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FİZİKSEL TIP

FIBRINOGEN VERSUS CONVENTIONAL ACUTE PHASE REACTANTS IN THE ASSESSMENT OF DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS

ROMATOİD ARTRİTLİ HASTALARDA HASTALIK AKTİVASYONUNUN İZLENMESİNDE KONVANSİYONEL AKUT FAZ REAKTANLARINA KARŞI FİBRİNOJEN

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SUMMARY

The aim was to compare levels of plasma fibrinogen and conventional acute phase reactants (APRs), such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in monitoring disease activity in patients with rheumatoid arthritis (RA).

Twenty patients with RA and 20 healthy controls were included in this study. Laboratory activities were assessed by ESR, CRP and fibrinogen. Disease activity was determined using the Ritchie Articular Index (RAI). The serum levels of ESR, CRP and fibrinogen were significantly higher in RA patients than in healthy controls ($p<0.001$). RAI scores were 17.5 ± 8.92. There were clear significant correlations between RAI and acute phase reactants such as ESR ($r=0.45$; $p<0.05$), CRP ($r=0.78$; $p<0.001$) and fibrinogen ($r=0.64$; $p< 0.01$).

Our results suggest that plasma fibrinogen levels are more reliable than ESR, but not CRP in the assessment of disease activity in patients with RA.

Key Words: *Rheumatoid arthritis, ritchie articular index, fibrinogen, ESR and CRP*

ÖZET

Çalışmanın amacı, romatoid artritli (RA) hastalarda hastalık aktivitesinin izlenmesinde Eritrosit sedimantasyon hızı (ESR) ve C-reaktif protein (CRP) gibi konvansiyonel akut faz reaktanları ile plazma fibrinojen düzeylerini karşılaştırmaktı.

RA'li 20 hasta ve 20 sağlıklı kontrol çalışmaya dahil edildi. Laboratuar aktivitesi ESR, CRP ve fibrinojen ile değerlendirildi. Hastalık aktivitesi Ritchie Articular Index (RAI) kullanılarak belirlendi. RA'li hastalarda ESR, CRP ve plazma fibrinojen düzeyleri, kontrol grubuna göre anlamlı olarak daha yüksekti ($p<0.001$). RAI skorları 17.5 ± 8.92 idi. RAI ile ESR, CRP ve fibrinojen gibi akut faz reaktanları arasında anlamlı korelasyonlar vardı (sırasıyla, $r=0.45$; $p<0.05$, $r=0.78$; $p<0.001$, $r=0.64$; $p< 0.01$).

Sonuçlarımız, RA'li hastalarda hastalık aktivitesinin değerlendirilmesinde plazma fibrinojen seviyelerinin ESR'den daha güvenilir, ancak CRP kadar güvenilir olmadığını gösterdi.

Anahtar sözcükler: *Romatoid artrit, ritchie articular index, fibrinojen, ESR ve CRP*

INTRODUCTION

Rheumatoid arthritis (RA), is a chronic multi-system disease, causes many systemic manifestations, the most characteristic of which is the symmetrical involvement of peripheral articulations by inflammatory synovitis. Although the cause of RA is unknown, it is generally considered an autoimmune disease (1, 2). RA is characterized by mild or moderate flares of active disease alternating with periods of almost or totally inactive inflammation. The acute-phase response to tissue injury and inflammation is accompanied by a dramatic increase in the hepatic synthesis of plasma proteins known as acute-phase reactants (APRs). The APRs play a major role in the assessment of the inflammatory response (3, 4). The some APRs are erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen.

ESR is a nonspecific screening test for inflammatory diseases. The ESR is an index of the acute phase response, mainly reflecting the concentrations of fibrinogen and the γ-globulins. The test can be used to monitor malignant disease or inflammatory, including RA. It is commonly used to assess the acute phase response. CRP is a protein produced by the liver that is present in the serum especially during acute inflammation in the body. Measurement of CRP levels may be useful in screening for RA and in monitoring disease activity. The CRP, ho-

wever, may complement the ESR in monitoring of chronic inflammation circumstances as in rheumatic diseases (5, 6).

Fibrinogen, while of primary importance as a coagulation protein, is also an acute-phase protein reactant. As such, it is increased in disease processes involving tissue damage or inflammation. Changes in fibrinogen may impair the reliability of erythrocyte sedimentation measurements (7). The Ritchie Articular Index (RAI) was used as a clinical measure to evaluate disease activity. There are many literatures that RAI is used for this purpose (8, 9).

The aim of this study was to compare levels of plasma fibrinogen and conventional APRs such as ESR and CRP in monitoring disease activity in patients with RA.

MATERIAL AND METHOD

Twenty patients with RA and 20 healthy controls were included in this study. All patients fulfilled the commonly used criteria for RA American College of Rheumatology (ACR) criteria (10). Clinical assessments included demographic data: age, sex, weight and duration of disease. In the patients with RA (n = 20), 16 patients were females and 4 males (mean age; 48.7 ± 12.4, range; 32-75 years). The mean disease duration was 6.60 ± 6.08 years (range; 1-20 years). In the controls (n = 20) were 5 males and 15 females (mean age: 42.4 ± 8.4 range: 27-55 years) with healthy hospital personnel without a history of inflammatory disease.

Ten patients were taking a combination of methotrexate and glucocorticoids and 7 were only taking methotrexate, and 3 were receiving nonsteroidal anti-inflammatory drugs at the time of sampling. The patients were allowed to continue their previous regimens of drugs. We excluded patients who had sings or symptoms of severe renal, hepatic, bleeding disorders, disseminated intravascular coagulation, lymphoproliferative and other malignant diseases. The exclusion criteria for the controls group were the same as for the RA group. The groups were matched according to age, sex and weight. Laboratory activity was assessed by ESR, CRP and fibrinogen. Disease activity was determined using the RAI, assessed by determination of the joint index score (11). Laboratory parameters included ESR and CRP in peripheral blood were measured. ESR was determined according to the Westergren method and CRP by a nephelometric method (Beckman Array Protein System, USA). Plasma fibrinogen levels were measured with a commercially available kit an autoanalyzer (Dade-Behring, Germany).

Statistical analysis was done using the SPSS Base 7.5 statistical package. Values are given as mean ± SD. Differences between groups were performed using the Mann-Whitney U test. Correlations between variables were assessed by using Spearman's rank correlation coefficient. P values of <0.05 were regarded as significant.

RESULTS

The demographic characteristics of the patients or controls groups are shown in Table I. There was no statistically significant differences between two groups with respect to demographic data such as age, sex and weight (p>0.05).

Table I: Baseline characteristics of rheumatoid arthritis patients and healthy controls

	Patients (n=20)	Healthy controls (n=20)	p
Sex (F/M)	16 / 4	15 / 5	ns
Age (years)	48.70 ± 12.47	43.05 ± 12.90	ns
Duration of disease (years)	6.60 ± 6.08	—	
ESR (mm/h)	43.45 ± 15.14	15.40 ± 8.08	<0.001
CRP (mg/dl)	1.98 ± 1.02	0.38 ± 0.19	<0.001
Fibrinogen (mg /dl)	408.8 ± 133.8	273.3 ± 64.4	<0.001
RAI scores	17.5 ± 8.92	—	

ns: not significant

RAI scores and laboratory findings of RA patients and healthy controls that entered the study are shown in Table I. The serum levels of ESR, CRP and fibrinogen were significantly higher in RA patients than in healthy controls (p<0.001). RAI scores were 17.5 ± 8.92.

We examined a correlation between RAI values and APRs levels of the patients with RA. There were clear significant correlations between RAI and other acute phase reactants such as ESR, CRP and fibrinogen (r=0.45; p<0.05, r=0.78; p<0.001, r=0.64; p< 0.01 respectively) (Figs I-III).

DISCUSSION

APRs are a group of plasma proteins, the levels of which alter in response to tissue injury, inflammation or malignancy. Inflammation resulting from any form of tissue injury causes an increase in the concentration of a number of liver-derived plasma proteins, which appear to have important functions in the inflammatory process (12). The measurement of acute

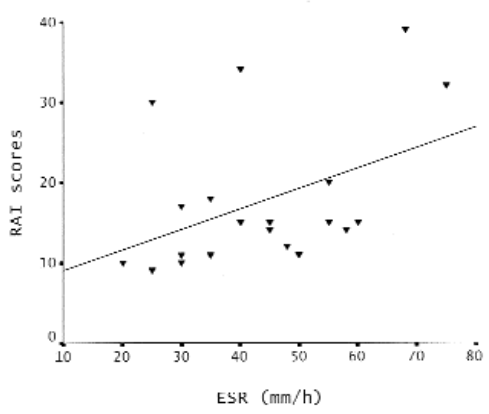

Figure I: Positive correlation between ESR and RAI in 20 patients with rheumatoid arthritis. Statistical analysis was performed using Spearman's rank correlation coefficient (r=-0.45, p<0.05).

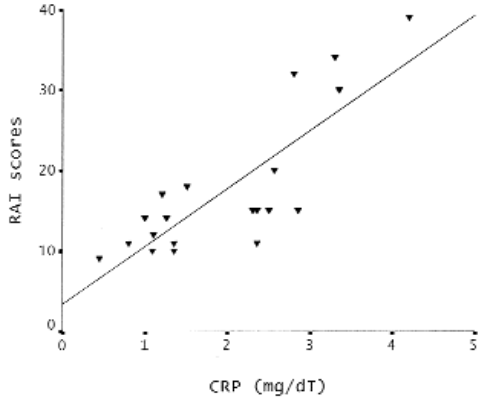

Figure II: Positive correlation between CRP and RAI in 20 patients with rheumatoid arthritis. Statistical analysis was performed using Spearman's rank correlation coefficient (r=-0.78; p<0.001).

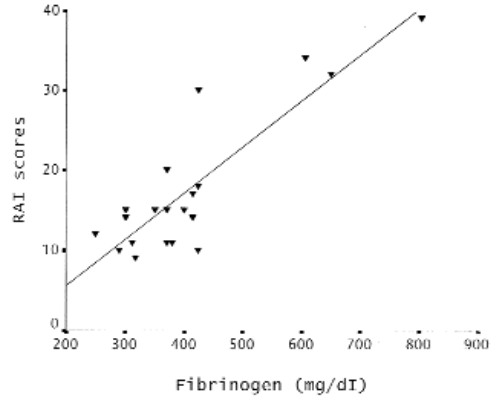

Figure III: Positive correlation between plasma fibrinogen and RAI in 20 patients with rheumatoid arthritis. Statistical analysis was performed using Spearman's rank correlation coefficient (r=-0.64; p<0.01).

phase proteins in plasma provides a clinically valuable indication of the presence of inflammation (13). There are many papers in the literature reporting the presence of correlations between RAI and conventional APRs (14, 15).

ESR and CRP are the most widely used assays to measure the laboratory aspect of the acute phase response, being of great value in monitoring disease activity in RA. ESR provides a non-specific screening test for the presence of an acute phase reaction. Elevations of the ESR are typically associated with increases in acute phase reactants (including fibrinogen) tumor necrosis factor and immunoglobulins secondary to infectious immune-mediated or tumor-related conditions. However, the ESR may be affected by many factors and mainly by fibrinogen. While clinically useful in primary care the general lack of specificity can limit its usefulness. In many patients the ESR will stop at a higher than normal level, even if the patients clinical status has dramatically improved (16).The influence of various other factors on the ESR (including diurnal variation, anemia, food intake, and red cell morphology) makes it an imprecise guide to disease activity in most cases (17). An isolated elevated ESR is not useful for prognosis, but sustained extreme elevation of the ESR is associated with a very poor prognosis (16, 18). Increased ESR may also be secondary to hypergammaglobulinaemia and anaemia without co-existing inflammation. The results of the present study revealed that RAI showed the most significant correlation with CRP and the least significant correlation with ESR among three APRs. CRP is exclusively made in the liver and is secreted in increased amounts within 6 hours of an acute inflammatory stimulus. Therefore, it is a more sensitive early indicator of an acute phase response than is the ESR (19). As a conclusion, that CRP is superior to ESR in terms of rapidity of response and specificity for inflammation is confirmed by various studies in the literature (20, 21). Fibrinogen is also useful for detection of chronic inflammatory disease such as RA. ESR, an indirect index of the APRs concentrations, correlates most closely with fibrinogen concentrations (22). While the ESR rises slowly in response to increasing production of fibrinogen by the liver and falls slowly as well, CRP rises quickly after an inflammatory event and returns to normal within a week (23). The appearance and duration of such acute phase proteins in the blood varies from protein to protein. CRP rise within a few hours of stimulation. Fibrinogen has a slower rise. Since CRP is

itself an acute phase reactant, its measure reflects the level of inflammation directly, rather than the more indirect reflection of inflammation that the ESR provides. In our study, fibrinogen is more superior to ESR with respect to showing a relationship with RAI. This result was accordance with literature (24). Fibrinogen is a protein made by the liver to promote blood clotting. Increased fibrinogen levels may be seen with inflammation, pregnancy and in women taking oral contraceptives. It is known that plasma fibrinogen level is increased in RA patients (25, 26). None of our cases was pregnant and was using oral contraceptive. So, we think that fibrinogen levels were not affected by pregnancy or oral contraceptive. The strong correlation indicates that plasma fibrinogen levels could be used instead of ESR in monitoring RA patients. This would increase the specificity of the examination as ESR may be influenced by several factors other than the inflammatory response.

Our results suggested that plasma fibrinogen levels may more useful than the ESR, but not the CRP in the assessment of disease activity in RA patients.

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