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Evaluation of C-Reactive Protein Levels In The Differentiation Of Non-Alcoholic Steatohepatitis and Simple Liver Steatosis

Non-Alkolik Steatohepatit ve Basit Karaciğer Yağlanması Ayrımında C-Reaktif Protein Düzeylerinin Değerlendirilmesi

ABSTRACT

Objective:

Non-alcoholic fatty liver disease (NAFLD) is a broad-spectrum disease that has increased in recent years due to increased sedentary life and obesity. It was aimed to determine C-reactive protein (CRP) levels, its association with simple steatosis and non-alcoholic steatohepatitis (NASH) and its diagnostic value in this study.

Methods:

A total of 165patients who had a diagnosis of fatty liver disease (simple steatosis group and NASH group) and 99 healthy controls without liver disease were included in the study. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, CRP levels were evaluated and ultrasonographic evaluation of liver was performed in all groups. Histopathological evaluation was performed by biopsy in 65 patients who were thought to have NASH.

Results:

AST and ALT values were found to be significantly higher in the NASH group than the other groups. CRP levels were detected lowest in control group and highest in NASH group ($p < 0.001$). AST values were also significantly higher in patients with fibrosis grade 3-4 compared to the control group.

Conclusion:

Our study showed that CRP level is a suitable marker for differentiation of simple steatosis and NASH.

Key Words:

Non-alcoholic fatty liver disease, C-reactive protein, Non-alcoholic steatohepatitis

ÖZ

Amaç:

Non-alkolik yağlı karaciğer hastalığı (NAFLD), artan sedanter hayat ve obezite nedeniyle son yıllarda artış gösteren geniş spektrumlu bir hastalıktır. Bu çalışmada, C-reaktif protein (CRP) düzeylerinin, basit steatoz ve non-alkolik steatohepatit (NASH) ile ilişkisini ve tanısal değerini belirlemek amaçlanmıştır.

Metodlar:
Yağlı karaciğer hastalığı tanısı alan 165 hasta (basit steatoz grubu ve NASH grubu) ve karaciğer hastalığı olmayan 99 sağlıklı kontrol çalışmaya dahil edildi. Tüm gruplarda aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), total bilirubin, direkt bilirubin, CRP düzeyleri değerlendirildi ve karaciğerin ultrasonografik değerlendirmesi yapıldı. NASH olduğu düşünülen 65 hastada biyopsi ile histopatolojik değerlendirme yapıldı.

Bulgular:
AST ve ALT değerleri NASH grubunda diğer gruplara göre anlamlı olarak yüksekti. CRP düzeyleri kontrol grubunda en düşük, NASH grubunda en yüksek saptandı ($p < 0.001$). Fibrozis derecesi 3-4 olan hastalarda kontrol grubu ile kıyaslandığında, AST değerinin anlamlı düzeyde yüksek olduğu saptandı.

Sonuç:
Çalışmamız, CRP düzeyinin basit steatoz ve NASH ayrımı için uygun bir belirteç olduğunu göstermiştir.

Anahtar Sözcükler:
Non-alkolik yağlı karaciğer hastalığı, C-reaktif protein, Non-alkolik steatohepatit

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a broad spectrum between simple fatty to non-alcoholic steatohepatitis (NASH). NASH, a more serious form of the disease, can progress to cirrhosis and hepatocellular carcinoma (1,2). In recent years, with the epidemic of obesity, NAFLD has been increasing rapidly all over the world (3). With the prevalence of 17-33% in Western countries, NAFLD has been reported to be the most common liver disease in the world, (4). The leading cause of abnormal liver function tests in USA is also NAFLD, with a rate of 14-24% in the general population (5,6). Since it is associated with dyslipidemia, hypertension, insulin resistance and obesity, it may be considered as the liver component of metabolic syndrome (7).

CRP (C-reactive protein), an acute phase reactant protein, was found to be associated with inflammation and fatty liver in many studies (8,9). It is known that low-level inflammation plays a role in hypertension, cardiovascular diseases, metabolic syndrome, type 2 diabetes and some cancers (10). The association of increased CRP levels and NAFLD has been demonstrated in some studies (11,12). The stage of NAFLD is the key factor in determining the prognosis and making treatment decision. Thus, to distinguish simple steatosis from steatohepatitis is important and a non-invasive strategy is needed to detect all stages of NAFLD. The importance of evaluating serum markers as a noninvasive test to differentiate simple steatosis from NASH has been discussed in some clinical studies (13,14). However, a definitive serum marker has not yet been established in predicting the severity of NAFLD.

It was aimed to determine C-reactive protein (CRP) levels, its association with simple steatosis and non-alcoholic steatohepatitis (NASH) and its diagnostic value in this study.

MATERIAL and METHODS

Patients:

A hundred and sixty-five patients who had a diagnosis of fatty liver disease between June 2017 and June 2018 in our outpatient clinic formed the study group. A hundred healthy controls without liver disease were also included.

Study design:

The study groups were as follows:

Group 1 - Healthy group: This group included patients who admitted to the outpatient clinic with nonspecific gastrointestinal complaints (dyspepsia, reflux and irritable bowel syndrome) without any liver disease.

Group 2 - Simple steatosis group: this group included patients who were found to have fatty liver with USG, who were with normal liver function tests and asymptomatic for liver disease.

Group 3 - NASH group: Patients with hepatic steatosis on USG, biochemical examination of liver dysfunction, no other pathology to explain liver dysfunction, and liver biopsy with the diagnosis of NASH due to liver dysfunction and diagnosed as NASH.

AST, ALT, total bilirubin, direct bilirubin, CRP levels were measured in all groups and ultrasonographic evaluation was performed. CRP values between 0-5 mg/dl were considered normal.

Histopathological evaluation was performed by biopsy in 65 patients with suspected NASH. Histopathological evaluations were performed by an experienced pathologist and biopsy identified nonalcoholic steatohepatitis with macrovascular fattening in more than 30% of hepatocytes and detection of aneurysm and / or necrosis in hepatocytes. Fibrosis was classified between 0 and 4 according to the modified Brunt score.

Exclusion criteria:

Patients who had non-adipose findings on ultrasound were excluded from the study. Viral hepatitis was excluded by HbsAg, Anti-HCV, Anti HbcIGG and Anti Hbs. ANA, AMA, ASMA and anti-LKM tests were negative to rule out autoimmune hepatitis. Patients under the age of 18, patients with alcohol use over 20 grams per day, patients with continuous drug use, patients with cirrhosis, patients with gastrointestinal bypass, cholestatic liver disease, patients with obstructive jaundice and pregnant women were excluded from the study. The study was performed in accordance with the Declaration of Helsinki and the local ethics committee had given its approval (2021-289). All patients were informed about the study and gave their informed constent.

Statistical analysis

IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) was used to analyze data. Descriptive statistics were given as number of units (n), percentage (%), mean ±

standard deviation (x ± ss). A p-value below 0.05 was considered statistically significant. The normal distribution of the numerical variables was evaluated by the Shapiro Wilk normality test and Q-Q graphs. Comparisons between the groups were made with paired-samples t test in variables with normal distribution. The relationship between categorical variables was examined by exact method of Chi-Square test. Bonferroni corrected two-ratio z test was used for intra-group comparisons, if the chi-square test was previously found to be significant.

RESULTS

A total of 264 patients (99 patients in group 1, 100 patients in group 2 and 65 patients in group 3) were included in the study. The mean age was 38.9 in the control group, 51.8 in the simple steatosis group and 46.2 in the NASH group (p <0.001). There was no difference between the groups in terms of gender distribution. The demographic characteristics of the groups were summarized on table I.

Table I: Comparison of demographic characteristics of study groups.

	Control (n=99)	NAFLD (n=100)	NASH (n=65)	p
Age (mean±SD)	38.9±11.9	51.8±10.8	46.2±12	<0.001[a,b,c]
Sex (n, %)				
Male	44 (44.4)	37 (37)	33 (50.8)	0.207
Female	55 (55.6)	63 (63)	32 (49.2)	

NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis,

a: Control-NAFLD; b:Control-NASH; c: NAFLD-NASH.

AST and ALT values were significantly higher in the NASH group than the other groups. In the simple steatosis group, the mean AST-ALT values were normal but higher than the normal group. Since bilirubin values were evaluated only in simple steatosis and NASH groups, statistical data were examined between these two groups. Mean bilirubin levels were found to be similar between simple steatosis and NASH groups.

CRP levels were found to be lowest in the normal group and highest in NASH patients and the differences were found to be statistically significant (p <0.001). Table II summarizes the laboratory values by groups.

Table II: Comparison of laboratory findings of study groups.

	Control		NAFLD		NASH		p
	n	mean±SD	n	mean±SD	n	mean±SD	
AST	99	18.2±4.8	100	22.9±11.8	65	61.0±38.8	<0.001[a,b,c]
ALT	99	18.2±8.3	100	30.3±22.8	65	102.5±91.9	<0.001[a,b,c]
T.BIL			100	0.67±0.31	65	0.85±0.78	0.044[c]
D.BIL			100	0.28±0.24	65	0.33±0.40	0.146
CRP	99	0.32±0.47	100	0.57±0.66	41	0.77±1.27	<0.001[a,b]

NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, T.BIL: Total Bilirubin, D.BIL: Direct Bilirubin, CRP: C-Reactive Protein, SD: standart deviation,

a: Control-NAFLD; b: Control-NASH; c: NAFLD-NASH.

Biopsy revealed 9 patients with stage 0, 45 patients with stage 1-2 and 11 patients with stage 3-4 fibrosis. When the laboratory values were compared between the groups according to fibrosis, AST levels were significantly higher in patients with fibrosis grade 3-4 when compared to the control group (p = 0.049). However, no significant difference was determined between CRP levels and fibrosis (Table III).

Table III: Comparison of laboratory findings according to fibrosis between study groups.

	Fibrosis						
	0		1&2		3&4		p
	n	Mean ±SD	n	Mean ±SD	n	Mean ±SD	
AST	9	51.8±53.1	45	58.5±33.7	11	78.6±44.0	0.049[a]
ALT	9	140.3±207.0	45	99.3±58.5	11	84.6±54.6	0.627
TBIL	9	0.73±0.29	45	0.72±0.30	11	1.45±1.73	0.226
DBIL	9	0.28±0.10	45	0.26±0.12	11	0.66±0.90	0.128
CRP	4	0.74±0.83	29	0.82±1.48	8	0.58±0.43	0.962

AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, T.BIL: Total Bilirubin, D.BIL: Direct Bilirubin, CRP: C-Reactive Protein, SD: standart deviation,

a: fibrosis 0-3,4.

In terms of adipose grade on USG, no significant difference was observed between NASH and simple steatosis (Table IV).

Table IV: Characteristics of liver steatosis grade between study groups.

USG	Control n (%)	NAFLD n (%)	NASH n (%)	p
G0	99 (100)	0 (0)	3 (4.6)	
G1	0 (0)	33 (33)	19 (29.2)	
G2	0 (0)	57 (57)	32 (49.2)	<0.001[a,b]
G3	0 (0)	9 (9)	11 (16.9)	
G4	0 (0)	1 (1)	0 (0)	

NAFLD: Non-alcoholic fatty liver disease, NASH: Non-alcoholic steatohepatitis, USG: ultrasonography, G: Grade,

a: Control-NAFLD; b: Control-NASH; c: NAFLD-NASH.

DISCUSSION

It is very important to differentiate NASH because it can cause cirrhosis in patients with NAFLD. Nowadays, the gold standard for separating NASH from simple steatosis is liver biopsy which is an invasive method. Several biomarkers have been studied in the literature to reduce the need for liver biopsy, but no definitive marker has yet been identified (15).

In many studies, it was shown that there was a relationship between NAFLD and low-grade inflammation (16-18). It is known that CRP level is an independent marker in cardiovascular diseases where low inflammation takes the lead in pathogenesis as well as metabolic abnormalities (19,20). In clinical studies, CRP levels were found to be related to metabolic syndrome and its components. Although CRP production mainly occurs in the liver, fatty tissue, especially visceral fatty tissue, has an important role in CRP production (11). In our study, CRP levels were found to be higher in patients with simple steatosis and NASH compared to controls and the difference was significant. The relationship between CRP level and NAFLD was first demonstrated by Park et al. In this study, CRP was found to be an independent risk factor for NAFLD (21). In many subsequent studies, results supporting this finding were obtained (11,12,22-26).

In our study, no significant association was found between CRP levels and the degree of fibrosis detected by biopsy. In the study of Oruç et al., similarly to our study, serum CRP levels were found to be increased in steatohepatitis and fatty liver when compared to the control group, but no significant difference was found between the levels of simple steatosis and steatohepatitis (23). In 2 other studies, serum CRP levels were also increased in these patients, but there was no correlation between CRP and fatty liver's stage (8,27).

Looking at the pathogenesis of NAFLD, it seems that there are still unclear points. Oxidative stress and insulin resistance are considered as 2 major mechanisms in the pathogenesis of NAFLD, both of which are associated with high CRP levels. Proinflammatory cytokines, synthesized by macrophages in fatty tissue include tumor necrosis factor, CRP, interleukin (IL)-6 and IL-8. These cytokines disrupt the insulin signaling system and cause insulin resistance (18,28). Insulin resistance increases fatty acids in the liver, leading to the accumulation of fat in the liver (29). The other mechanism, oxidative stress, acts independently of liver inflammation induced by cytokines. Accumulation of triglycerides in the liver increases oxidative stress and further inflammation results in liver damage (6). It has also been reported that antioxidant capacity is low in patients with NAFLD (30). CRP levels were higher in patients with low antioxidant capacity (31). Malhi et al. showed that inflammation and apoptosis due to free fatty acids are key factors in NASH progression (32).

In a study in which patients were followed for more than 30 years, fatty liver stage was determined by ultrasound and a relationship was found between NAFLD stage and CRP levels (33). In another study in which 4138 healthy men were followed up for 7 years, it was determined whether the risk of NAFLD increases or not in those with high CRP levels and the NAFLD development risk was found to increase as CRP levels increased. They even stated that these healthy people may need to be monitored for NAFLD development (34).

In our study, control group was significantly younger than the other groups. It is known that the development of NAFLD and especially the development of NASH is a process that lasts for years, so it is expected that these patients will be older (35).

There are some limitations in our study. The diagnosis of fatty liver was made by ultrasound and biopsy was not performed in patients whose liver test was not high. If the study was conducted with a larger number of patients, it could have made the intergroup evaluation stronger.

In our study, CRP levels were found to be significantly higher in the simple steatosis and NASH group compared to the control group. Therefore, we think that CRP level alone is a good marker for NAFLD. However, we do not recommend the use of CRP as an indicator of fibrosis since we cannot find a relationship between fibrosis and CRP level.

CONCLUSION

Differentiation of simple steatosis and NASH in NAFLD patients is important to determine prognosis and treatment method. Liver biopsy is the gold standard in the evaluation of these patients. Since liver biopsy is an invasive and expensive procedure, there is a search for a specific non-invasive biomarker to differentiate simple steatosis and NASH. The data show that CRP level is an appropriate marker for differentiating NASH from simple steatosis. However, studies with different markers are needed to determine the stage of fibrosis.

Ethics Committee Approval:
This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Local ethics committee İzmir Katip Çelebi University (approval number: 2021/0289).

Informed Consent:
All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Author Contributions:
Concept – S.G., B.P.; Design – S.G., H.A.; Supervision – S.G., B.P., H.A.; Data Collection and/or Processing – S.G., B.P.; Analysis and/ or Interpretation – S.G., B.P., H.A.; Literature Search - S.G., B.P., H.A.; Writing Manuscript - S.G., B.P., H.A.; Critical Review - S.G., B.P., H.A.

Conflict of Interest:
The authors have no conflict of interest to declare.

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