.000
Central obesity	155 (68)	45 (60)	0.209
High triglyceride (mg/dL)	163 (62.7)	55 (67.1)	0.512
Low HDL (mg/dL)	103 (41.2)	31 (37.8)	0.607
High blood pressure	36 (14.3)	15 (20.0)	0.276
High fasting blood sugar	34 (13)	0	<0.001

Table 2
Associations between increased ALT activity and metabolic factors in NAFLD patients.

Variable	Standard error	Significance	Odds ratio	95% CI for odds ratio	
				Lower	Upper
Insulin resistance	0.285	0.013	2.025	1.158	3.541
High fasting blood sugar (>100 mg/dL)	0.376	0.902	0.955	0.457	1.995
Uric acid (mg/dL)	0.099	0.221	0.886	0.729	1.076
Ultrasonographic grading of NAFLD		0.027			
Ultrasonography (grade 1)	1.037	0.134	4.732	0.620	36.118
Ultrasonography (grade 2)	0.563	0.003	5.271	1.748	15.889
Ultrasonography (grade 3)	0.575	0.025	3.614	1.171	11.153

elevated ALT levels. As can be seen in Table 1, patients with normal or elevated ALT levels were comparable to each other regarding anthropometric measurements. There was also no gender bias between the two groups. As well, there was no difference in lipid profiling or systolic/diastolic blood pressure between the two patient groups. Metabolic syndrome was also equally distributed for the two study groups.

Bivariate analyses using *t* test and chi square showed that patients with pathologically augmented ALT levels had significantly higher NAFLD grades in their ultrasonographic evaluations (Table 1). Moreover, these patients represented significantly higher HOMA levels, levels of serum insulin levels, fasting blood glucose, and uric acid. The prevalence of insulin resistance was also higher in the patients with increased serum ALT concentrations.

For evaluating independent associations between the study indicators and serum ALT concentration in NAFLD patients, we conducted multifactorial logistic regression models (Table 2). Regression showed that ultrasonographic grading of NAFLD and insulin resistance was the only variables which were significantly associated with abnormal ALT levels.

4. Discussion

The prevalence of diabetes mellitus in Iran is shockingly

high, especially in young population[18]; and it would not be hyperbolic to proclaim that diabetes mellitus is the mother of morbidity of all vital organs. Thus, for investigating organ damages induced by different diseases, independently, we have to censor the impact of diabetes mellitus in our patient population by excluding them from the study. To our view, this is the major power of our study over others, who have entered their patients into analysis, without excluding diabetic patients.

The pathogenesis of NAFLD is not clearly defined, but there is a strong evidence in the literature that insulin resistance and visceral adiposity play major roles[18-20]. In our study, the prevalence of metabolic syndrome in patients with NAFLD was 26.4%, which is higher than that in the US general population (23.7%)[21] but is surprisingly lower than that reported in Iranian general population which was reported to be as high as 30%-31%[22,23]. On the other hand, the prevalence of metabolic syndrome in our NAFLD population is also relatively lower than that in other NAFLD series (32.3%)[24]. With no doubt, these discrepancies come from the selection criteria employed in this study which excluded diabetic patients, and shows that how much our data can be affected by including diabetic patients into NAFLD analysis.

Overwhelming data suggests that diabetes mellitus is associated with elevated serum ALT levels and vice versa[25-28]. This fact thoroughly messes findings of any study on potential associations of ALT levels in NAFLD patients. Most especially, when we have a serum ALT increase in a non-diabetic NAFLD patient, we need to know associations of this liver enzyme abnormality irrespective of what diabetes mellitus induces. This makes our study unique. Some previous studies have suggested that elevated ALT levels and fatty livers were independently associated with increased risk of metabolic syndromes[29,30]. On the other hand, consistent to our results, a community-based study in Taiwan, a country with a relatively low prevalence of diabetes mellitus[31] showed no increased prevalence of metabolic syndrome for NAFLD patients with elevated ALT levels. Putting together, we suggest that serum ALT level seems not be a good independent predictor of metabolic syndrome in NAFLD patients.

Several metabolic factors have been associated to increased ALT activity in patients with NAFLD, including BMI, insulin resistance, and metabolic syndrome components, *e.g.*, central obesity, raised triglycerides, reduced HDL-C, and raised fasting glucose[24]. In the current study, we found that patients with pathologically increased levels of ALT represented no higher serum levels of triglyceride, HDL-C levels, BMI, and prevalence of central obesity than those in patients with normal serum ALT levels. All the abovementioned are proved to be present in diabetes mellitus. An interesting study on type 2 diabetic patients has shown that a low HDL level in type 2 diabetes is always simultaneous with an increased serum triglyceride level[32]. Excluding patients with diabetes mellitus from the population of the current study, we found no association between augmented ALT levels and neither HDL levels nor triglyceride, which is consistent to the study of Bo *et al*[32].

Elevated serum ALT levels of patients enrolled in this study were significantly associated with higher grades of NAFLD in ultrasonographic evaluations, fasting blood sugar, fasting serum insulin levels, insulin resistance, and serum uric acid. To evaluate any independent associations of the increased ALT in NAFLD patients, a multifactorial logistic regression model was conducted. In this model, insulin resistance and ultrasonographic grading of the disease were shown to be significantly associated with increased serum ALT values.

Association between serum ALT levels, even within the normal range, and NAFLD development has been previously demonstrated[33]. To our knowledge, the present study is the first that shows non diabetic NAFLD patients representing a higher serum ALT level are significantly more likely to have higher NAFLD grades. It has been previously shown that serum ALT is associated with insulin resistance in NAFLD patients[30], but our finding is in a population after exclusion of diabetic patients. Another interesting finding of the current study is that abnormal ALT levels, independent to NAFLD severity grade, is significantly associated with insulin resistance. This finding is of outmost importance, because as mentioned before, insulin resistance has been hypothesized as one of the main pathogenesis of NAFLD, but we showed that increased serum ALT is independently associated with higher NAFLD grades, which might be indicative of existence of some factors, other than insulin resistance in the pathogenesis of NAFLD. However, due to the indirect nature of this conclusion, further experimentation is needed for confirming that. The male preponderance observed in the current study can be explained by the type of our center, as a referral military hospital; and it does not mean that NAFLD in Iran is more common in males.

In conclusion, this study showed that the relevance and associations of increased ALT serum levels in NAFLD patients are different from what was supposed before. By excluding diabetic patients from our population, we found that increased ALT levels is not associated with dyslipidemias, and previous observations were highly likely due to the effects of diabetes on both ALT and serum lipid concentrations. On the other hand, this study suggests that the only independent associates of ALT increase in NAFLD patients are insulin resistance and NAFLD grading on ultrasonographic evaluations. Further studies are needed to confirm our results.

Conflict of interest statement

We declare that we have no conflict of interest.

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