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Diagnostic value of serum procalcitonin in determining the activity of inflammatory bowel disease

İnflamatuvar barsak hastalığı aktivitesinin belirlenmesinde serum prokalsitonin seviyesinin önemi

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Background/aims: *Procalcitonin and C-reactive protein are two acute-phase reactant proteins, although procalcitonin is a more specific marker for bacterial infections. Procalcitonin level might also be helpful to predict the disease activity of inflammatory bowel disease. This study aimed to compare the diagnostic value of serum procalcitonin and C-reactive protein as indicators of disease activity in inflammatory bowel disease.* ***Methods:*** *Patients admitted to the inflammatory bowel disease inpatient clinic with suspected inflammatory bowel disease who had not yet been treated with immunosuppressive treatments were included. Disease activity, white blood cell count, sedimentation rate, serum procalcitonin and C-reactive protein levels were evaluated in 45 newly diagnosed inflammatory bowel disease patients (9 Crohn's disease and 36 ulcerative colitis). Fifty healthy volunteers were analyzed as a control group.* ***Results:*** *Crohn's disease patients had higher procalcitonin and C-reactive protein levels than healthy controls (Procalcitonin: 0.143±0.081 vs. 0.065±0.008 ng/ml, p<0.05; C-reactive protein: 29±7.5 vs. 2.9±0.5 mg/dl, p<0.001, respectively). Ulcerative colitis patients also had slightly higher procalcitonin levels and significantly higher C-reactive protein levels than controls (Procalcitonin: 0.107±0.042 ng/ml; C-reactive protein: 23±5.5 mg/dl). Two Crohn's disease patients had procalcitonin value above 1 ng/ml. Receiver operating characteristic curve analysis demonstrated that C-reactive protein is the best marker of disease activity in inflammatory bowel disease while procalcitonin has low sensitivity and specificity. Serum procalcitonin levels were highly correlated with serum C-reactive protein but no other disease activity parameters.* ***Conclusions:*** *Although still within normal ranges, procalcitonin levels were slightly elevated in Crohn's disease but not in ulcerative colitis patients compared to healthy controls. Serum C-reactive protein is a reliable marker for disease activity in inflammatory bowel disease. Procalcitonin has no diagnostic value in determining disease activity.*

Key words: Procalcitonin, C-reactive protein, Crohn's disease, ulcerative colitis

Amaç: *Prokalsitonin ve C-reaktif protein akut faz reaktanı olarak davranan iki proteindir. Prokalsitonin bakteriyel enfeksiyonlar için daha spesifik bir gösterge olarak kabul edilmektedir. Bu çalışmada serum prokalsitonin ve C-reaktif protein seviyelerinin inflamatuvar barsak hastalığı aktivitesinin bir göstergesi olarak karşılaştırılması planlanmıştır.* ***Yöntem:*** *İnflamatuvar barsak hastalığı kliniğinde yatarak yeni tanı almış, immunsüpresif ilaç kullanmayan ardışık hastalar çalışmaya dahil edilmiştir. Hastalık aktivitesi, sedimantasyon hızı, C-reaktif protein ve prokalsitonin seviyeleri 45 inflamatuvar barsak (9 Crohn ve 36 ülseratif kolit) hastasında değerlendirilmiştir. Sağlıklı 50 gönüllü kontrol grubu olarak incelenmiştir.* ***Bulgular:*** *Crohn hastalığı olgularında prokalsitonin ve C-reaktif protein sağlıklı kontrollerden daha yüksek bulunmuştur (Prokalsitonin: 0.143±0.081 kş. 0.065±0.008 ng/ml, p<0.05 ve C-reaktif protein: 29±7.5 kş. 2.9±0.5 mg/dl, p<0.001). Ülseratif kolit hastalarında prokalsitonin kontrollerden hafif yüksek bulunmuştur ancak fark anlamlı değildir. C-reaktif protein ise ülseratif kolitte anlamlı olarak kontrollerden yüksektir. (Prokalsitonin: 0.107±0.042 ng/ml ve C-reaktif protein: 23±5.5 mg/dl). İki Crohn hastalığı olgusunda prokalsitonin değeri 1 ng/ml üzerinde saptanmıştır. Serum prokalsitonin, C-reaktif protein ile koreledir ancak diğer aktivite göstergeleri ile korelasyonu yoktur.* ***Sonuçlar:*** *Serum prokalsitonin seviyesi normal sınırlarda olmakla birlikte, Crohn hastalarında kontrolerden hafif yüksektir. Ülseratif kolit hastalarında ise prokalsitonin seviyesi sağlıklı kontrollerden farklı değildir. Serum C-reaktif protein seviyesi inflamatuvar barsak hastalığında aktivitenin güvenilir bir göstergesidir ancak prokalsitoninin aktivite göstergesi olarak değeri yoktur.*

Anahtar kelimeler: Prokalsitonin, CRP, Crohn, ülseratif kolit

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are both idiopathic inflammatory bowel diseases (IBD) generally complicated with systemic or local infections (1). Although some clinical activity

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indexes are commonly used in IBD, specific and sensitive laboratory markers that correlate with disease activity and associated complication are still lacking (2).

C-reactive protein (CRP) is a widely used marker of inflammation and it has been shown to correlate with disease activity, especially in CD patients (3). It increases rapidly during inflammatory processes and resolves early after amelioration of the inflammation. However, in UC patients, CRP response is usually moderate (4). Sedimentation rate (ESR) is also a commonly used marker in IBD, though it increases later and is dependent on the age and blood erythrocyte number (5).

Procalcitonin (PCT), a prohormone of calcitonin, is an acute-phase protein containing 116 amino acids (6). It has been shown to be a specific marker for bacterial infections, while its level remains low during viral infections (7). Furthermore, it has been related to disease activity in autoimmune diseases (8, 9). PCT might be a helpful marker to predict the disease activity of IBD. This study aimed to compare the diagnostic value of serum PCT and CRP as indicators of disease activity in IBD.

MATERIALS AND METHODS

Patients admitted to the inpatient IBD clinic during 2006 were evaluated. The diagnosis of IBD was confirmed by a typical history, appropriate endoscopic and radiologic imaging studies as well as histopathological evaluations (10). All consecutive patients newly diagnosed with IBD (9 CD and 36 UC) were included in the study. Patients with concomitant diseases including diabetes, hematological disorders, any malignancies, obvious infection or sepsis, chronic liver disorder or any liver diseases were excluded. Previously diagnosed IBD patients were not included in the study since they were either under immunosuppressive treatment or in remission, which both might have unknown effects on serum PCT levels. Patients included in the study were culture-negative for stool and no parasitic infestations were diagnosed. Febrile patients were evaluated further by blood and urine culture and pulmonary X-rays, showing no sign of infection. Fifty age- and sex-matched healthy volunteers were included as a control group.

Disease activity was assessed by the Crohn's disease activity index (CDAI) for CD (11). Patients with an activity score <150 were considered to be in remission, and those with an activity score >150 were considered to have active disease. UC patients with a Truelove index of "mild" were considered to be in remission, and patients with an index of "moderate" or "severe" had active disease (12).

Blood samples were collected on the day of definitive diagnosis for biochemical analysis. White blood cell count and ESR were evaluated in all patients. Serum levels of PCT were measured by a commercially available Kryptor based PCT kit (Brahms, Germany). Normal PCT level was defined as <0.5 ng/ml. Serum CRP was determined by nephelometric method. Serum PCT, CRP and ESR were compared between groups.

Written consent was taken from all patients. All analyses were performed using the SPSS 12.0 for Windows. Values are expressed as mean ± SD or median. Statistical analysis was performed by using the Mann-Whitney test and the Kruskal-Wallis one-way analysis of variance on ranks. A receiver operating characteristic (ROC) curve analysis was used to calculate specificity and sensitivity. A p value <0.05 was considered statistically significant.

RESULTS

Nine CD and 36 UC patients (mean age: 47.11±15.08 years; 21 male, 24 female) were included in the study. The age and gender distribution was similar to the control group (46±12.00 years; 24 male, 26 female) (Table 1).

We found that serum PCT levels were within normal ranges in most of the IBD patients. CD patients had significantly higher PCT and CRP levels than healthy controls (PCT: 0.143±0.081 vs. 0.065±0.008 ng/ml, p<0.05; CRP: 29±7.5 vs. 2.9±0.5, p<0.001) (Table 2). Two CD patients with

Table 1. General characteristics of IBD patients and controls

	CD (n: 9)	UC (n: 36)	Controls (n: 50)
Male/Female	4/5	15/21	24/26
Age (years: mean ± SD)	48±4.6	46.7±4.7	46±12.0
Intestinal location (n)	Small bowel only (n: 3)	Pancolitis (n: 7)	-
	Colon only (n: 2)	Left colon (n: 12)	-
	Small bowel and colon (n: 4)	Proctitis (n: 17)	-

Table 2. Serum PCT and CRP levels in IBD and control groups

	PCT (ng/ml)	CRP (mg/dl)
CD n (9)	**0.14±0.08****	**29±7.5***
Active CD n (5)	0.18±0.121	36.2±20.8*
Inactive CD n (4)	0.09±0.058	17.3±6.6
UC n (36)	**0.10±0.040**	**23±5.5***
Active UC n (21)	0.07±0.012	29.7±10.1*
Inactive UC n (15)	0.13±0.067	17.9±6.7
Total (IBD) n (45)	**0.11±0.038**	**23.9±4.6***
Controls n (50)	**0.06±0.008**	**2.9±0.5**

*p<0.001, **p<0.05 compared to controls. Serum PCT levels were within normal ranges in most of the IBD patients. CD patients had slightly higher PCT levels than UC patients and significantly higher levels than controls. Serum CRP levels were similar in both CD and UC patients and were significantly higher than in controls.

entero-enteric fistula had PCT level above 1 ng/ml. In CD, the serum CRP was significantly increased in patients with active disease (n:5) (36.2±20.08 vs. 17.3±6.6), while PCT levels were similar between groups (Table 2).

Although within normal ranges, UC patients also had slightly higher PCT levels and significantly higher CRP levels than controls (PCT: 0.107±0.042, p: ns; CRP: 23±5.5, p<0.001). PCT level was not affected by disease localization. The difference between PCT levels was insignificant between active and inactive UC patients (Table 2).

Serum PCT levels were highly correlated with serum CRP (r:0.43, p<0.01) but not with any other disease activity parameters in IBD. PCT was also not affected by age or gender. CRP was the best marker to predict the activity of IBD (AUC: 0.88, 95% CI: 0.80-0.95; p<0.001). PCT cut-off value of 0.05 resulted in 67% sensitivity and 42% specificity for diagnosis of active IBD (AUC: 0.57, 95% CI: 0.44-0.70, p: ns) (Figure 1).

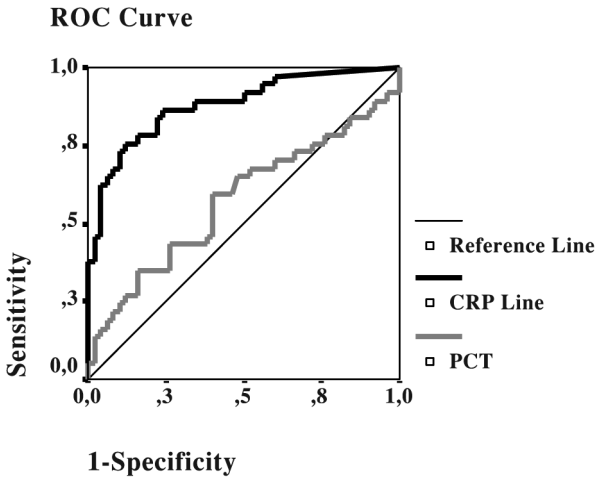

Figure 1. ROC curve analysis demonstrates that serum CRP is a better marker for activity of IBD. Even with low cut-off values, PCT has low sensitivity and specificity in IBD.

DISCUSSION

Different inflammatory markers are used as disease activity indexes in IBD (13). Classic and widely used markers include ESR, white blood cell count, and CRP (2). PCT is a 116 amino acids protein mainly produced by C cells of the thyroid gland as a prohormone of calcitonin (6). The probable other sites of PCT production during inflammation and infections are the intestine, monocytes and some neuroendocrine cells. Plasma level of PCT increases during bacterial infections and sepsis (14). There are some data showing that serum PCT level is a useful marker in many inflammatory disorders. Ammori et al. (15) showed that plasma concentrations of PCT appear to reflect the derangement in gut barrier function in patients with acute pancreatitis. Similarly, Sarbinowski et al. (16) showed that serum PCT levels increase significantly after colorectal surgery. Those findings suggested that inflammatory and infectious disease of the bowel might increase serum PCT levels.

We found that serum PCT levels were within normal ranges in most of the IBD patients. Only two patients with fistulated CD had high PCT levels, probably due to local inflammation. Serum PCT level, while still remaining within the normal ranges, was higher in CD patients than controls. As with CRP, PCT response seems to dominate in CD disease while it is subtle in UC. Similar to Fagan et al. (17), we found that serum CRP was still the best marker of disease activity in IBD.

Herrlinger et al. (18) was the first to show the diagnostic value of PCT in self-limited infectious colitis. They included IBD patients with no sign of infection as a control group (6). They found that PCT was useful to discriminate the infectious colitis from IBD. However, they did not exclude patients in remission or those receiving immunosuppressive treatments. The effects of local and systemic steroids on CRP synthesis is well demonstrated, though their effects on the synthesis of PCT are not known (19). We can speculate that steroids might affect PCT level by changing PCT synthesis or causing occult infections. Since we included only the recently diagnosed patients who were not using steroids, our results solely reflect the disease activity. Our study has some limitations, since we included only a small group of newly diagnosed patients

admitted to hospital and they had high disease activity scores. It would be better to follow up newly diagnosed IBD patients with serum PCT and CRP levels to demonstrate the real changes in PCT levels with immunosuppressive treatments, remission or concomitant infections. After well-organized long-term follow-up studies, PCT measurements could be extended to outpatient IBD clinics.

In conclusion, although within normal ranges, PCT levels were slightly elevated in CD patients but not UC patients compared to controls. Serum CRP is a reliable marker for disease activity; however, PCT has no diagnostic value in determining disease activity in IBD. PCT should be evaluated in further studies as a marker to predict the IBD-associated infections and complications.

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