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Non-alcoholic steatohepatitis with normal aminotransferase values

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Abstract

AIM: To investigate the aspects of liver histology in patients with non-alcoholic steatohepatitis (NASH) who had normal aminotransferase levels.

METHODS: Thirty-four patients diagnosed with liver steatosis by ultrasonographic examination participated in the study. We compared all non-alcoholic fatty liver disease and NASH cases, according to aminotransferase level, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio and presence of metabolic syndrome.

RESULTS: Sixteen of 25 patients with high aminotransferase levels were diagnosed with NASH and nine with simple fatty liver according to liver histology. Among the nine patients with normal aminotransferase levels, seven had NASH and two had simple fatty liver. The patients with normal and high liver enzyme levels had almost the same prevalence of NASH and metabolic syndrome. Liver histology did not reveal any difference according to aminotransferase levels and AST/ALT ratio.

CONCLUSION: Aminotransferase levels and AST/ALT ratio do not seem to be reliable predictors for NASH. Despite numerous non-invasive biomarkers, all patients with fatty liver should undergo liver biopsy.

Key words: Non-alcoholic steatohepatitis; Liver enzymes; Liver histology

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common liver pathology that begins from simple steatosis and then progresses to steatohepatitis and ends with cirrhosis or liver failure[1,2]. While simple steatosis is accepted as a benign state, steatohepatitis, because of elevated liver enzymes [alanine aminotransferase (ALT) and aspartate aminotansferase (AST)] and certain metabolic abnormalities such as diabetes, obesity, dyslipidemia, hypertension and insulin resistance is assessed as a serious condition[3-6]. Nevertheless, according to the literature, some non-alcoholic steatohepatitis (NASH) patients can have normal aminotransferase levels or conversely some patients with high liver enzymes may not have steatohepatitis[7]. It has emerged that some NAFLD patients may not fulfill all criteria concerned with metabolic syndrome and do not have insulin resistance[8]. Some studies have revealed that NAFLD can progress in the absence of metabolic disorders, as defined also in lean and non-diabetic patients, males and children[9]. We aimed to show that NASH can occur without an increase in liver enzyme levels and that there may not be progression of NASH in fatty liver patients with high liver enzymes. More attention has been paid to these issues in recent years; but, further research especially related to large populations should be performed.

MATERIALS AND METHODS

Study design and patients

In the present retrospective study, we aimed to establish

the presence of patients with normal liver enzymes who were diagnosed histologically with NASH, to compare NAFLD and NASH patients according to liver enzyme levels, and to establish whether histological aspects of NAFLD differ with liver enzyme levels. This study included 34 patients who attended the Gastroenterology Division of Uludag University. The patients were diagnosed with liver steatosis by ultrasonography and complete clinical, anthropometric and laboratory evaluations and liver biopsies were performed. Exclusion criteria were as follows: alcohol consumption of $\geqslant$ 20 g/d, pregnancy, presence of hepatitis B and C infection, autoimmune liver diseases, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, toxic liver diseases, primary biliary cirrhosis, primary sclerosing cholangitis, respectively.

Laboratory studies

Anthropometric, clinical and laboratory features of all NAFLD cases with both high and normal liver enzyme levels were recorded. Anthropometric parameters consisted of height, weight, body mass index (BMI), waist and hip circumferences and waist/hip ratio. Overweight and obesity were defined as BMI $\geqslant$ 25 kg/m^2 and $\geqslant$ 30 kg/m^2, respectively. Biochemical assessments included ALT, AST, γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), bilirubin, albumin, high-density lipoprotein (HDL)-cholesterol, triglycerides, glucose, insulin levels and oral glucose tolerance test (OGTT). The diagnosis of type 2 diabetes, impaired glucose intolerance (IGT), impaired fasting glycemia were dependent on American Diabetes Association (ADA) criteria and patients taking oral antidiabetics or insulin therapy were accepted as having diabetes. The cut-off values of ALT and AST were 0-43 and 0-40 IU/L, respectively. Resting blood pressure $\geqslant$ 140/90 mmHg or treatment with antihypertensive drugs indicated hypertension. Cut-off levels of hypertriglyceridemia and low HDL-cholesterol status were $\geqslant$ 150 mg/dL and $\leqslant$ 40 mg/dL, respectively. Lipid-lowering drug therapy indicated dyslipidemia. Fasting insulin level was 6-27 μU/mL and presence of insulin resistance was defined when homeostasis model assessment of insulin resistance (HOMA-IR) value was $\geqslant$ 2.70. Description of metabolic syndrome was made according to World Health Organization criteria (BMI $\geqslant$ 30 kg/m^2, increased waist/hip ratio of $>$ 0.90 in men and $>$ 0.85 in women, fasting blood glucose $\geqslant$ 110 mg/dL, presence of IGT, HOMA-IR $\geqslant$ 2.70, triglycerides $\geqslant$ 150 mg/dL, HDL-cholesterol $\leqslant$ 40 mg/dL in men and $\leqslant$ 50 mg/dL in women, arterial blood pressure $\geqslant$ 140/90 mmHg and microalbuminuria)[10]. At least three of these criteria were required to diagnose the metabolic syndrome. Liver biopsy was performed according to the severity of the clinical features and permission from the patients. The study was approved by the hospital ethics committee.

Histological assessment

All liver biopsy specimens were evaluated by a liver pathologist according to the criteria of Brunt *et al*[11]. NASH was diagnosed according to the criteria as presented below: steatosis (mild, moderate and severe) and two of the three features: (1) necro-inflammation with mononuclear cells and/or polymorphonuclear leukocytes, (2) ballooning degeneration of hepatocytes and (3) perisinusoidal and/or bridging fibrosis.

Statistical analysis

Statistical analysis was performed by using the SPSS statistical software version 15.0 for Windows. $P < 0.05$ was considered to indicate statistical significance. According to the data distribution, independent *t*-test and Mann-Whitney test were used to compare continious variables related to the case groups. Pearson's Chi-square test and Fischer's absolute Chi-square test were used to compare categorical variables.

RESULTS

The features of 34 patients (12 male, 22 female) with liver steatosis who attended the Gastroenterology Division of Uludag University were investigated. Slight and blunt abdominal pain were present in 77.7% of patients with elevated liver enzymes and in 64.0% of patients with normal liver enzymes. The prevalence of hepatomegaly was 44.4% and 28% in the high liver enzyme and normal liver enzyme group, respectively. All 34 patients underwent liver biopsy according to their clinical and laboratory aspects. Twenty-five patients had elevated and the remaining nine had normal liver enzyme levels. Sixteen of 25 patients with high liver enzymes were diagnosed with NASH and nine of 25 as simple fatty liver with respect to liver histology. When we analyzed the nine patients with normal ALT levels, seven were diagnosed with NASH and two with simple fatty liver according to liver histology.

Anthropometric, clinical and laboratory results of all NAFLD patients according to high and normal liver enzyme groups are presented in Table 1. The patients with high and normal aminotransferase levels had almost same prevalence of NASH (77.7% *versus* 64.0%). Only the proportion of patients with hypertriglyceridemia in the normal liver enzyme group was significantly higher than in the group with elevated liver enzyme. However according to the Table 1, the number and proportions of the other metabolic risk factors in high and normal liver enzyme levels groups did not differ. Moreover, a comparison was performed between the elevated and normal aminotransferase level groups in NASH patients and there were no significant differences (Table 2). The prevalence of metabolic syndrome was similar in NASH patients both with elevated or normal aminotransferase levels.

There were seven patients with normal aminotransferase levels who were diagnosed with NASH. Six of these were female (mean age: 52.8 years) and one was male. Five of the female patients were obese (average BMI: 31 kg/m^2) and one was morbidly obese (BMI: 49.3 kg/m^2). All six female patients had metabolic syndrome (five of whom had three risk factors and one had four risk factors). Two of the six female

Table 1 Anthropometric, clinical and laboratory features of all NAFLD cases according to liver enzyme levels *n* (%)

	According to liver enzyme levels (*n* = 34)		*P*
	Normal liver enzyme (*n* = 9)	Elevated liver enzyme (*n* = 25)	
Age (yr)	52.0 ± 6.16	49.8 ± 6.77	> 0.05
Gender (male/female)	1/8 (11.2/88.8)	10/15 (40/60)	> 0.05
Hepatomegaly	4 (44.4)	7 (28.0)	> 0.05
BMI (kg/m^2)			
Normal weight	0 (0)	1 (4)	> 0.05
Overweight	0 (0)	2 (8)	> 0.05
Obese	7 (77.8)	20 (80.0)	> 0.05
Morbid obese	2 (22.2)	2 (8.0)	> 0.05
Waist/hip ratio	6 (66.7)	19 (76.0)	> 0.05
Systolic blood pressure (mmHg)[1]	130 (110-150)	120 (110-180)	> 0.05
Diastolic blood pressure (mmHg)[1]	76 (60-90)	70 (60-120)	> 0.05
Hypertension	4 (44.4)	12 (48.0)	> 0.05
HDL-Cholesterol (mg/dL)	43.56 ± 7.99	45.52 ± 7.04	> 0.05
Low-HDL level	6 (66.7)	11 (44.0)	> 0.05
Triglycerides (mg/dL)[1]	187 (43-360)	125 (39-304)	> 0.05
Hypertriglyceridemia	7 (77.8)	8 (32.0)	< 0.05
Fasting glucose (mg/dL)[1]	101 (73-164)	101 (87-195)	> 0.05
Diabetes	2 (22.2)	6 (24.0)	> 0.05
Impaired glucose tolerance	3 (33.3)	7 (28.0)	> 0.05
Fasting insulin (μU/mL)[1]	11.8 (6-23.66)	15.23 (4.76-47.3)	> 0.05
Insulin resistance-HOMA-IR	2 (22.2)	14 (56.0)	> 0.05
AST (IU/L)[1]	17 (14-29)	49 (33-92)	< 0.05
ALT (IU/L)[1]	13 (13-33)	81 (32-166)	< 0.05
GGT (IU/L)[1]	19 (15-33)	42 (15-426)	< 0.05
ALP (IU/L)[1]	96 (52-113)	81 (51-154)	> 0.05
NASH	7 (77.7)	16 (64.0)	> 0.05
Metabolic syndrome	8 (88.8)	19 (76)	> 0.05

[1]Data expressed as median (minimum-maximum); BMI: Body mass index; HDL: High-density lipoprotein; ALP: Alkaline phosphatase; GGT: Gamma glutamyl transpeptidase. Only the prevalence of hyperglyceridemia in NAFLD patients with normal liver enzyme levels was higher than in those with elevated liver enzyme.

Table 2 Features of NASH patients according to high and normal aminotransferase levels *n* (%)

	NASH cases (*n* = 23)		*P*
	Normal aminotransferase levels (*n* = 7)	Elevated aminotransferase levels (*n* = 16)	
Age (yr)	52.8 ± 5.04	50.44 ± 5.12	> 0.05
Gender (male/female)	1/6 (14.2/85.8)	6/10 (37.5/62.5)	> 0.05
Hepatomegaly	2 (28.5)	5 (31.2)	> 0.05
BMI (kg/m^2)			
Normal weight	-	-	
Overweight	-	-	
Obese	6 (85.7)	14 (87.5)	> 0.05
Morbid obese	1 (14.3)	2 (12.5)	> 0.05
Waist/hip ratio	5 (71.4)	12 (75.0)	> 0.05
Systolic blood pressure (mmHg)[1]	130.0 (110-150)	120 (110-180)	> 0.05
Diastolic blood pressure (mmHg)[1]	80 (60-90)	70 (60-120)	> 0.05
Hypertension	3 (42.9)	7 (43.8)	> 0.05
HDL-Cholesterol (mg/dL)	43.86 ± 8.97	44.19 ± 4.07	> 0.05
Low-HDL level	4 (57.1)	9 (56.3)	> 0.05
Triglycerides (mg/dL)	183.57 ± 95.82	130.44 ± 59.46	> 0.05
Hypertriglyceridemia	5 (71.4)	5 (31.3)	> 0.05
Fasting glucose (mg/dL)[1]	101 (73-164)	102.83 (87-195)	> 0.05
Diabetes	2 (28.6)	4 (25.0)	> 0.05
Impaired glucose tolerance	3 (42.9)	6 (37.5)	> 0.05
Fasting insulin (μU/mL)	11.8	13.96	> 0.05
Insulin resistance-HOMA-IR	1 (14.3)	9 (56.3)	> 0.05
AST (IU/L)[1]	18 (14-29)	46 (33-92)	< 0.05
ALT (IU/L)[1]	21 (15-39)	77 (32-158)	< 0.05
GGT (IU/L)[1]	21 (15-33)	40 (16-119)	< 0.05
ALP (IU/L)[1]	96 (52-111)	78.5 (55-152)	> 0.05
Metabolic syndrome	6 (85.7)	12 (75.0)	> 0.05

[1]Data expressed as median (minimum-maximum); BMI: Body mass index; HDL: High-density lipoprotein; ALP: Alkaline phosphatase; GGT: Gamma glutamyl transpeptidase. There was no difference between the features of NASH patients with high and normal aminotransferase levels.

patients had overt diabetes, two had impaired glucose tolerance and the remaining two had normal OGTT results. Two female patients who were non-diabetic had insulin resistance determined by HOMA test. Three female patients had hypertension and five had hypertriglyceridemia. The male patient with NASH was 46 years old with central obesity (BMI: 30.5 kg/m^2). He also had insulin resistance (HOMA-IR:3.46), but had no other risk factors such as diabetes, hypertriglyceridemia, hypertension and microalbuminuria; therefore he was not diagnosed with metabolic syndrome.

In Table 3, the findings of all NASH patients according to the presence of metabolic syndrome are presented and evaluated. According to Table 3, average age, the prevalences of female gender, hypertension, low-HDL level and hypertriglyceridemia were significantly higher in patients with metabolic syndrome than those in patients without metabolic syndrome. Interestingly, among the 18 NASH patients with metabolic syndrome twelve had elevated and six had normal liver enzyme levels as stated at Table 2. Similarly, among the 5 NASH patients without metabolic syndrome, there were four patients with elevated and one with normal liver enzyme levels. But these results were not statistically significant. In addition, the proportion of patients with obesity was similar in both the elevated and normal liver enzyme groups with metabolic syndrome.

Table 4 represents the features of liver histology in all NAFLD patients according to liver enzyme levels. In Table 4, patients with elevated liver enzyme levels seemed to have more severe liver histology than those with normal liver enzyme levels, but this was not statistically significant.

Liver histology in patients with normal liver enzyme levels (1 male and 8 female patients) was described in detail below. Histologically defined NASH was present in one male and six female patients. Among six female patients, four had mild, one had moderate and one had severe necroinflammmation, and fibrosis (stage 1) was detected only in two patients. In one male patient with NASH, the features of liver histology consisted of moderate steatosis and necroinflammation, but no fibrosis. Simple fatty liver was detected in two female patients in the normal liver enzyme group and one had mild and the other had moderate steatosis.

Table 5 shows the features of liver histology in all NAFLD patients according to AST/ALT ratio

Table 3 Features of NASH patients with high and normal aminotransferase levels according to the presence of metabolic syndrome *n* (%)

	NASH cases (*n* = 23)		*P*
	With metabolic syndrome (*n* = 18)	Without metabolic syndrome (*n* = 5)	
Average age (yr)	52.7 ± 4.34	45.4 ± 3.20	< 0.05
Gender (male/female)	3/15 (16.7/83.3)	4/1 (80.0/20.0)	< 0.05
Hepatomegaly	5 (29.4)	2 (50)	> 0.05
BMI (kg/m^2)			
Normal weight	-	-	
Overweight	-	-	
Obese	15 (83.3)	5 (100)	> 0.05
Morbid obese	3 (16.7)	0 (0)	> 0.05
Waist/hip ratio	13/(72.2)	4 (80.0)	> 0.05
Hypertension	10 (55.6)	0 (0)	< 0.05
Low HDL level	13 (72.2)	0 (0)	< 0.05
Hypertriglyceridemia	10 (55.6)	0 (0)	< 0.05
Diabetes	5 (27.8)	1 (20.0)	> 0.05
Impaired glucose tolerance	8 (44.4)	1 (20.0)	> 0.05
Insulin resistance-HOMA-IR	6 (75)	4 (80.0)	> 0.05
AST (IU/L)	38. 06 ± 16.63	53.60 ± 27.04	> 0.05
ALT (IU/L)	57.39 ± 32.127	84.8 ± 49. 37	> 0.05
AST/ALT > 1	3 (16.6)	1 (20.0)	> 0.05
GGT (IU/L)[1]	29.5 (15-83)	33 (16-119)	> 0.05
ALP (IU/L)	83.44 ± 18.19	98.20 ± 38.78	> 0.05

[1]Data expressed as median (minimum-maximum); BMI: Body mass index; HDL: High-density lipoprotein; ALP: Alkaline phosphatase; GGT: Gamma glutamyl transpeptidase. There were significant differences between NASH cases with or without metabolic syndrome according to average age, gender and the presence of hypertension, low-HDL level and hypertriglyceridemia.

values. However, there were no statistically significant differences between patient groups according to AST/ALT ratio. Table 6 compares patients with NASH and without NASH according to anthropometric, clinical and laboratory features; and only the prevalence of obesity was significantly different between these two groups.

DISCUSSION

An increase in ALT value is regarded as a parameter for the diagnosis of NASH. The criteria for establishing a diagnosis of NASH are elevated aminotransferases (ALT and AST), histological features resembling to those in alcoholic steatohepatitis and exclusion of other liver diseases[2-4]. However, anthropometric, clinical and histological aspects of NASH with normal ALT levels have not been investigated extensively. In this retrospective study, we aimed to describe the anthropometric, clinical and histological features of NASH patients with normal ALT values and to compare these with NASH cases that had elevated ALT levels.

There have been many studies on normal ranges for serum ALT levels. The new cut-off values for upper limits of serum ALT levels are now proposed as 30 U/L for men and 19 U/L for women[12]. Amarapurkar *et al*[13] have expressed that after excluding other liver disorders, normal ALT may not exclude severe liver diseases and, hence, liver biopsy may be necessary

Table 4 Liver histology according to the level of liver enzymes in all NAFLD cases *n* (%)

Liver histology	All NAFLD patients	
	Patients with normal aminotransferase levels (*n* = 9)	Patients with elevated aminotransferase levels (*n* = 25)
Steatosis		
Mild	5 (55.5)	12 (48.0)
Moderate	3 (33.3)	7 (28.0)
Severe	1 (11.2)	6 (24.0)
Necroinflammation		
Absent	2 (22.2)	9 (36.0)
Mild	4 (44.4)	3 (12.0)
Moderate	2 (22.2)	10 (40.0)
Severe	1 (11.2)	3 (12.0)
Fibrosis		
Absent	7 (77.7)	16 (64.0)
Perisinusoidal/pericellular	2 (22.3)	6 (24.0)
Periportal	0 (0)	2 (8.0)
Bridging	0 (0)	1 (4.0)

Due to the small number of patients, statistical evaluation and *P* values were not available. Patients with elevated liver enzyme levels seemed to have more sever liver histology than those with normal liver enzyme levels, but this was not statistically significant.

Table 5 Liver histology according to AST/ALT ratio values in all NAFLD cases *n* (%)

Liver histology	All NAFLD patients	
	Patients with AST/ALT > 1 (*n* = 6)	Patients with AST/ALT < 1 (*n* = 28)
Steatosis		
Mild	2 (33.3)	15 (53.5)
Moderate	2 (33.3)	7 (25.0)
Severe	2 (33.4)	6 (21.5)
Necroinflammation		
Absent	3 (50.0)	3 (10.7)
Mild	0 (0)	12 (42.9)
Moderate	1 (16.7)	11 (39.2)
Severe	2 (33.3)	2 (7.2)
Fibrosis		
Absent	4 (66.6)	18 (64.3)
Perisinusoidal/pericellular	1 (16.6)	7 (25.0)
Periportal	0 (0)	3 (10.7)
Bridging	1 (16.6)	0 (0)

Due to the small number of patients statistical evaluation and *P* values were not available. There were no significant differences between patient groups according to AST/ALT ratio.

to detect the seriousness of liver diseases. Likewise, Kunde *et al*[14] have stated that the diagnostic use for ALT to determine NASH was insufficient in their study. Fracanzani *et al*[15] have expressed the view that normal ALT is not a reliable criterion to exclude patients from liver biopsy. Mofrad *et al* have found that histological features of NAFLD may progress in persons with normal ALT values and the liver histology in these persons is not very different from that in patients with high ALT levels and in addition having a low or normal ALT level is not a reliable indicator against the presence of steatohepatitis[7]. Sorrentino *et al*[16] have detected that

Table 6 Comparison between patients with NASH and without NASH according to anthropometric, clinical and laboratory features *n* (%)

	All NAFLD patients		*P*
	Patients with NASH (*n* = 23)	Patients without NASH (*n* = 11)	
Age (yr)	51.17 ± 5.11	48.82 ± 9.05	> 0.05
Gender: male/female	7/16 (30.4/69.6)	4/7 (36.4/63.6)	> 0.05
Hepatomegaly	7 (29.2)	4 (36.4)	> 0.05
Obesity (BMI ⩾ 30)	23 (100)	8 (72.7)	< 0.05
Waist/hip ratio	17 (63.6)	7 (73.9)	> 0.05
Systolic blood pressure (mmHg)[1]	120 (110-180)	130 (110-180)	> 0.05
Diastolic blood pressure (mmHg)[1]	70 (65-110)	70 (60-120)	> 0.05
Hypertension	10 (45.5)	6 (60)	> 0.05
HDL-Cholesterol (mg/dL)	44.09 ± 5.77	46.91 ± 9.66	> 0.05
Low-HDL level	13 (56.5)	4 (36.4)	> 0.05
Triglycerides (mg/dL)	146.61 ± 74.43	174.18 ± 83.85	> 0.05
Hypertriglyceridemia	10 (43.5)	5 (45.5)	> 0.05
Fasting glucose (mg/dL)[1]	102.33 (73-195)	100 (83-125)	> 0.05
Diabetes	6 (26.1)	2 (18.2)	> 0.05
Impaired glucose tolerance	9 (39.1)	1 (9.1)	> 0.05
Fasting insulin (μU/mL)[1]	13.44 (4.76-47.3)	16.60 (6-21.80)	> 0.05
Insulin resistance-HOMA-IR	13 (81.3)	6 (66.7)	> 0.05
AST (U/L)[1]	40 (14-92)	51 (14-78)	> 0.05
ALT (U/L)[1]	67 (15-158)	82 (13-166)	> 0.05
GGT (U/L)[1]	33 (15-119)	43 (15-426)	> 0.05
ALP (U/L)[1]	81 (52-152)	81 (51-154)	> 0.05
AST/ALT > 1	4 (17.3)	2 (18.1)	> 0.05
Metabolic syndrome	18 (78.3)	9 (81.8)	> 0.05

[1]Data expressed as median (minimum-maximum); BMI: Body mass index; HOMA: Homeostasis model assessment; HDL: High-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma glutamyl transpeptidase. There was a significant difference between patients with or without NASH according to the presence of obesity only.

liver enzyme levels are not reliable markers of NASH. However, Chen *et al*[17] have determined that elevated serum ALT level may be associated with NAFLD but it is not a reliable parameter for metaboloic risk factors. Furthermore, Amarapurka *et al*[18] have added that high levels of transaminases are non-specific and may not indicate the progression of NASH. Therefore, liver biopsy is necessary in grading and staging of NASH to predict disease progression. Lizardi-Cervera *et al*[19] have also revealed that the number of patients with NASH was not increased with high levels of AST. Sebastiani *et al*[20] have revealed that the usefullness of non-invasive biomarkers is very restricted in general practice.

In our study, the patients were comparable with respect to age, gender, anthropometric features, imaging aspects and laboratory findings. Interestingly, in NAFLD patients only the prevalence of hypertriglyceridemia in normal liver enzyme group was higher than those with elevated liver enzyme. All other clinical, histological and laboratory findings of patients with normal ALT were no different from those with elevated ALT in the NAFLD group. Moreover, the prevalence of NASH in NAFLD patients with elevated and normal aminotransferase (ALT) levels was similar. These findings suppose that NASH can progress without an increase in ALT levels and this raises the suspicion that this parameter may not be a reliable marker of NASH. In the present study patients with elevated and normal ALT levels in the NASH group had no significant differences, including the prevalance of metabolic syndrome and insulin resistance. These results suggest that cases with normal aminotransferase levels can also have steatohepatitis and metabolic syndrome and not only simple fatty liver and, hence, a liver biopsy is not an incorrect approach for these patients. We found that the histopathological features of the liver were more severe in NASH patients with high liver enzyme levels than in those with normal liver enzyme levels; but, the difference was not statistically significant.

We compared the NASH patients according to the presence of metabolic syndrome; we did not detect any difference according to liver enzyme levels. Consequently, in our opinion, liver biopsy for cases diagnosed with fatty liver by imaging methods may be beneficial even if they have normal aminotransferase levels.

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COMMENTS

Background

Nowadays certain non-alcoholic steatohepatitis (NASH) cases are detected without an elevation in liver enzyme levels. To make a distinction between NASH and simple fatty liver the approach for all non-alcoholic fatty liver disease (NAFLD) patients should be assessed again regarding the utility and reliability of noninvasive biochemical and imaging modalities as opposed to liver biopsy which still remains the gold standard.

Research frontiers

It was almost impossible formerly to recognize the prognosis of fatty liver, and certain fatty liver patients with elevated liver enzymes may not have NASH. To avoid serious outcomes of NASH such as cirrhosis, hepatocellular carcinoma and liver failure, and to detect these complications early, the accurate and definitive dignosis of NASH, and protective measures, life style modification and appropriate treatment are essential.

Innovations and breakthroughs

The authors demonstrated that anthropometric, clinical, laboratory and imaging features of NAFLD patients including certain noninvasive markers may not reflect or always be in agreement with the histological aspects of liver biopsy in NASH. The importance and accuracy of liver histopathology should not be disregarded.

Applications

After initial evaluation and discrimination of NAFLD patients by anthropometrical, clinical, laboratory and imaging studies, liver biopsy which is the gold standard should be considered and performed when available.

Terminology

While simple fatty liver is only an accumulation of triglycerides in liver and is accepted to be a benign condition, it is not definitely known which patients will keep their stationary state or which patient and when will progress to steatohepatitis. NASH indicates necroinflammation and fibrosis in liver and may progress to cirrhosis, hepatocellular carcinoma and liver failure.

Peer review

This article is useful for the purpose of evaluating and establishing principles for the best approach in patients with NAFLD.

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