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Serum levels of acute phase proteins in patients with nonalcoholic steatohepatitis

Nonalkolik steatohepatitli hastalarda serum, akut faz proteinleri düzeyleri

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Background/aims: A simple and practical method of detecting the degree of the inflammatory response during the development of nonalcoholic steatohepatitis has not been developed to date. In this study the serum levels of acute phase proteins in patients with nonalcoholic steatohepatitis and whether these levels had any relationship with histopathological findings in the liver were evaluated. **Methods:** The study included 18 patients with NASH diagnosed by liver biopsy (13 males and five females with a mean age of 44 years) and 16 healthy volunteers as a control group (11 males and five females, with a mean age of 40 years). The serum levels of C-reactive protein, C-reactive ceruloplasmin, ferritin, transferrin, alpha-1-acid glycoprotein, alpha-2-macroglobulin, alpha-1-antitripsin, albumin, haptoglobulin and lipoprotein (a) were determined by nephelometric method in both groups. In patients with nonalcoholic steatohepatitis, liver histopathology was assessed using a modified scoring system based on the classification defined by Brunt. **Results:** Serum C-reactive, ferritin, alpha-2-macroglobulin and ceruloplasmin concentrations in patients with nonalcoholic steatohepatitis were significantly higher than those of the control group (p=0.0001, p= 0.001, p= 0.007, p=0.01 respectively), but serum transferrin, albumin, haptoglobin, alpha-1-acid glycoprotein, alpha-1-antitripsin and lipoprotein (a) levels were not different. There was no difference in C-reactive protein levels regarding the degree of hepatic steatosis and inflammation and the stage of liver fibrosis. Acute phase proteins had no correlation with liver histology. **Conclusions:** Measurement of serum C-reactive protein, ferritin, ceruloplasmin and alpha-2-macroglobulin levels may be useful in assessing patients at risk of nonalcoholic steatohepatitis and those with high C-reactive protein and ferritin but normal transferrin should be considered for liver biopsy.

Key words: Nonalcoholic steatohepatitis, acute phase proteins, C-reactive protein

Amaç: *Nonalkolik steatohepatitin gelişimi esnasında ortaya çıkan inflamasyonun şiddetini belirlemede basit parametreler henüz tanımlanmamıştır. Bu çalışmada nonalkolik steatohepatitisli hastalarda akut faz proteinlerinin serum düzeylerindeki değişikliklerin inflamasyon şiddetini belirlemede faydalı olup olamayacağını belirlemek için serum akut faz proteinlerinin düzeylerini ölçmeyi ve bu düzeyler ile karaciğerdeki histopatolojik bulgular arasında herhangi bir ilişkinin olup olmadığını araştırmayı amaçladık.* ***Yöntem:*** *Çalışmaya karaciğer biyopsisi ile tanı konulan 18 nonalkolik steatohepatitis'li hasta ile 16 sağlıklı gönüllü dahil edildi. Hasta ve kontrollerin serum C-reaktif protein, ferritin, transferin, seruloplazmin, alfa-1 asit glikoprotein, alfa-2 makroglobulin, alfa-1 antitripsin, albumin, haptoglobulin ve lipoprotein (a) düzeyleri nefelometrik metodla ölçüldü. Hastaların biyopsi materyalleri Brunt'ün modifiye skorlama sistemine göre değerlendirildi.* ***Bulgular:*** *Hastaların serum C-reactive protein, ferritin, seruloplazmin* Tue *alfa-2 makroglobulin düzeyleri kontrollerden önemli oranda yüksekti (p=0.0001, p=* 0.007, *p= 0.007, p=0.01). Serum transferrin, albumin, alfa-1 asit glikoprotein, haptoglobin, alfa-1 asit glikoprotein ve lipoprotein (a) düzeyleri hasta ve kontrol grupları arasında önemli bir farklılık göstermiyordu. Nonalkolik steatohepatitisli hastalarda serum akut faz proteinleri ve karaciğer histopatolojisi arasında herhangi bir ilişki tesbit edilmedi. Sonuç: Serum C-reactive protein, ferritin, serüloplazmin ve alfa-2 makroglobulin düzeylerine bakılması nonalkolik steatohepatitis riski olan hastaların değerlendirilmesinde faydalı olabilir. Özellikle C-reactive protein ve ferritin düzeyi yüksek, transferrin saturasyonu normal hastalar karaciğer biyopsisi açısından değerlendirilmelidir.*

Anahtar kelimeler: Nonalkolik steatohepatit, akut faz proteinleri, C-reactive protein.

INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is an advanced form of nonalcoholic fatty liver disease (NAFLD) and has at least three components among the tetrad of steatosis, hepatocellular injury, focal mixed cell-type inflammation, and fibrosis. It has been suggested that progression from simple steatosis to steatohepatitis and then advanced fibrosis is caused by two distinct events. Firstly, insulin resistance leads to the accumulation of fat within hepatocytes, and secondly, mitochondrial reactive oxygen species cause lipid peroxidation, cytokine induction, and the induction of Fas ligand. The lipid peroxidation products [malondialdehyde (MDA), 4-hydroxynonenal (HNE)]

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and the some cytokines [tumor necrosis factor—alpha (TNF-cc), transforming growth factor-beta (TGF-p) and interleukin (IL)-8] can start the inflammatory response in the liver which either directly causes cellular damage or draws the inflammatory cells to the liver parenchyma (1-4).

The acute phase response (APR) comprises a cascade of systemic responses upon tissue injury as a result of neoplasia, trauma or infection. Inflammatory processes are the main causes of the initiation of these defence mechanisms. Cytokines are the predominantly responsible mediators for APR whereby the liver is the main target organ. It has become clear that the acute phase cytokines (IL-1, IL-6, IL-8, TNF- a, TGF-0) modulate protein synthesis by hepatocytes. One of the most striking changes is the alteration in plasma concentrations of a group of proteins named as the acute phase proteins (APPs) which may increase (positive APPs) or decrease (negative APPs) in the plasma during the acute phase reaction. The APPs have been found to have an essential role in the inhibition of extracellular proteases, modulation of immune cell function and neutralization and clearance of harmful components from the circulation (5-8).

Although alterations of serum concentrations of APPs in inflammatory conditions such as inflammatory bowel disease, acute pancreatitis and chronic liver disease is well established, it is not known whether the serum levels of APPs change in patients with nonalcoholic steatohepatitis. The ability to measure inflammatory activity in nanalcoholic steatohepatitis is desirable for assessing its degree and clinical course, but convenient and simple parameters are lacking. At present, the noninvasive imaging studies (ultrasonography, computerized tomography, magnetic resonance imaging) and serum aminotransferase elevation are not sufficiently sensitive in detecting the degree of the inflammatory response occuring during the development of nonalcoholic steatohepatitis (9). The aim of this study was to determine ther whe alterations in the serum concentration of APPs in patients with NASH by measuring the serum levels of APPs in patients with NASH and healthy controls. Serum levels of APPs and any relationship to histopathologic findings in the liver was then examined and the value of this method in determining the severitiy of nonalcoholic steatohepatitis was evaluated.

MATERIALS AND METHODS

The study included 18 patients with nonalcoholic steatohepatitis who attended the Gastroenterology Clinic of Atatürk University during 2001. The diagnosis of nonalcoholic steatohepatitis was made according to the following criteria: 1) abnormal liver function tests at least for there months and absence of previous liver disease history, 2) sonographic diagnosis of liver steatosis, 3) histologic diagnosis of fatty infiltration, lobular or portal inflammation and/or Mallory bodies, fibrosis or cirrhosis. Informed consent was obtained from each subject. This study protocol was approved by the Ethics Committee of Atatürk University School of Medicine.

Absence of alcohol consumption in all patients was required and confirmed by family members. No drug history causing liver steatosis (corticosteroids, estrogen, methotrexate, tetracycline, calcium channel blockers, amiodaron) and there was no history of surgery. Body mass index (BMI) was calculated and those with; BMI greater than 30 were defined as obese (10). Detailed physical examination and laboratory investigations were performed in patients with NASH.

In all patients, serum aspartate aminotranspherase (AST), alanine aminotranspherase (ALT), total bilirubin (T. Bl), alkaline phosphatase (ALP), gamma-glutamil transpeptidase (GGT), total protein, albumin, total cholesterol and triglyceride levels, prothrombin time, hepatitis B serology (HbsAg, Anti-HBs and Anti-HBc), anti-HCV, HCV RNA polymerase chain reaction, autoantibodies (antinuclear, anti-smooth muscle, anti-mitochondrial) levels were measured.

The control group consisted of 16 healthy volunteers who were workers with no history of liver disease, drug usage, surgery or alcohol comsumption. Biochemical liver function tests and sonographic examination of the liver were within normal limits in this group. Calculation BMI was under taken in this group.

The Assay procedure of APPs

Patients with NASH and healthy subjects entered the study after obtaining their informed consent. Venous blood was collected in vacutainers without additive, allowed to clot for 30 min at room temperature and centrifuged at 3000 g for five min so that was obtained serum on the same day as liver biopsy. Serum aliquots were stored at-80° C until

biochemical analyses. Hemolysed samples were excluded. The serum levels of C-reactive protein (CRP), ceruloplasmin (Cp), ferritin, transferrin (Trf), alpha-1-acid glycoprotein (AAG), alpha-2-macroglobulin (AMG), alpha-1-antitripsin (AAT), albumin, haptoglobulin (Hpt) and lipoprotein (a) [Lp (a)] were determined by nephelometric method (Beckman Array 360 Protein System, USA).

Liver Histopathology

Liver biopsy was performed in all patients and stained with hemotoxylen-eosine and Sudan-black stains. All liver biopsies were interpreted by pathologists under coded identification without knowledge of the patient's clinical and biochemical data. Histologic grading and staging was performed using a modified scoring system based on a recent classification defined by Brunt (11). Hepatic inflammation was graded as follows: O = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe. Presence and absence of Mallory bodies was recorded in all liver biopsies. The degree of fibrosis was assessed using a 5 grade scale: O = none, normal connective tissues; 1 = minimal, foci of pericellular fibrosis; 2 = mild, perivenular and pericellular fibrosis in zone 3 and 2 regions; 3 = moderate, bridging and septal fibrosis; 4 = cirrhosis. The level of fatty infiltration was assessed and graded on a scale *of I to 3:1* = mild (10 % - 30 % of hepatocytes affected); 2 = moderate (30 % - 70 % of hepatocytes affected); 3 = severe (> 70 % of hepatocytes affected).

Statistical analysis

The clinical and laboratory characteristics of patients were expressed as medians (range), Or number (proportion) of the patients. All results are given as mean ± standard deviation (SD). Mean values were compared by unpaired student's t test for parametric data. The correlation among numerical data was analyzed by the Pearson correlation coefficient (r). To compare the ratios, chi-square test was used. All analyses were conducted using a computer based statistics software (SPSS for Windows 9.0, 1997, SPSS Inc. Chicago, USA). A p value less than 0.05 was accepted as statistically significant.

RESULTS

The main clinical and laboratory characteristics of the patients with NASH and controls are summarized in Table 1. Most of the patients (72%) were male. The median BMI in patients with NASH was 28.5 kg/m2. Eight patients (44%) were obese, four patients (22%) had diabetes mellitus, and 11 patients (60 %) had hyperlipidemia, with hypertriglyceridemia in 9 patients (82 %) of them. In the control group, 10 subjects (62 %) were male, and the mean age was 40 ± 10.3 years. The median BMI in this group was 27.3 kg/m^2.

Table 1. Clinical and laboratory characteristics of patients with NASH and controls.

	Mean (± SD) / number (%)	
	NASH Group	**Control group**
Total number	18	16
Age (years)	44 ± 7.1	40 ± 10.3
Gender (M / F)	13 / 5	11 / 5
BMI (kg/m^2)	28.5 ± 3.3	27.2 ± 4.1
Obesity	8 (44 %)	6 (33 %)
Diabetes Mellitus	4 (22 %)	-
Hyperlipidemia	11 (60 %)	-
Hypercholesterolemia	5 (28 %)	-
Hypertriglyceridemia	9 (50 %)	-
AST (U/L)	45.8 ± 17.9	22.9 ± 14.8
ALT (U/L)	88.9 ± 61.5	25.3 ± 15.2
AST / ALT> 1	4 (22 %)	-
ALP (U/L)	163.05 ± 42.6	151.6 ± 60.7
Total bilirubin (mg/dL)	0.92 ± 0.25	0.84 ± 0.15
Albumin (g/dL)	4.87 ± 0.13	4.52 ± 0.09
Prothrombin time (seconds)	12.39 ± 0.96	12.8 ± 1.02

The histologic data of the patients with nanalcoholic steatohepatitis are shown in Table 2. There was mild or moderate liver fatty infiltration in sixteen patients (89 %), with only two patients (11 %) having severe liver fatty infiltration. In patients with NASH minimal, mild or moderate hepatic inflammation was found in 11 %; 72 % and 17 %, respectively, but none of them had severe hepatic inflammation. Ballooning degeneration was found in 11 patients (61 %). Eight patients (44 %) had no fibrosis, whereas ten (56 %) had pericellular or perisinusoidal fibrosis (39 %) or periportal fibrosis (17 %). Howerer, no patients had bridging fibrosis, cirrhosis and MH bodies.

The serum levels of APPs measured in both the patients with NASH and controls are shown in

Table 2. Hepatic histopathologic findings of the patients with NASH (n = 18)

Histopathological features	Number (percent)
The level of liver fatty infiltration	
1	6 (33.3 %)
2	10 (55.5 %)
3	2 (11.1 %)
The degree of hepatic inflammation	
Minimal	7 (38.8 %)
Mild	8 (44.4 %)
Moderate	3 (16.6 %)
Severe	0
The degree of fibrosis	
0	8 (44.4 %)
1	7 (38.8 %)
2	3 (16.6 %)
3	0
4	0

Table 3. The mean serum C-reactive protein level (4.76 ± 2.04 mg/dl) in the patient group was significantly higher than that (1.66 ± 0.63 mg/dl) of the control group (p<0.0001). When the cut-off value of C-reactive porotein is taken as 5 mg/dL, no difference was found in the C-reactive porotein level according to the degree of hepatic steatosis and inflammation and liver fibrosis (p=0.34, p=0.14, p=0.4, respectively). Although the mean serum ferritin level in the patient group was higher than that of the control group (p = 0.001), the mean serum transferrin level in this group was not (p= 0.08). There was no relationship between the serum concentrations of ferritin and transferrin and the degree of hepatic steatosis and inflammation and liver fibrosis in patients with NASH. The mean serum levels of AAG, Hpt, AAT and Lp (a), which have high contents of sialic acid, in patients and controls were not significantly different (p = 0.62; p = 0.76; p = 0.72; p = 0.61, respectively). Also, no correlation was found between the four kinds of APPs and histopathologic findings of the liver in the patients with NASH. The mean serum level of AMG in patients was significantly higher than thad of the control group (p = 0.007), but there was no correlation between the serum concentrations of AMG and APPs and the degree of hepatic steatosis and inflammation or the stage of liver fibrosis in patients with NASH (p = 0.06, r = - 0.45; p = 0.42, r = - 0.20; p = 0.44, r = 0.19). The mean serum level of Cp in the patient group was higher than the control group (p = 0.01), but there was no correlation between the serum concentration and histopathologic features (steatosis, inflammation and fibrosis) of the liver in patients with NASH. In addition, no relationship was found betveen the serum concentrations of all APPs measured and the serum levels of aminotransferases, triglyceride and total cholesterol in patients with NASH.

Table 3. Serum acute phase protein levels of patients with NASH and control groups.

APPs	NASH (n = 36)	Control (n = 32)	p
CRP (mg/L)	4.76 ±2.04	1.66 ± 0.63	**0.0001**
Ferritin (ng/mL)	173.11 ± 91.04	81.87 ± 54.70	**0.001**
Transferrin (mg/dL)	299.83 ± 44.15	274.56 ± 36.20	0.08
Albumin(g/dL)	4.12 ± 0.13	4.72 ± 0.09	0.79
AAG (mg/dL)	89.47 ± 22.77	93.20 ± 20.65	0.62
AMG (mg/dL)	221.77 ± 65.38	167.81 ± 40.91	**0.007**
Haptoglobin (mg/dL)	112.26 ± 84.29	104.84 ± 56.79	0.76
Ceruloplasmin (mg/dL)	41.60 ± 13.19	31.95 ± 6.72	0.01
AAT (mg/dL)	169.94 ± 45.80	161.06 ± 24.61	0.72
Lp (a) (mg/dL)	13.06 ± 9.61	12.01 ± 7.50	0.61

CRP: C-reactive protein; AAG: Alpha-1 acid glycoprotein; AMG: Alpha-2 macroglobulin; AAT: Alpha-1 antitrypsin; Lp(a): Lipoprotein (a)

DISCUSSION

Nonalcoholic steatohepatitis is an asymptomatic disease in a large proportion (48%-100%) of patients. Laboratory features of NASH are nondiagnostic. Although mild to moderate elevations of serum aminotransferase levels are present in 70%-100% of patients with NASH, there is no significant correlation between the degree of serum aminotransferase elevation and the histologic features. Elevated aminotransferase levels cannot be used to distinguish benign steatosis from NASH because steatosis alone can cause elevation, even without evidence of overt cellular injury on the liver biopsy (12-15).

The C-reactive protein is an important test to diagnose and to monitor patients with inflammatory conditions such as inflammatory bowel disease, acute pancreatitis and hepatocellular carcinoma (16-18). Since NASH is an inflammatory condition of liver, an increased C-reactive protein level may be expected. Gupto et al (19) reported that the expression of C-reactive protein is upregulated in alcohol-induced acute liver injury and serial measurements of serum C-reactive protein are useful in assessing the clinical activity of alcoholic hepatitis. Recently, it was reported that

C-reactive protein levels increase in parallel with the progression of chronic liver disease such as chronic hepatitis and liver cirrhosis (20,21). In this study, we found that the serum concentrations of C-reactive protein in patients with NASH were significantly increased. This finding may be helpful in the diagnostic work-up of patients with fatty liver disease. To clarify whether C-reactive rotein is useful in assessing the hepatic damage in patients with NASH, further studies including only steatosis cases and a larger number of patients are required.

Isolated and nonspecific increases in serum ferritin levels are frequently found in the absence of iron overload and are associated with inflammation, liver necrosis and alcohol abuse (22). Bacon et al. (23) reported abnormal results of serum transferrin and ferritin levels in 18 (58%) of 31 patients with NASH, but none of their patients had histologic evidence of hemochromatosis. Subsequent studies of patients with NASH have shown increased serum ferritin levels in 53%-62% and elevated transferrin saturation in ll%-22% (15,24). A high serum ferritin level associated with increased liver iron concentration but normal transferrin saturation is typical of a polymetabolic syndrome that a French group has suggested is a new iron overload entity, possibly related to the insulin resistance syndrome (25,26). Fargion et al. (27) documented that hyperferritinemia with normal transferrin saturation is a hallmark of a glucose/lipid metabolism disorder and that patients with increased serum ferritin and normal transferrin saturation, a mild iron overload and multipi coexisting metabolic alterations are at high risk of developing NASH. In addition, they observed no correlation between liver iron concentration and histological grade and stage within a group of patients with NASH. The findings in this study of high serum ferritin and normal transferrin saturation in patients with NASH are concordand with the results of previous studies. The increase in ferritin level may be due to a synergistic induction of synthesis due to increased iron stores and hepatic steatosis. It is also possible that an increase in ferritin occurs as a result of acute phase response.

As a new finding, increased serum ceruloplasmin and AMG levels were determined in patients with NASH. The importance of this finding as a part of acute phase reaction is unclear. Ceruloplasmin exhibits oxidase activity. Also, oxidation of Fe^{2}* to Fe^{3+}, catalysed by ceruloplasmin, may be important for the binding of iron to transferrin. Increased serum Cp concentration in the patients may due to high serum ferritin level with normal transferrin saturation (28).

There have been several reports that the serum concentrations of APPs with high sialic content [Lp(a), AAG, Hp, AAT] alter together in many conditions (29,30). Min et al. (31) suggested that although there was no difference between the serum concentration of both Lp(a) and APR of patients with hypoalbuminaemia and those with normoalbuminaemia, there was a significant difference in the serum AAT and Hp concentration. Normal serum concentrations of Lp(a), AAG, Hpt and AAT in our patients could be explained by different kinetics of acute phase reactants, or a different time of increase or decrease. Also, these substances may not have a role in the pathogenesisofNASH.

In conclusion, increased serum C-reactive protein, ferritin, ceruloplasmin and AMG concentrations may be helpful in assessing patients at risk of NASH. In this study, the fact that no relationship between APPs and liver histology was observed, is probably due to the small number of cases. Noninvasive simple parameters that reflect the degree of inflammation and fibrosis of the liver in patients with NASH would facilitate improved understanding and treatment of the disease.

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