Age Adjustment Corrects for Apparent Differences in Erythrocyte Sedimentation Rate and C-Reactive Protein Values at the Onset of Seropositive Rheumatoid Arthritis in Younger and Older Patients

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ABSTRACT. ***Objective.*** To evaluate the effect of age adjustment on baseline erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in patients with late-onset rheumatoid arthritis (LORA, age ≥ 55 yrs) and younger-onset RA (YORA, age < 55 yrs) in a cohort with early, rheumatoid factor (RF) positive RA that has not received disease modifying antirheumatic drugs (DMARD).

Methods. In an ongoing prospective cohort study of 263 patients with seropositive RA who were enrolled within 14 months of symptom onset, baseline assessments included ESR, CRP, tender and swollen joint counts, and functional status. Westergren ESR determinations were performed in the rheumatologist's office or in a local laboratory using appropriate methods. CRP were performed at the Specialty Laboratories in Santa Monica, CA, using Behring nephelometry. Percentages of patients with greater than the upper limit of normal (ULN) laboratory values using both age-unadjusted and age-adjusted ESR and CRP values were determined. The late-onset and younger-onset RA patients were compared using Wilcoxon rank-sum and chi-square tests.

Results. At study entry, both the YORA and LORA patients had comparable symptom duration, disease activity scores, tender and swollen joint counts, and Health Assessment Questionnaire values. RF, CRP, and ESR were significantly higher ($p < 0.05$) in LORA patients. Although the percentages of patients with age-unadjusted ESR and CRP above ULN were higher in LORA patients, the percentages exceeding the age-adjusted ULN did not differ significantly between the YORA and LORA groups.

Conclusion. In patients with late-onset and younger-onset RA with similar disease duration and severity, the apparent discrepancy in elevation of both the baseline ESR and CRP disappears after age-adjustment. (J Rheumatol 2005;32:1040–2)

Key Indexing Terms:
EARLY RHEUMATOID ARTHRITIS ACUTE PHASE REACTANTS ELDERLY
ERYTHROCYTE SEDIMENTATION RATE C-REACTIVE PROTEIN AGE ADJUSTMENT

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory arthritis that leads to destruction of joints. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are non-specific acute phase reactants that can increase with an inflammatory condition, infection, or malignancy. Despite their non-specificity, these commonly used laboratory endpoint measures of disease activity in patients with RA correlate with disease activity and radiographic damage[1].

The Westergren ESR increases with age. Based on a cohort of 27,912 healthy adults, a simple formula was developed for age-adjusting ESR values for the upper limit of

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normal (ULN)[2]. The age-adjusted ULN formula for ESR is age/2 for men and for women is (age + 10)/2. Based on a cohort of > 22,000 patients, plasma CRP increases with age; the age-adjusted ULN for men is age/50 and for women is age/50 + 0.6[3].

Many studies suggest differences in patients with late-onset (LORA) and younger-onset (YORA) RA[4-6]. Whether there are distinct clinical differences between the 2 groups is controversial[7,8]. Although most studies show an increase in ESR and CRP in patients with LORA in comparison to those with YORA, these studies did not adjust for increases related to age. We evaluate the effect of age adjustment of baseline ESR and CRP in patients with late and younger onset RA in a cohort with early, rheumatoid factor (RF) positive disease.

MATERIALS AND METHODS

Patients. Patients included in this study are a subset of a group of patients with early RA participating in a longterm observational study by the Western Consortium of Practicing Rheumatologists, a regional consortium of rheumatology practices in the Western United States and Mexico. The study, which was reviewed and approved by the UCLA institution review board, was originally designed to evaluate the longitudinal impact of early, active, seropositive RA on disease activity, functional ability, and structural damage.

Patients in this recent-onset subset had a diagnosis of early RA (≤ 14 mos since symptom onset), had no previous disease modifying antirheumatic drug (DMARD) treatment, were seropositive (RF 1:80 titer, or ≥ 40 IU/ml), with ≥ 6 swollen joints and ≥ 9 tender joints, and had at least 2 sets of scored joint radiographs. Patients with symptom onset > 14 months prior to study enrollment or negative RF were excluded. Using standard methods, detailed physician assessment at baseline included all core set outcome measures required to calculate the disease activity score (DAS)[9,10], tender and swollen joint counts, Westergren ESR, and CRP. DAS was calculated according to the published algorithm using the Ritchie index, swollen joint count of 44 joints, and unadjusted ESR in mm/h. Westergren ESR were performed at entry in the rheumatologist's office or a local laboratory. CRP and RF measurements were performed by Specialty Laboratories in Santa Monica, CA. Behring nephelometry for CRP was performed for all samples[11,12].

Patients were asked to complete a mailed questionnaire at study entry regarding demographics, health, medication, 0-100 mm visual analog scale (VAS) for pain, 0-3 for patient global assessments, and the Health Assessment Questionnaire-Disability Index (HAQ-DI)[13].

Methods. Late-onset RA was defined as patients with onset of RA at ≥ 55 years. Baseline characteristics of patients with seropositive YORA (age < 55 yrs) and LORA were compared. Age-unadjusted ULN for ESR and CRP was 22 mm/h and 0.5 mg/dl, respectively. The ESR values were age-adjusted for the ULN by gender: female: (age +10)/2, male: age/2. CRP values were age-adjusted for the ULN by gender as well: females (age/50) + 0.6 and males age/50. The ratios of observed results to age-adjusted results for ESR and CRP at baseline were obtained, and the percentages of patients higher than normal were calculated for patients with YORA and LORA.

Statistical analysis. The Wilcoxon rank sum test was used to compare the YORA and LORA groups for continuous and ordinal variables and the chi-squared test was used for dichotomous variables. Transformations were used for ESR and CRP (logarithm and square root, respectively) in these models to stabilize the variance across the range of values.

RESULTS

Baseline demographic variables of LORA and YORA (Table 1) include similar duration and disease activity as assessed by DAS-28, HAQ-DI, tender and swollen joint counts, patient and physician global scores, and pain VAS. The RF concentration, a laboratory test known to increase with age was noted to be different (p = 0.03) between older and younger patients (290, 503 IU/ml). Duration and disease activity were similar between the YORA and LORA groups as assessed by DAS, HAQ-DI, tender and swollen joints, patient and physician global scores, and pain VAS. Late-onset RA patients had significantly higher unadjusted ESR and CRP than younger-onset RA patients; ESR means were 49 and 36 mm/h and CRP means were 3.5 and 2.4 mg/dl, respectively (Table 2). ESR and CRP values above the age-unadjusted ULN were more frequent in LORA than in YORA patients (85% vs 71% for ESR and 80% vs 70% for CRP). However, after age adjustments, these differences were no longer present.

Table 1. Baseline characteristics of patients with younger-onset (YORA) and later-onset (LORA) disease. Values are reported as mean (SD) unless otherwise stated.

Variable [range]	YORA n = 167	LORA n = 96	p
Age, min–max yrs (median)	21–54 (42)	55–78 (63)	
Disease duration, mo [0–14]	6.2 (3)	6.3 (3.6)	0.80
DAS	4.7 (1.2)	4.8 (1.2)	0.77
HAQ [0–3]	1.2 (0.7)	1.2 (0.7)	0.46
Tender joint count [0–69]	23 (13)	23 (13)	0.76
Swollen joint count [0–66]	19 (11)	20 (11)	0.51
RF, IU/ml	290 (306)	503 (720)	0.03
Pain VAS [0–100]	59 (27)	65 (27)	0.16
Patient global [0–3]	1.3 (0.7)	1.3 (0.7)	0.95
Total Sharp score	0.17 (0.44)	0.17 (0.29)	0.25

DAS: disease activity score; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; VAS: visual analog scale.

Table 2. Baseline ESR and CRP for patients with younger-onset (YORA) and later-onset (LORA) disease.

	YORA n = 167	LORA n = 96	p
ESR, mm/h, mean (SD)	36 (23)	49 (27)	0.0001
CRP, mg/dl, mean (SD) (mg/dl)	2.4 (3.4)	3.5 (4)	0.004
ESR, % patients above ULN (> 22 mm/h)	71	85	0.007
ESR, % patients above age-adjusted ULN*	68	65	0.64
CRP, % patients above ULN (> 0.5 mg/dl)	70	80	0.07
CRP, % patients above age-adjusted ULN*	61	64	0.63

* Age adjustments for ESR: male: age/2; female: (age +10)/2; CRP: male: age/50; female: (age/50)+0.6. ULN: upper limit of normal.

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DISCUSSION

Baseline characteristics in this RF-positive, early RA cohort of patients include similar activity at baseline in both older and younger patients with the same disease duration. Although RF, ESR, and CRP were significantly increased in the older patients with RA at baseline, all 3 laboratory tests are known to increase with age[2,3,11,14]. The percentages of our patients with ESR and CRP values above the ULN was higher in the group with LORA. With published age-adjustment formulas for ESR and CRP, the ESR and CRP differences between the younger-onset and late-onset groups disappeared. The differences that we and others have found in the unadjusted acute phase reactants can be accounted for by correcting for age-related processes. After correction the differences between the groups are not statistically significant, and the size of the difference (3%) is also not clinically significant. The LORA and YORA groups are in this sense more similar to each other than previously thought.

In summary, ESR and CRP are used commonly to evaluate disease activity in patients with RA. In an RF-positive, early RA cohort that included patients with both late-onset and younger-onset disease, age-adjustment for the ULN accounts for the apparent discrepancy in frequency of elevation of baseline ESR and CRP.

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