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Is myeloperoxidase level in ascites a predictive factor for spontaneous bacterial peritonitis?

Assitdeki myeloperoksidaz düzeyi spontan bakteriyel peritonit için prediktif bir faktör müdür?

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Abstract

Aim: Myeloperoxidase is mainly found in the azurophilic granules of human polymorphic nucleated neutrophils, and it is one of the enzymes that has a role in the host defense. Deteriorations in both humoral and cellular immunity, and decreases in the filtration functions of liver and the antimicrobial capacity of ascites fluid increase the risk of spontaneous bacterial peritonitis in patients with cirrhosis. The aim of this study is to evaluate if there is a difference in the serum-ascites myeloperoxidase levels of patients with ascites due to liver cirrhosis and other non-cirrhotic diseases, which are clinical conditions that spontaneous bacterial peritonitis is frequently seen.

Materials and Methods: This study included a total of 51 patients (28 males and 23 females) with ascites due to liver cirrhosis and non-cirrhotic diseases, and 16 healthy subjects (8 males and 8 females). Serum-ascites albumin gradient was calculated, and myeloperoxidase and leukocyte count were determined in both blood and ascites fluid.

Results: Serum-ascites albumin gradient, and blood leukocyte count were statistically similar between patients with ascites due to liver cirrhosis and non-cirrhotic diseases. There was no significant difference between serum myeloperoxidase levels, age and sex of patients with cirrhosis due to liver cirrhosis and non-cirrhotic diseases, and control group subjects. Myeloperoxidase levels in ascites of patients with liver cirrhosis were significantly lower than patients with non-cirrhotic diseases.

Conclusion: Since myeloperoxidase has an important role in immune system, we concluded that decreases in myeloperoxidase might have a role in increased spontaneous bacterial peritonitis in liver cirrhosis.

Keywords: Myeloperoxidase; Ascites; Cirrhosis.

Öz

Amaç: Myeloperoksidaz başlıca insan polimorfnükleer nötrofillerin azurofilik granüllerinde yer alıp, konakçı savunmasında rol alan enzimlerinden biridir. Sirozlu hastalarda hem humoral ve hem de hücresel immünitedeki bozukluk, karaciğer filtrasyon fonksiyonundaki azalma ve assit sıvısının antimikrobiyal kapasitesinin azalması spontan bakteriyel peritonit riskini artırmaktır. Bu çalışmanın amacı spontan bakteriyel peritonitin sık görüldüğü karaciğer sirozu ve karaciğer sirozu dışı hastalıklara bağlı assit gelişen bireylerdeki serum-assit myeloperoksidaz düzeyi arasında bir fark olup olmadığını araştırmaktır.

Gereç ve Yöntemler: Çalışmaya karaciğer sirozu ve karaciğer sirozu dışı hastalıklara bağlı 28' i erkek ve 23'ü kadın toplam 51 assitli birey ve 8'i erkek, 8'i kadın toplam 16 sağlıklı birey olmak üzere üç grup dahil edildi. Serum-assit albümin gradiyenti hesaplandı, kan ve assit sıvısında myeloperoxidaz ve beyaz küre bakıldı.

Bulgular: Karaciğer sirozu ve karaciğer sirozu dışı nedenlerden gelişen assitli bireylerin serum-assit albümin gradiyentleri, kan beyaz küre sayısı yönünde istatistiksel olarak anlamlı bir ilişki bulunamadı. Karaciğer sirozu ve karaciğer siroz dışı nedenlerden dolayı gelişen assitli bireyler ve kontrol grubu bireylerin serum myeloperoksidaz düzeyleri, yaş ve cinsiyet yönünde de anlamlı bir ilişki bulunamadı. Karaciğer sirozuna bağlı gelişen assitdeki myeloperoksidaz düzeyi, karaciğer sirozu dışı nedeniyle oluşan assitteki myeloperoksidaz düzeyinden anlamlı daha düşük bulundu.

Sonuç: Sonuç olarak myeloperoksidazın immün sistemde önemli bir rolü olması nedeniyle, myeloperoksidaz düşüklüğünün karaciğer sirozunda spontan bakteriyel peritonitinin artışının bir nedeni olabileceğini düşündük.

Anahtar Kelimeler: Myeloperoksidaz; Assit; Siroz.

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INTRODUCTION

Eighty percent of causes of ascites are cirrhosis, and remaining 20% are non-cirrhotic factors. Determining the specific etiology of ascites is highly important for designing the treatment. The serum ascites albumin gradient is rather convenient in the differential diagnosis of portal hypertension, but does not determine the specific etiological diagnosis (1).

Ascites infection without a detectable and surgically treatable intra-abdominal infection focus is called spontaneous bacterial peritonitis (SBP) (2, 3). SBP is a frequent and serious complication of liver cirrhosis. Gram-negative aerobic bacteria and non-enterococcal streptococcus species are the most frequently isolated bacteria from the ascites of these patients (4). Bacteria can enter into systemic circulation because of the inadequacy of cellular and humoral immunity in cirrhotic patients, and disseminate to ascites when bacteremia advances. Some of the mechanisms in SBP are intestinal bacterial transmission, functional deteriorations of the reticuloendothelial system, acute gastrointestinal system (GIS) hemorrhage, and decreases in serum complement levels (5, 6). SBP is observed in 10-30% of hospitalized patients with cirrhosis (3). And, it is still a fatal complication despite early diagnosis and targeted antibiotherapy against the etiological microbial agent (7).

Myeloperoxidase (MPO) is an enzyme in mammalian neutrophil granules, which plays an important role in the elimination of bacteria after phagocytosis. MPO enzyme that's secreted from activated polymorphic nuclear leukocytes and monocytes in the inflammation area plays an important role in the formation of oxidants by the human immune system (8, 9). MPO exhibits antibacterial efficiency in an environment, which H_2O_2 is together with thiocyanate ions or halogen ions. This enzyme has 3 subtpyes as I, II, and III (10, 11).

The aim of this study was to evaluate whether there is a difference between myeloperoxidase levels of ascites fluid and serum of patients who had ascites due to liver cirrhosis and other non-cirrhotic causes.

MATERIALS and METHODS

Cumhuriyet University Faculty of Medicine Ethical Committee approved the study at 04.04.2007 with approval number of 4/3. This study is a case-control cross-sectional study.

Patients with ascites due to liver cirrhosis and non-cirrhotic diseases were recruited during a one-year period at Cumhuriyet University Hospital Internal Medicine Department. Patients were informed of the study protocol, and their consents were taken. Of a total of 67 patients (36 males, 31 females), 20 were cirrhotic patients (10 males, 10 females). Of these patients, 12 had Hepatitis B, 6 had Hepatitis C, and 2 had cryptogenic liver cirrhosis. Remaining 31 patients (18 males, 13 females) were non-cirrhotic patients, and 24 had cardiac failure, 6 had nephrotic syndrome, and 1 had Budd-Chiari syndrome.

The control group was formed by age and sex matched 16 healthy individuals (8 males, 8 females) from the same neighborhood, whom were from similar geographical and cultural background.

Exclusion criteria were as follows:
1. Having acute peritonitis at the recruitment period
2. Having exudative paracentesis fluid
3. Having the acute disease
4. Having fever
5. Being on an antibiotic treatment for any reason
6. Having a coagulopathy

Histories were taken and physical examinations were performed initially. Patients with cirrhosis, whom were diagnosed according to hepatobiliary ultrasonography, endoscopic evaluations, and liver biopsy, and patients with non-cirrhotic ascites were all undergone paracentesis. Area of paracentesis was cleaned by iodine solutions, and sterile needles were used.

Twenty milliliters of ascites fluid were taken during paracentesis for routine analyses. 5 ml of this fluid was used for biochemical analyses, and another 5 ml for microbiological analyses. Total white blood cells and PMNLs were counted from ascites fluid. Remaining ascites fluid and blood samples taken on the same day were anticoagulated with heparin, and after centrifuged they kept in 1.5 cc Eppendorf tubes on -80°C, at the Research Center of Cumhuriyet University Faculty of Medicine (CUTFAM).

Total protein amount, leukocyte count-leukocyte formulation (PMNLs and lymphocyte count) and LDH levels were determined at the ascites fluid. Classical determinations of transude and exudate was performed. Patients with transude characterized ascites fluid were included in the study. PMNLs of these patients were below 250 /mm^3. Patients with hemorrhagic ascites fluid were excluded. And, serum-ascites albumin gradient was calculated.

Serum and ascites albumin levels were determined by using a Synchron LX20 autoanalyzer with the Synchron System albumin kit and colorimetric method. White blood cells were counted by a Coulter Gen-S System equipment and Coulter Scatter PAK kit and laser method. MPO levels in ascites fluid and plasma were determined by using a Myeloperoxidase Activity Assay kit that manufactured by Northwest Life Science Specialties LLC, and according to NWLSSTM The Myeloperoxidase activity determination method by ELISA, which defined by Weiss and coworkers (1982).

Statistical Analyses

Statistical analyses in this study were performed with IBM SPSS statistics version 22.0 and by using Kruskall-Wallis test, Mann-Whitney U test, and Chi-square test. Data were presented by mean ± standard deviation, frequency, and percent in the tables. A type-I error level of 5% was used for the analyses.

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RESULTS

A total of 67 cases was recruited for the study. They were separated into three groups. The first group was formed of 20 patients with liver cirrhosis, 10 (50%) of them were males and 10 (50%) were female. The mean age of this group was 61.3±2.51 years (45-75 years). The second group was formed of 31 patients with ascites due to other causes than cirrhosis, 18 (58.1%) were male and 13 (41.9%) were female. The mean age of this group was 60.38±13.13 years (45-75 years).The third group was formed of 16 controls, 8 (50%) were males and 8 (50%) were females. The mean age of this group was 57.18±8.29 years (40-70 years).

There were no statistically significant differences between age and sex distribution of patients with cirrhosis, patients without cirrhosis, and controls (p>0.05) (Table 1).

No significant difference was found between the MPO activities of the groups (p>0.05), but MPO activities of patients with ascites due to cirrhosis and non-cirrhotic diseases were significantly different (p<0.05). MPO activity in the ascites fluid due to liver cirrhosis was lower (Table 2).

There were no significant differences between the serum-ascites albumin gradient and blood leukocyte levels of first and second groups (p>0.05) (Table 3).

No significant differences were found between the serum and ascites MPO levels, serum-ascites albumin gradient, and serum leukocyte levels of males and females with ascites due to liver cirrhosis (p>0.05) (Table 4).

Similarly, no significant differences were found between the serum and ascites MPO levels, serum-ascites albumin gradient, and serum leukocyte levels of males and females with ascites due to causes other than liver cirrhosis (p>0.05) (Table 5).

Table 1. The descriptive statistics of patients according to the groups

Groups	Age(years)	Male n(%)	Female n(%)	Total n(%)
Cirrhotic	61.30±2.51	10 (50.0)	10 (50.0)	20 (100)
Non-cirrhotic	60.38±13.13	18 (58.1)	13 (41.9)	31 (100
Control	57.18±8.29	8 (50.0)	8 (50.0)	16 (100)
Result		KW=2.18	x^2=0.4	
		p=0.336	p=0.804	
		p>0.05	p>0.05	

Table 2. The comparison of serum-ascites MPO activity according to the groups

Groups	Number of patients (n)	A-MPO (U/mL)	S-MPO (U/mL)
Cirrhotic	20	193.37 ± 55.32	174.33 ± 49.25
Non-cirrhotic	31	225.34 ± 53.50	201.18 ± 56.64
Control	16	-	201.18±56.64
Result		KW=2.59	p=0.007
		p=0.274	p<0.05
		p>0.05	

A-MPO, ascites myeloperoxidase level; S-MPO, serum myeloperoxidase level

Table 3. The comparison of serum-ascites albumin gradient and white blood cells according to the groups

Groups	Number of patients (n)	WBC(/mm^3)	SAAG(mg/dL)
Cirrhotic	20	8740.00 ± 3187.87	1.30 ± 0.37
Non-cirrhotic	31	8161.29 ± 4026.13	1.32 ± 0.40
Result	-	p=0.498	p=0.961
		p>0.05	p>0.05

WBC, White blood count; SAAG, serum ascites albumin gradient

Table 4. The comparison of serum-ascites MPO levels, albumin gradient and white blood cells according to sex in the patients with *ascites caused by cirrhosis*

Parameters	Male	Female	P value
S-MPO(U/ml)	153.38± 58.63	195.29±26.58	p=0.131
A-MPO(U/ml)	196.35±32.93	190.39±39.11	p=0.520
SAAG(mg/dl)	1.24±0.40	1.36±0.35	P=0.544
WBC(/mm^3)	9080.00±3305.14	8400.00±3205.20	p=0.545

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Table 5. The comparison of serum-ascites MPO levels, albumin gradient and white blood cells according to sex in the patients with *ascites caused by non-cirrhosis*

Parameters	Male	Female	P value
S-MPO U/ml)	193.03±52.23	210.08±63.03	p=0.645
A-MPO (U/ml)	227.44±55.77	222.44±52.28	p=0.968
SAAG(mg/dl)	1.33±0.40	1.32±0.41	p=0.936
WBC (/mm ^{3})	8794.44±4147.78	7284.61±3836.41	p=0.280

DISCUSSIONS

Myeloperoxidase is secreted from the azurophilic granules of PMNLs, and this enzyme causes deteriorations in tissues (12, 13). MPO plays a basic role in the formation of oxidants by the immune system during the oxidative burst process. Particularly, a MPO-H_2O_2-Cl system of activated phagocytes is suggested to have an important role in tissue damage due to inflammation (e.g. atherosclerosis, glomerulosclerosis, and ischemia-reperfusion damage), and determination and quantification of specific biomarkers of this oxidized system might reflect the disease stage (14,15).

Chronic portal hypertension causes significant changes in the vascular anatomy and gastrointestinal microcirculation. Anatomical and physiological changes in the gastrointestinal system (GIS) due to portal hypertension negatively affect the prognosis of the patients (16). In our cases, 90% of them had portal hypertension. Serum-ascites albumin gradient were calculated ≥1.1 in these patients, and no significant difference was found between the groups. Leukocyte, PMNL, total protein, and LDH were evaluated in the ascites fluid to determine spontaneous bacterial peritonitis. Ascites of all of our patients were transudate. Exudates were excluded. There was no significant difference between the blood leukocytes of the three groups.

Hashimato et al. evaluated the effects of PHT on the intestinal mucosa, and they showed that increased bacteria in the intestinal lumen of patients with cirrhosis were shifted from the intestinal lumen to lymph nodes, and caused spontaneous infections (17).

Wang et al. showed that levels of bowel bacteria are increased in rats with portal venous obstruction, and there is an association between this condition and gastrointestinal motility. MPO from the neutrophils, which were activated in response to bacterial translocation, exerts bactericidal activity by catalyzing H_2O_2 and Cl ions to hypochlorous acid. This hypochlorous acid is a strong radical, which have a toxic effect on the tissue. Increased bacterial translocation due to deterioration of hemodynamic circulation, and consecutive neutrophil chemotaxis explain the high levels of MPO in the portal hypertension (18).

Guvenc et al. found that MPO levels were increased in the small intestine and colon tissues of mice with PHT when compared to control group, but the difference were not statistically significant (19).

Many clinical and experimental studies were conducted to define the mechanisms that cause distortions in the barrier mechanism of intestinal mucosa, and translocation of local bacteria in PHT (20,21). Chronic PHT is characterized by pathological increments in the portal pressure and formation of porto-systemic collaterals. PHT increases microvascular intestinal blood flow, but this is associated with 41-51% decrease in the intestinal arterial pressure, which eventually causes hypoperfusion and hypoxemia (22). Mucosal hypoperfusion, mucosal hypoxia and structural changes due to mucosal xanthine oxidase (XO) activation are observed in the bowel mucosa with internal organ vasodilation (23). Free radicals from the oxygen act as the pioneers of increased intestinal permeability and initiate the mechanism that secretes reactive oxygen metabolite complexes that kills the normal cells and connective tissue (24). Continuing oxidative stress cause constant cellular lipid peroxidation and death (25).

Schimpl et al. found significant bacterial translocation, intestinal mucosal lipid peroxidation and increased mucosal MPO activity from PMNLs in their study of mice with chronic PHT and fully obstructed bile duct. Bacterial translocation in these mice with chronic PHT and fully obstructed bile duct was found to be significantly associated with intestinal mucosal lipid peroxidation and activation of PMNLs. Competitive XO inhibitor, allopurinol, significantly decreased bacterial translocation, intestinal mucosal lipid peroxidation and mucosal MPO activity in mice with chronic PHT and fully obstructed bile duct. The clinical appropriateness of this study was contradictive, because mice and humans are two distinct regarding XO activities in liver and intestine (26).

Exploration of bacterial translocation, which is the most important step of spontaneous ascites infections in mouse models of experimental cirrhosis and spontaneous peritonitis, has overruled the transmigration theory (27). Major mechanisms needed for bacterial translocation in animal models are excess bacterial growth in the intestine, increased permeability of the intestinal mucosal barrier, failures in immune response of the host, and self-related factors of bacteria (28).

In a study of Bagci et al. SBP was observed in 20.58% of the hospitalized patients with ascites. Decreases of total protein of ascites fluid (lower than 1 gr/dl), previous ascites infection, and previous gastrointestinal bleeding increases the risk of spontaneous ascites infection. Moreover, increased serum total bilirubin levels may be

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a predictor of spontaneous ascites infection in patients with cirrhosis and ascites (29).

In our study, we evaluated the MPO levels in ascites fluid and serum due to liver cirrhosis and non-cirrhotic diseases (other than malignity related ascites). We found that MPO levels in ascites fluid due to liver cirrhosis are lower than the ascites fluid due to other reasons. Accordingly, we concluded that decreased MPO might be a reason for increased SBP.

A previous study was evaluated blood myeloperoxidase levels as an indicator of oxidative stress in liver cirrhosis, and found that MPO levels in cirrhotic patients were higher than the controls (30). In our study, we compared the MPO levels between all three groups, and found that there was no significant difference.

MPO enzyme that's secreted from the activated PMNLs and monocytes at the inflammation site plays a basic role in the formation of oxidants by the human immune system (31). The oxidants that formed by this enzyme play important roles with phagosomes, enzymes and bacterial protein series from the PMNLs and monocytes at the extracellular site to kill the microorganisms (31). But, despite the high levels of coordination and control of this process, still there may be tissue damage and this damage constitutes the mainstay of connection of pathologies of some chronic inflammation related diseases and damage caused by this enzyme (17). For this reason, oxidants from MPO were associated with Type 2 DM, benign lung diseases, autoimmune diseases, atherosclerosis, renal damage, some cancers, multiple sclerosis, and Alzheimer's disease (32, 33).

MPO was shown to be important in bacterial burst, and killing of both bacteria and fungus in animal models, and also infection incidences were increased in humans with complete or partial MPO failure, which is seen by 1:1000 or 1:2000 frequencies. MPO failure is also present in chronic granulomatous disease, which is known to be associated with severe and fatal infection. Actually, oxidants from MPO were proven to affect cellular induction events (34,35).

As a conclusion, we found in this study that MPO levels in ascites due to liver cirrhosis were lower than the levels in ascites due to non-cirrhotic diseases, and this difference was also found to be statistically significant. We think that lower levels of MPO in ascites fluid due to liver cirrhosis from ascites fluid due to non-cirrhotic diseases might contribute to increased spontaneous bacterial peritonitis in liver cirrhosis. For a definite conclusion of MPO is a predictive factor for spontaneous bacterial peritonitis, further studies with larger populations and covering additional predictive factors are needed.

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