High Sensitivity C-Reactive Protein as a Disease Activity Marker in Rheumatoid Arthritis

PATRICK H. DESSEIN, BARRY I. JOFFE, and ANNE E. STANWIX

ABSTRACT. ***Objective.*** To elucidate the potential contribution of high sensitivity C-reactive protein (hs-CRP) testing in the assessment of disease activity in rheumatoid arthritis (RA).

Methods. We recorded clinical and psychological variables, the hs-CRP, and erythrocyte sedimentation rate (ESR) in 146 consecutive patients with RA. We analyzed the associations between the ESR and hs-CRP versus the other recorded variables.

Results. The median (interquartile range) ESR (mm/h) and hs-CRP (mg/l) were 15 (7–36) and 5 (2.3–13.9), respectively. Thirty-two (22%) patients had an hs-CRP < 2 mg/l, 61 (42%) an hs-CRP of 2–8 mg/l and 53 (36%) an hs-CRP > 8 mg/l. In patients with an hs-CRP of 2–8 mg/l, the swollen joint counts and the physician disease activity scales were higher, and remission rates were lower than in patients with an hs-CRP of < 2 mg/l. The hs-CRP was consistently more closely associated with disease activity, depression, and helplessness than was the ESR.

Conclusion. High sensitivity CRP testing reveals systemic inflammation that is generally not detectable with routine CRP assays and that is associated with disease activity in RA. (J Rheumatol 2004;31:1095–7)

Key Indexing Terms:
HIGH SENSITIVITY C-REACTIVE PROTEIN
RHEUMATOID ARTHRITIS
ERYTHROCYTE SEDIMENTATION RATE
DISEASE ACTIVITY

Currently, disease activity in rheumatoid arthritis (RA) is monitored by the use of a series of surrogate markers[1,2]. These comprise functional ability, visual analog scales for pain and global disease activity, joint counts, and the acute phase reactants erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)[1,2].

Most studies in RA have used routine CRP testing methods. Their lower detection limit is often 8 mg/l or more[3]. However, CRP values as measured by high-sensitivity (hs-CRP) assays have revealed that the mean CRP in the general population is consistently below 2 mg/l[4]. In a recent report on 177 RA patients with a normal routine CRP (<10 mg/l), 47% had raised hs-CRP concentrations[3].

Our objectives were to determine whether an hs-CRP of 2 to 8 mg/l is associated with disease activity in RA and whether the hs-CRP and ESR perform equally well at predicting other disease activity measures in this disease.

MATERIALS AND METHODS

Patient cohort. The patient cohort consisted of 146 consecutive patients who were seen for followup during August and September 2002 at one of our clinics (Milpark Hospital). In order to exclude recently enrolled patients, those who had been followed at our clinic for < 6 months were excluded. All patients met the American College of Rheumatology (ACR) criteria for RA[5], and patients were considered in remission only if they fulfilled the ACR criteria for clinical remission for at least 2 consecutive months, which is in accordance with the recommendations by Pinals, *et al*[6].

Methods. We prospectively recorded the following clinical, psychological and laboratory variables: Health Assessment Questionnaire-Disability Index (HAQ-DI)[7]; 10 cm visual analog scales for pain, fatigue, global disease activity according to the patient (Pt disease activity) and the physician (MD disease activity), respectively; duration of morning stiffness; 36 joint count for tenderness, swelling, and deformity[8,9]; Arthritis Impact Measurement Scales for depression and anxiety, and helplessness index[10]; ESR (mm/h) as determined by standard methodology; hs-CRP (mg/l, range 0.05–170) (immunoturbidimetric assay on Olympus OSR6185, Olympus Diagnostics, Lismeehan, Ireland); rheumatoid factor (latex). The study was approved by the Ethics Committees for Research on Human Subjects (Medical) at the University of the Witwatersrand and the Milpark Hospital, respectively.

Statistical analysis. To determine if an hs-CRP of 2–8 mg/l was associated with disease activity, we stratified patients according to low (< 2 mg/l), intermediate (2–8 mg/l) and high (> 8 mg/l) hs-CRP levels. Data were analyzed using the Kruskal-Wallis one-way analysis of variance (ANOVA), simple linear regression analysis and chi-squared tests. The Bonferroni procedure was applied when multiple comparisons were made. Results were expressed as median (interquartile range) unless indicated otherwise.

RESULTS

Patient demographics. One hundred and seventeen (80%) patients were women, 124 Caucasian, 15 Asian, 4 Black, and 3 of mixed ancestry. Their age (range) and disease duration (range) were 57.5 (24.7–90) and 11.8 (0.95–58.3) years, respectively. One hundred and eighteen (81%) patients tested positive for rheumatoid factor.

From the Department of Rheumatology and the Centre for Diabetes and Endocrinology, Johannesburg Hospital and Milpark Hospital, University of the Witwatersrand, Johannesburg, South Africa.

P.H. Dessein, MD, FCP(SA); A.E. Stanwix, MRCP(UK), Department of Rheumatology; B.I. Joffe, DSc, Centre for Diabetes and Endocrinology.

Address reprint requests to Dr. P.H. Dessein, P.O. Box 1012, Melville 2109, Johannesburg, South Africa. E-mail: Dessein@lancet.co.za

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Table 1. Disease outcome in patients with low, intermediate, and high hs-CRP, respectively. Results are expressed as median (interquartile range) unless otherwise noted.

Variable	hs-CRP < 2 mg/l (n = 32)	hs-CRP 2–8 mg/l (n = 61)	hs-CRP > 8 mg/l (n = 53)
Disease activity			
HAQ-DI (0–3)	0.340 [0–0.800]	0.125 [0–0.688]	0.900 [0.39–1.55]†
Tender joints (0–36)	0 [0–4]	1 [0–3.6]	3 [0–13.3]†††
Swollen joints (0–33)	0 [0–0]	1 [0–2.8]*	4.2 [0–11.2]†
Pain (0–10)	1.6 [0–4.5]	1.8 [0.4–4.5]	4.3 [1.4–8.4]††
MD disease activity (0–10)	0 [0–1.5]	1.2 [0–3.0]**	4.0 [2–7.2]†
Pt disease activity (0–10)	1.2 [0–3.2]	1.7 [0.3–3.9]	4.5 [1.7–7.7]†
Stiffness (0–960 min)	0 [0–7]	2 [0–18]	20 [5–38]†††
Fatigue (0–10)	3.4 [1.8–5.2]	2.5 [0.1–6.3]	4.7 [2–6.2]
ESR (1–128 mm/hr)	8 [2–15]	11 [6–24]	42 [21–57]†
hs-CRP (0.2–178 mg/l)	1 [0.5–1.4]	4.2 [2.8–5.9]***	20 [12.4–35.5]†
Disease severity			
Joint deformities (0–36)	0 [0–4]	0 [0–6.3]	3 [0–19.6]‡
Psychological status			
Anxiety (2–8.8)	5.6 [4.4–6.4]	5.2 [3.6–6]	4.8 [3.6–6.4]
Depression (0–9)	4.2 [3.2–6]	4 [2.8–4.4]	4 [3.6–5.4]
Helplessness (0–7.9)	3.8 [2.8–5.3]	4 [2.8–5.1]	4.8 [3.1–6]
Remission, n (%)	16 (50)	16 (26)***	4 (7)†

* p = 0.0066 compared to patients with hs-CRP < 2 mg/l; ** p = 0.0033 compared to patients with hs–CRP < 2 mg/l; *** p < 0.0001 compared to patients with hs-CRP < 2 mg/l; † p < 0.0012 when compared to patients with hs-CRP 2–8 mg/l; †† p = 0.0033 compared to patients with hs-CRP 2–8 mg/l; ††† p < 0.0015 compared to patients with hs-CRP < 2 mg/l; ‡ p = 0.0054 compared to patients with hs-CRP < 2 mg/l; after application of Bonferroni procedure, significant at p < 0.0017; HAQ-DI: Health Assessment Questionnaire-Disability Index; MD: physician; Pt: patient; ESR: erythrocyte sedimentation rate.

Associations between the ESR and hs-CRP versus other disease outcome measures. In Table 1, we stratified patients according to low (< 2 mg/l), intermediate (2–8 mg/l) and high (> 8 mg/l) hs-CRP levels. Overall, disease activity variables increased with increases in hs-CRP. Most clinical variables were numerically higher in patients with intermediate hs-CRP as compared to those with low hs-CRP levels, respectively. This applied particularly to the swollen joint count and MD disease activity. Remission was less common (chi-square 7.5, p = 0.006) in patients with intermediate hs-CRP compared to patients with low hs-CRP levels, respectively.

In Table 2, we compared the ESR and hs-CRP as predictors of other recorded variables. The hs-CRP performed consistently better than the ESR at predicting disease activity, severity, and psychological status except for

Table 2. ESR and hs-CRP as predictors of disease outcome in 146 patients with RA.

Variable	ESR (mm/h)		hs-CRP (mg/l)	
	R^2	p	R^2	p
Disease activity				
HAQ-DI	0.167	< 0.0001	0.295	< 0.0001
Tender joints	0.139	< 0.0001	0.255	< 0.0001
Swollen joints	0.247	< 0.0001	0.332	< 0.0001
Pain	0.125	< 0.0001	0.182	< 0.0001
Pt disease activity	0.131	< 0.0001	0.192	< 0.0001
MD disease activity	0.280	< 0.0001	0.424	< 0.0001
Stiffness	0.151	< 0.0001	0.241	< 0.0001
Fatigue	0.034	0.0267	0.044	0.011
ESR	—	—	0.373	< 0.0001
Disease severity				
Deformed joints	0.068	0.0014	0.074	0.0009
Psychological status				
Anxiety	0	0.666	0	0.709
Depression	0.029	0.04	0.070	0.0012
Helplessness	0.063	0.002	0.148	< 0.0001

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anxiety, which was not associated with either of the acute phase reactants.

Discordance between hs-CRP and ESR. The correlation (R) between hs-CRP and ESR was 0.611. All patients (n = 18, 12%) with an hs-CRP > 23 mg/l had a high ESR (> 20 mm/h). The discordance in the remaining 128 (88%) patients is shown in Figure 1. Most patients with an intermediate or low hs-CRP did not have a high ESR.

DISCUSSION

The use of hs-CRP assays was recently recommended as a measure to identify low disease activity in RA[3,11]. We found that in 61 (42%) of our patients, the hs-CRP was 2–8 mg/l and the hs-CRP was predictive of disease activity. These patients were also less often in clinical remission[6] when compared to patients with an hs-CRP < 2 mg/l. Systemic inflammation that is generally not detectable by routine CRP testing may be common in RA. Since even mild disease activity is associated with poor longterm outcome in RA[1], hs-CRP testing should be helpful in deciding whether disease modifying agent therapy needs intensification.

Of interest, even in patients with an hs-CRP < 2 mg/l, only 50% met the ACR criteria for clinical remission[6]. This may indicate that reliance on the acute phase response alone is inadequate in monitoring disease activity and supports the use of multiple measures in assessing disease activity in RA[1,2,11-13].

We further found that the hs-CRP was consistently more strongly associated with other disease activity variables than the ESR. CRP and ESR were previously reported to be associated to a similar extent with disease activity in RA[12,13]. Whether this discrepancy relates to differences in the assays being used may need further study.

In conclusion, by using an hs-CRP assay, systemic inflammation that is generally not detectable with routine CRP tests was commonly found in RA. Also, hs-CRP performed consistently better than the ESR at predicting other disease activity variables.

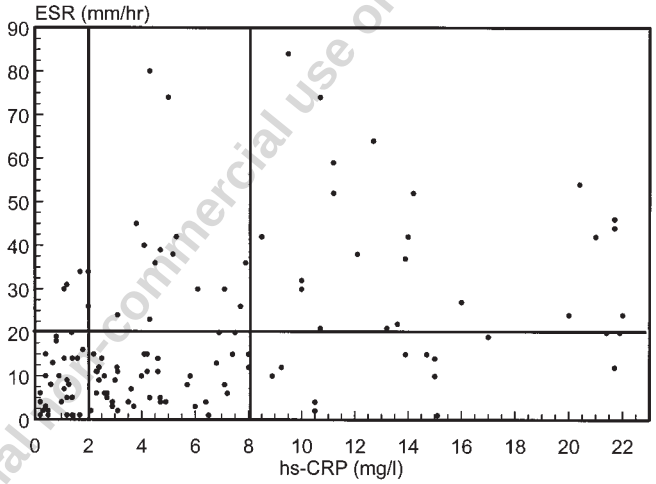

Figure 1. Discordance between ESR and hs-CRP in 128 RA patients with hs-CRP < 23 mg/l.

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