Comparative Usefulness of High Sensitivity C-Reactive Protein and C-Reactive Protein to Evaluate Inflammation in Patients with Rheumatoid Arthritis

Romatoid Artritli Hastalarda Inflamasyonu Değerlendirmek Için Yüksek Sensitiviteli C-Reaktif Protein ve C-Reaktif Proteininin Karşılaştırılmalı Faydası

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ABSTRACT Objective: Assessment of disease activity is very important for successful management of rheumatoid arthritis (RA). The use of high sensitivity C-reactive protein (hs-CRP) assays was recently recommended as a measure to identify low disease activity in RA. The aim of this study was to compare hs-CRP and C-reactive protein (CRP) levels to evaluate inflammation in patients with RA and to investigate their association with disease activity and the number of swollen/tender joints. **Material and Methods:** Eighty-six patients with RA and 65 age and sex matched healthy controls were enrolled in this study. All patients fulfilled the American College of Rheumatology (ACR) classification criteria for RA. Disease Activity Score (DAS) 28 was used for the assessment of disease activity. Number of swollen joints, number of tender joints and global assessment of the patient by using visual analog scale (VAS) were noted. CRP, hs-CRP, erythrocyte sedimentation rate (ESR) of the patients with RA and controls were measured. We analyzed the association between hs-CRP, CRP and ESR versus other clinical variables. **Results:** The patients with RA had significantly higher levels of ESR, hs-CRP and CRP compared with controls (p< 0.05). The hs-CRP was more closely associated with DAS 28 (r: 0.73, p< 0.001), VAS (r: 0.69, p< 0.001), number of swollen joints (r: 0.46, p= 0.005) and number of tender joints (r: 0.42, p= 0.001) than CRP. **Conclusion:** Our findings suggested that hs-CRP might be used to evaluate disease activity and inflammation in RA and that hs-CRP testing might reflect systemic inflammation in a more accurate way than routine CRP assays.

Key Words: Arthritis, rheumatoid; C-reactive protein

ÖZET Amaç: Romatoid artritin (RA) başarılı tedavisi için hastalık aktivitesinin belirlenmesi çok önemlidir. Yüksek sensitiviteli C-reaktif protein (hs-CRP) son zamanlarda RA'da düşük hastalık aktivitesini belirlemek için bir ölçüm yöntemi olarak önerilmektedir. Bu çalışmanın amacı RA'lı hastalarda inflamasyonu değerlendirmek için hs-CRP ve C-reaktif protein (CRP) seviyelerini karşılaştırmak ve hastalık aktivitesi ve şiş/hassas eklem sayıları ile ilişkisini araştırmaktır. **Gereç ve Yöntemler:** RA'lı 86 hasta; yaş ve cinsiyet olarak eşleştirilmiş 65 sağlıklı kontrol bu çalışmaya dahil edildi. Bütün hastalar Amerika Romatizma Birliği (ACR)'nin RA sınıflama kriterlerini tam olarak karşılıyordu. Hastalık aktivite skoru 28 (DAS 28) hastalık aktivitesini değerlendirmek için kullanıldı. Şiş eklem sayısı, hassas eklem sayısı, görsel anolog skala (VAS) ile hastanın global değerlendirmesi not edildi. CRP, hs-CRP ve eritrosit sedimentasyon hızı (ESR) RA'lı hastalarda ve kontrollerde ölçüldü. hs-CRP, CRP ve ESR ile diğer klinik değişkenler arasındaki ilişki analiz edildi. **Bulgular:** RA'lı hastalar kontrollerle karşılaştırıldığında anlamlı olarak daha yüksek ESR, hs-CRP ve CRP değerlerine sahipti (p< 0.05). hs-CRP, CRP'ye göre DAS 28, (r: 0.73, p< 0.001) VAS (r: 0.69, p< 0.001), şiş eklem sayısı (r: 0.46, p= 0.005) ve hassas eklem sayısı (r: 0.42, p= 0.001) ile daha yakından ilişkiliydi. **Sonuç:** Bizim bulgularımız hs-CRP'nin RA'da hastalık aktivitesini ve inflamasyonu değerlendirmek için kullanılabileceğini ve hs-CRP testinin CRP'ye oranla sistemik inflamasyonu daha doğru olarak yansıttığını gösterdi.

Anahtar Kelimeler: Romatoid artrit; C-reaktif protein

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting about 1% of the general population worldwide.[1] Assessment of disease activity is important for successful management of RA. Features of active RA can be assessed by clinical tools like HAQ, DAS 28 and can be represented by biological markers like the CRP and by inflammatory cytokines.[2-4] Currently available measures of disease activity in RA are unsatisfactory and no single laboratory test correctly reflects the disease status.[5]

Among laboratory test, ESR) is widely used and is the oldest.[6] It depends on aggregation of red blood cells (RBCs), which is influenced by large asymmetrical plasma proteins such as fibrinogen, alpha-2 macroglobulin and immunoglobulins.[7]

With regard to acute phase reactant proteins, CRP is the most widely used. It was first described in 1951 and is composed of nonglycosylated polypeptide subunits each of 27.000 dalton encoded on a single gene on chromosome 1 with no polymorphism. Its concentration raises 500-fold in acute inflammation. It is has been most widely studied in RA and is valuable in monitoring disease activity.[8]

The use of hs-CRP assays was recently recommended as a measure to identify low disease activity in RA.[9,10] The hs-CRP is an acute phase reactant for trauma and infections and is mainly produced in the liver in response to systemic inflammations, resulting in increased blood CRP levels.

The aim of this study was to compare hs-CRP and CRP levels to evaluate inflammation in patients with RA and to investigate their association with disease activity, and number of swollen/tender joints.

MATERIAL AND METHODS

Eighty-six patients with RA and 65 age and sex matched healthy controls, who were attending the outpatient clinic of our university hospital, were enrolled in this study. All patients fulfilled the ACR classification criteria for RA. DAS 28 was used for the assessment of disease activity. Number of swollen joints, number of tender joints and global as-

sessment of patients using VAS were noted. CRP, hs-CRP, and ESR of the patients with RA and controls were measured. In addition, the association between hs-CRP, CRP and ESR versus other clinical variables were investigated.

To circumvent other factors that could influence the serum concentrations of hs-CRP, the following exclusion criteria were used: history of recent surgery or trauma within 2 months preceding the study; renal insufficiency (creatinine >1.5 mg/dL); malignancy or liver cirrhosis; febrile disorders; other acute or chronic inflammatory disease at study entry; history of recent infection; acute myocardial infarction (MI) with an onset of <3 months, and history of coronary artery disease. Patients were also excluded if fever (body temperature >37.5°C) was observed during blood sampling.

ESR (mm/h) was determined by standard methodology. The serum concentration of CRP and hs-CRP was measured by immunonephelometry (BN2™ System, Dade Behring Inc, Newark, DE, USA).

Informed consent was obtained before the examination and approval for the study was granted by the local ethical committee of the university. All parametric results were expressed as mean ± SD for each group. Comparisons between patient and control groups were made by the student t test. For correlation analysis, Pearson coefficient of correlation was used. Local statistical significance was assumed as p< 0.05 for all parameters.

RESULTS

Clinical features of the patients with RA and controls are shown in Table 1.

The patients with RA had significantly higher level of ESR and hs-CRP and CRP values compared with controls (p< 0.001) (Table 2).

ESR showed a high correlation with DAS 28 (r: 0.75, p< 0.001). However the correlation with VAS (r: 0.38, p= 0.001) and the number of swollen joints (r: 0.33, p= 0.007) was moderate. ESR showed no correlation with the number of tender joints (r: 0.28, p= 0.065). A statistically significant correlation was observed between CRP and DAS

TABLE 1: Clinical features of patients with rheumatoid arthritis and controls.

	Patient group	Control group
Age	47.3 ± 15.8	46.9 ± 14.8
Sex	63 F/23 M	48 F/17 M
Number of swollen joints (0-28)	1.6 ± 1.2	
Number of tender joints (0-28)	5.1 ± 2.6	
Visual analog scale (mm)	51.1 ± 27.5	
DAS 28	4.9 ± 2.7	

DAS 28: Disease activity score 28, F: Female, M: Male.

TABLE 2: Laboratory findings of patients and control.

	Patients (n: 86)	Controls (n: 65)	p
ESR (mm/h)	41.3 ± 15.3	14.7 ± 12.9	< 0.001
CRP (mg/L)	35.4 ± 11.3	3.2 ± 1.8	< 0.001
hs-CRP (mg/L)	13.5 ± 5.2	2.1 ± 1.3	< 0.001

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, hs-CRP: High sensitivity C-reactive protein.

28 (r: 0.59, p< 0.001), and VAS (r: 0.54, p< 0.001) scores. However CRP showed no correlation with the number of swollen joints (r: 0.22, p= 0.087) and moderate correlation with the number of tender joints (r: 0.31, p= 0.028).

The hs-CRP was more closely associated with DAS 28 (r: 0.73, p< 0.001) and VAS (r: 0.69, p< 0.001) than CRP. Also, hs-CRP showed good correlation with ESR (r: 0.58, p<0.001) and moderate correlation with the number of swollen joints (r: 0.46, p= 0.005) and the number of tender joints (r: 0.42, p= 0.001). The results of ESR, CRP and hs-CRP as predictors of disease activity in patients with RA are shown in Table 3.

DISCUSSION

Both ESR and CRP are extensively used for monitoring disease activity in RA. Unlike CRP, ESR is affected by RBC characteristics, abnormal immunoglobulins, age, sex, smoking, menstrual cycles, drugs, dietary lipids and fibrinogen. In this background, it is surprising that some investigators state that ESR is a sensitive test. Bull et al, have reported ESR as the single most useful test to monitor disease severity. However, up to 40% of active RA patients has a normal ESR despite radiographic progression.[7,11,12]

CRP is an acute-phase constituent that has been measured for more than 70 years in the diagnosis and monitoring of active infection and inflammation, because it is one of the most fundamental and earliest host responses to inflammatory injury.[13] However, the clinical importance of CRP has been limited for many decades because of its large intra-individual variation and methods of measurement that were not thoroughly sensitive and accurate.

Now, a method of detecting hs-CRP is available and many study results demonstrate its greater value, especially as a potential risk marker for cardiac diseases.[14-18] The use of hs-CRP assays was recently recommended as a measure to identify low disease activity in RA.[9,10] In our study, the patient group had a significantly higher level of ESR, CRP and hs-CRP compared with the control group. This is an expected finding, because RA is a chronic inflammatory disease and causes elevation in markers of inflammation. This result also showed that hs-

TABLE 3: ESR, CRP and hs-CRP as predictors of disease activity in 86 patients with RA.

(n: 86)	ESR (mm/h)		CRP (mg/L)		hs-CRP	
	r	p	r	p	r	p
DAS 28	0.75	< 0.001	0.59	< 0.001	0.73	< 0.001
VAS	0.38	0.001	0.54	< 0.001	0.69	< 0.001
Number of swollen joints (0-28)	0.33	0.007	0.22	0.087	0.46	0.005
Number of tender joints (0-28)	0.28	0.065	0.31	0.028	0.42	0.001
ESR (mm/h)	1	-	0.46	< 0.001	0.58	< 0.001

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, hs-CRP: High sensitivity C-reactive protein, DAS 28: Disease activity score 28, VAS: Visual analog scale.

CRP testing could be safely used to evaluate inflammation in RA.

Elevated acute phase reactant levels are associated with early synovitis and erosions as detected by magnetic resonance imaging, with inflammatory cellular infiltrates in synovium and with osteoclastic activation and reduced bone density.[19-21] Both CRP and ESR predict radiographic progression.[22,23] Long term studies have identified time integrated values of ESR and CRP as significant correlates of disease progression over periods of up to 20 years.[24,25] When we made the correlation analysis of ESR, CRP and hs-CRP with DAS 28, VAS, number of swollen joints and number of tender joints, we found that hs-CRP was more closely associated with all clinic parameters; however, ESR showed slightly better correlation with DAS 28 than hs-CRP (r: 0.75 p< 0.001 versus r: 0.73 p< 0.001). ESR is one of the four parameters, which are used in the calculation of DAS 28 and thus, the better association of ESR with DAS 28 may be explained with this estimation. Recently Dessein et al showed that hs-CRP was consistently more strongly associated with disease activity variables HAQ-disability index, tender joints, swollen joints, pain, stiffness) than the ESR in patients with RA.[26] However, they did not use DAS 28 for the assessment of disease activity in their study.

Our results suggested that hs-CRP was more closely associated with DAS 28, general assessment of patient with VAS, number of swollen joints, number of tender joints and ESR compared with CRP. Correlations of hs-CRP with DAS 28, VAS and ESR were good. These findings suggest that hs-CRP reflects disease activity and inflammation better than CRP. So hs-CRP may be used routinely to evaluate the extent or severity of inflammation and to monitor changes in disease activity over time in RA with CRP.

In conclusion, as a new laboratory test, hs-CRP may be used safely to evaluate disease activity and inflammation in RA and hs-CRP testing may reflect systemic inflammation in a more accurate way than routine CRP assays.

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