

CONCISE REPORT

Value of C reactive protein in the assessment of erosive osteoarthritis of the hand

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Objective: To investigate the value of serum C reactive protein (CRP) as a marker of erosive osteoarthritis (EOA) of the hand.

Methods: Ninety eight patients, 67 with EOA and 31 with non-EOA of the hand, were included in the study and analysed for radiographic score (RS), number of erosions, and joint count (JC) at clinical observation and at bone scintigraphy. CRP was assayed in a serum sample by a highly sensitive immunonephelometric method.

Results: The median (interquartile range) CRP level was 4.7 (2.4–6.9) mg/l in the EOA and 2.1 (0.5–4.9) mg/l in the non-EOA group ($p=0.001$). In all patients, CRP correlated with RS ($r_s=0.43$, $p<0.001$), and mainly with JC at clinical observation ($r_s=0.72$, $p<0.001$) and at bone scintigraphy ($r_s=0.47$, $p<0.001$). The correlation of CRP with RS and JC was confirmed at clinical observation and at bone scintigraphy in the EOA subgroup, but only with JC at clinical observation in the non-EOA subgroup.

Conclusions: CRP levels are higher in EOA than in non-EOA patients. These levels probably reflect the disease activity of EOA, as suggested by correlations between CRP and JC at clinical observation and at bone scintigraphy.

Erosive osteoarthritis of the hand (EOA) is a form of OA characterised by frequent inflammatory episodes and an aggressive course. Some authors believe that EOA is a subset of generalised OA, whereas others have questioned this interpretation, suggesting, by a long follow up with radiographs taken each year, that EOA merely represents a phase in the evolution of a normal nodal OA of the hand.^{1,2} However, there is general agreement that EOA represents a clinical expression of OA punctuated by inflammatory episodes with acute pain, swelling, and erythema affecting distal interphalangeal and proximal interphalangeal joints and characterised by the presence of articular surface erosions.¹ Despite these inflammatory aspects, at present no laboratory findings have been found which reflect the disease activity or severity associated with EOA.

Along with the erythrocyte sedimentation rate (ESR), C reactive protein (CRP) is probably the most popular laboratory marker of activity in joint diseases. A rise in CRP is one of the main hallmarks of inflammatory arthropathies, whereas in OA, commonly classified as a “non-inflammatory” arthropathy, CRP has until now been considered useless. However, serum CRP determination has recently been proposed in OA of the hip and knee, as a marker of disease severity.^{3,4} Furthermore, the recent availability of a new highly sensitive method for CRP (hsCRP) determination could probably improve the value of such determination.⁵ In EOA, perhaps the most inflammatory form of OA, CRP has only rarely been determined and, in addition, without leading

to any definitive opinion of its clinical value. Thus, we carried out a study on the value of hsCRP in the assessment of EOA. With this aim, we also investigated the relationship between hsCRP and other clinical, laboratory, radiological, and scintigraphic indices of disease activity or severity in EOA and non-EOA patients.

PATIENTS AND METHODS

Ninety eight patients, 67 with EOA (60 women, 7 men; mean age 61.7, range 46–80 years) and 31 with non-EOA (29 women, 2 men; mean age 55.9, range 41–81 years) of the hand, were included in the study. All patients satisfied the Altman criteria for OA of the hand⁶ before undergoing radiography. Anteroposterior radiographs of the hand were independently read by two equally experienced readers. Type of radiographic features and number of erosions were established according to the atlas of Altman *et al.*,⁷ and the radiographic score (RS) was graded by the Kallman scale.⁸ Patients showing at least two erosions in distal interphalangeal or proximal interphalangeal joints were considered eligible for the EOA group,⁹ whereas patients with erosions in metacarpophalangeal joints were excluded. Patients with other known arthropathies were also excluded. All patients were negative for rheumatoid factor. A bone scintigraphy with technetium-99m methylene diphosphonate and a scintillation camera, was carried out in 53 consecutive patients, 38 with EOA and 15 with non-EOA, who were subsequently evaluated for the number of affected joints, as defined by the number of joints (JC) with an uptake degree of at least 2–3 (on a scale 0 = absence of uptake; 3 = intense uptake). We also evaluated the number of clinically active joints, as defined by the presence of painful or tender joints. CRP levels were assessed by a highly sensitive immunonephelometric method (DADE Behring, Milan, Italy) on a BN II Analyzer; the lower limit of detection was 0.175 mg/l (analytical sensitivity 0.04 mg/l).

Statistical analysis

Data are reported as mean and SD except for serum hsCRP which is not normally distributed; for hsCRP the median and interquartile range are given. Mann-Whitney U or Fisher's exact tests were performed to analyse differences between the groups of patients and Spearman's rank test for correlations among variables. We used multivariate regression with the log transformed serum hsCRP values as dependent variable to adjust for body mass index (BMI), current smoking, former smoking, age, sex, and hormone replacement therapy. All tests were two tailed and a probability value of $p<0.05$ was considered significant.

Abbreviations: BMI, body mass index; CRP, C reactive protein; EOA, erosive osteoarthritis; ESR, erythrocyte sedimentation rate; hsCRP, high sensitivity CRP; IL, interleukin; JC, joint count; OA, osteoarthritis; RS, radiographic score

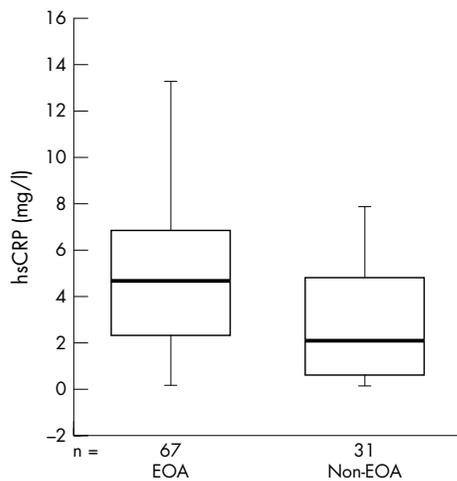


Figure 1 Serum levels of hsCRP in EOA and non-EOA of the hand ($p=0.001$, Mann-Whitney U test).

Statistical analysis was done with SPSS statistical software (release 11.0.1, SPSS Inc, Illinois, USA).

RESULTS

Among selected patients, none reported diabetes mellitus. Self reported alcohol consumption was lower than 20 g a day but no patient was an abstainer. Figure 1 shows that hsCRP was higher in EOA (4.7 (2.4–6.9) mg/l) than in non-EOA (2.1 (0.5–4.9) mg/l, $p=0.001$, Mann-Whitney U test). Controlling for demographic and clinical factors did not change our results ($p=0.002$, linear regression analysis). No difference was seen for the other indices considered, with the exception of JC at clinical observation and RS, both higher in EOA (10.7 (4.5) and 64.3 (29.7)) than in non-EOA (8.2 (4.5), $p=0.003$ and 27.8 (16.5), $p<0.001$; table 1). In the patient group as a whole, hsCRP was mainly associated with JC at clinical observation ($r_s=0.72$, $p<0.001$; fig 2), and at lower levels, with JC at the bone scintigraphy ($r_s=0.47$, $p<0.001$), RS ($r_s=0.42$, $p<0.001$), and number of erosions ($r_s=0.40$, $p<0.001$). Analysis of the subgroups showed that in EOA the high correlation of hsCRP with JC was confirmed at clinical observation ($r_s=0.68$; $p<0.001$) and showed an important correlation with JC at bone scintigraphy ($r_s=0.71$,

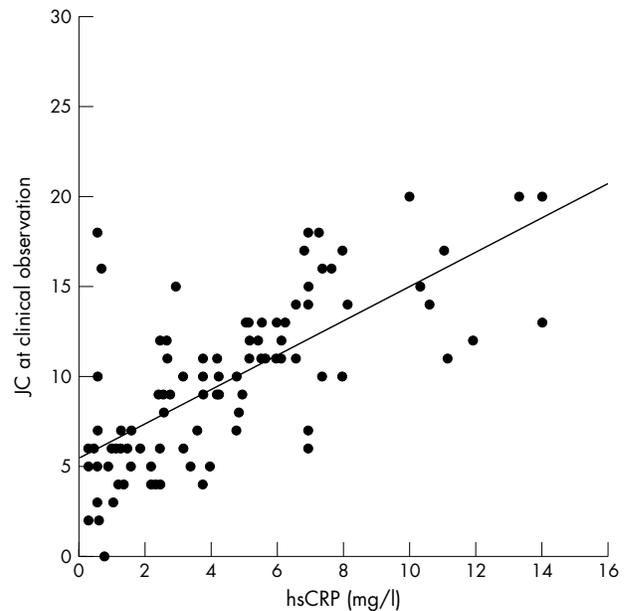


Figure 2 Correlation between hsCRP and JC of clinically active joints in all patients ($r_s=0.72$, $p<0.001$, Spearman's rank test).

$p<0.001$). In non-EOA, the only correlation found was between hsCRP and JC at clinical observation ($r_s=0.58$, $p=0.01$).

DISCUSSION

This study clearly demonstrates that EOA is more active and more severe than non-erosive nodal OA. In agreement with this observation, almost all indices of activity or severity considered, including in particular hsCRP, were worse in EOA than in non-EOA. The exact significance of the increase of hsCRP in EOA is difficult to explain. Furthermore, to our knowledge, this is the first study evaluating hsCRP in EOA. Our results are in agreement with previous reports showing slight increases of traditional CRP and ESR in this disease¹ but, in contrast with others,¹⁰ in which the levels of ESR and CRP were lower in EOA than in non-EOA. Remarkably, in this latter study, the other indices considered, including those evaluated by radiography and scintigraphy, were higher in

Table 1 Main features of EOA and non-EOA of the hand

Features	EOA (n=67)	Non-EOA (n=31)	p Value
Age (years)	61.7 (8.5)	55.9 (9.7)	0.02
Body mass index (kg/m ²)	24.2 (3.5)	24.6 (4.4)	NS
Women†	60	29	NS
Hormone replacement therapy†	8	5	NS
Smoking:‡			
Never	53	23	NS
Former	8	4	NS
Current	6	4	NS
Age of disease onset (years)	51.1 (9.7)	49.9 (8.2)	NS
Range	41–61	41–59	
Disease duration (years)	10.5 (9.9)	9.7 (8.5)	NS
hsCRP (mg/l)*	4.7 (2.4–6.9)	2.1 (0.5–4.9)	0.002‡
Number of clinically active joints	10.7 (4.5)	8.2 (4.5)	0.003
Number of scintigraphically active joints	6.3 (4.4)¶	5.1 (2.5)§	NS
Radiographic score	64.3 (29.7)	27.8 (16.5)	<0.001

Results are shown as mean (SD) unless otherwise indicated.

*Median (interquartile range) or †number of cases; p values for continuous variables from Mann-Whitney and for binary variables from Fisher's exact test; ‡multivariate regression analysis adjusted for BMI, current smoking, former smoking, age, sex, and hormone replacement therapy; ¶information available for 38 patients; §information available for 15 patients.

EOA than in non-EOA. As previously suggested by us,¹¹ one of the reasons for this discrepancy in CRP results may be due to the use of non-sensitive methods for the evaluation of CRP. Most of the traditional methods for CRP, which are not highly sensitive, can only detect a value of >6 mg/l, whereas this acute phase protein may be found in the blood at concentration of 0.00035 mg/l.¹² Thus, even in the presence of a 100-fold increase of CRP, the CRP variation may be undetectable by methods which are not highly sensitive. In agreement with this hypothesis, Loose *et al* found in 365 patients with OA median hsCRP concentrations of about 5 µg/ml, whereas 40 controls matched for age had median values of 1.9 µg/ml.¹³ In our study hsCRP in the whole group of patients correlated with RS and JC at bone scintigraphy in EOA, thus suggesting that this substance could have a role as a marker of disease activity.

The increase of hsCRP in EOA confirms the presence of inflammatory activity in this form of arthropathy and the possibility that a severe local injury such as OA also has a systemic component. It is largely known that almost all the serum concentration of CRP derives from hepatic production and that inflammatory cytokines, in particular interleukin (IL) 6, are mainly responsible for its synthesis. In turn it has been demonstrated that, even at lower levels than in inflammatory arthropathies, the principal proinflammatory cytokines such as IL1β, IL6, IL8, and tumour necrosis factor α are increased in the synovial fluid of OA.¹⁴ Thus, it seems logical that most of the circulating IL6 which can stimulate synthesis of CRP is derived from articular, mainly synovial, tissue. Obviously, because in OA of the hands the tissues producing cytokines are relatively small in comparison with OA of large joints, it may be that serum levels of CRP in EOA better reflect disease activity when more joints are affected by the inflammatory phase.

Owing to its high sensitivity, hsCRP will probably be suitable for inpatient evaluation in outcome studies. Another interpretation of the differences between the two types of hand OA, may be that patients with EOA may have serum levels of CRP "constitutionally" higher than those with non-EOA. In keeping with this hypothesis are the higher serum levels of soluble receptors of IL2, markers of lymphocyte activation, found in EOA in comparison with non-EOA.¹¹ Recently Stern *et al* have reported an association between EOA and a genomic region containing the IL1β 5810 single nucleotide polymorphisms in a Caucasoid population, further supporting a potential role for inflammation in the pathogenesis of this severe phenotype of hand OA.¹⁵ These hypotheses imply that EOA is a subset of OA with peculiar characteristics and predispositions and not an inflammatory phase of the normal OA course.

In conclusion, this study is the first demonstrating that hsCRP may be useful as a marker of EOA.

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