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Synovial C-reactive protein as a marker for chronic periprosthetic infection in total hip arthroplasty

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The aim of this study was to assess the role of synovial C-reactive protein (CRP) in the diagnosis of chronic periprosthetic hip infection. We prospectively collected synovial fluid from 89 patients undergoing revision hip arthroplasty and measured synovial CRP, serum CRP, erythrocyte sedimentation rate (ESR), synovial white blood cell (WBC) count and synovial percentages of polymorphonuclear neutrophils (PMN). Patients were classified as septic or aseptic by means of clinical, microbiological, serum and synovial fluid findings. The high viscosity of the synovial fluid precluded the analyses in nine patients permitting the results in 80 patients to be studied. There was a significant difference in synovial CRP levels between the septic (n = 21) and the aseptic (n = 59) cohort. According to the receiver operating characteristic curve, a synovial CRP threshold of 2.5 mg/l had a sensitivity of 95.5% and specificity of 93.3%. The area under the curve was 0.96. Compared with serum CRP and ESR, synovial CRP showed a high diagnostic value. According to these preliminary results, synovial CRP may be a useful parameter in diagnosing chronic periprosthetic hip infection.

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Periprosthetic joint infection is a common complication after total hip arthroplasty (THA). The incidence is approximately 1% after primary replacement and about 4% in revision arthroplasty.[1] Moreover, low-grade-infections, which are not detected by standard investigations, are often not taken into account and could conceal a higher incidence of infection. Currently, periprosthetic hip infection is the second most common cause for revision hip arthroplasty,[2] being associated with considerable morbidity, including loss of function and impaired quality of life. In some patients arthrodesis, resection arthroplasty or amputation may be required;[3] at the same time, the economic burden has increased dramatically over recent decades.[4]

The diagnosis of periprosthetic infection can be challenging because clinical presentations vary. Typical signs of infection, such as erythema, swelling, fever and increased blood infection markers, are not always present, and there is no test for infection that is totally reliable. Therefore, the diagnosis is usually made on the basis of a combination of different parameters, including clinical, serum and synovial fluid findings.[2,5] Modern inflammatory serum markers, such as interleukin (IL)-6, tumour necrosis factor (TNF)-α and procalcitonin, have not shown distinct advantages over the conventional inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and have therefore not found their way into routine clinical practice.[6] However, in recent years studies have focussed on the assessment of inflammatory proteins in the synovial fluid of infected total joint arthroplasties and have shown promising results.[7-9] Measuring the synovial CRP in periprosthetic joint infections, mainly in total knee arthroplasty, has been shown by two studies to be superior to measuring serum CRP.[10,11] Since the measurement of CRP is a standard test for the detection of inflammatory processes, its use as a synovial infection marker can be easily transferred into clinical practice. This is the first study to evaluate the role of synovial CRP exclusively in chronic periprosthetic hip infection. Approval for the study was obtained from our institution's ethical committee.

Patients and Methods

Experiments were carried out in the trauma department of Hannover Medical School and the orthopaedic surgery department of ENDO Clinic Hamburg. Between January 2012 and December 2013 we analysed a consecutive series of patients undergoing revision hip arthroplasty. For this study we focussed on

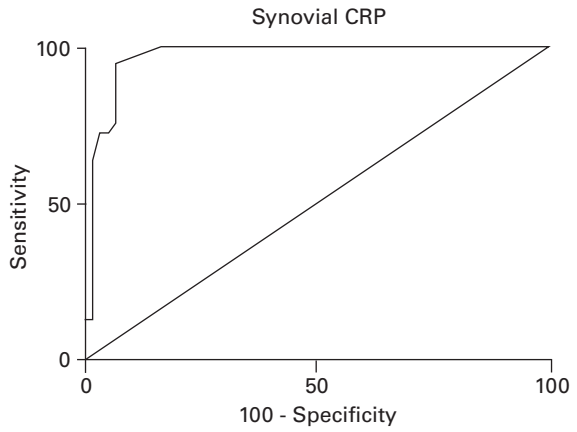

Fig. 1

Receiver Operating Characteristics curve for synovial C-reactive protein (CRP). Sensitivity is plotted against 100% specificity.

chronic infection, which means any periprosthetic joint infection which occurred at least six weeks after the index operation. Prior to surgery, synovial fluid was obtained by sterile aspiration for cell analysis (synovial white blood cell (WBC) count and percentage of polymorphonuclear cells (%PMN)), cultures and measurement of synovial CRP. Moreover, serum CRP and ESR were determined. Measurement of CRP concentrations in synovial fluid and serum was done by nephelometry, which is a common automated technique to assess the level of blood plasma proteins. This technique relies on determining the turbidity of diluted samples consisting of antigen-antibody-complexes. Samples of CRP molecules (antigen) and corresponding antibodies form small particles that scatter light that passed through it. From the amount of scattered light the concentration of the antigen can be calculated. Intra-operative synovial fluid and tissue were collected for culture. In addition, clinical examination was documented and the patient's history reviewed. Patients who had incomplete data within the study parameters were excluded. For the diagnosis of periprosthetic hip infection, one of the following four criteria were required: an open sinus tract or wound in communication with the joint; purulent synovial fluid; positive microbiological pre-operative or intra-operative synovial fluid or tissue culture; or a combination of serological and synovial findings, according to the American Academy of Orthopedic Surgeons' (AAOS) guidelines for the diagnosis of periprosthetic joint infection.[12] These guidelines require the assessment of serum CRP, ESR, WBC count and %PMN. Periprosthetic joint infection was assumed when three of these four parameters (serum CRP, ESR, WBC, %PMN) were elevated. There are different thresholds for acute and chronic infections. As we included exclusively chronic infections, thresholds were as follows: serum CRP > 10 mg/l; ESR > 30 mm/h; WBC > 1760 cells/mm^3; and %PMN > 73%.[12] Patients who did not meet these criteria were considered to have aseptic implant failures.

Statistical analysis. Statistical analyses were carried out using Prism 6 software (GraphPad Software Inc., La Jolla, California). For statistical purposes, CRP values below the sensitivity threshold of the nephelometric method (< 1 mg/l) were set to 1. A one-tailed *t*-test was used to analyse univariate unpaired data. The level of statistical significance was set at a p-value < 0.05. Receiver operating characteristic (ROC) curves were constructed to display the sensitivity and specificity of the different parameters for chronic hip infection. The area under the curve (AUC) for each parameter was calculated and the optimum cut-off points were determined by the maximised Youden's index.

Results

A total of nine patients were excluded from the study because of either a dry aspiration or the high viscosity of the synovial fluid, leaving 89 patients to be included. Because the nephelometric method is adapted for serum, which normally has a lower viscosity than the joint aspirate, the measurement of some fluids with high viscosity failed. Of the 89 patients (following the exclusion of nine reported above), 21 were classified as septic and 59 as aseptic. The mean age in the septic group was 65 years (39 to 85) and the cohort was predominantly male (n = 12, 57%), whereas the aseptic group was predominantly female (n = 35, 59%) and their mean age was 66 years (44 to 88). There were no significant differences in age and gender. The mean time to revision was significantly different in the septic group (61 months; 6 to 162) and the aseptic group (113 months; 6 to 385) (p < 0.019). The mean synovial CRP in the septic group was 15.5 mg/l (2 to 45), which was significantly higher than in the aseptic group (1.2 mg/l; 0 to 32). There was also a statistical difference for serum CRP, ESR, synovial WBC and %PMN between the septic and aseptic groups (Table I). According to the ROC, a synovial CRP threshold of 2.5 mg/l had a sensitivity of 95.5% and specificity of 93.3%. The AUC was 0.96, indicating a high diagnostic accuracy (Fig. 1). The sensitivities for serum CRP and ESR were 78.3% and 76.7%, respectively, whereas the specificities ranged up to 90.9% (Table II).

On the basis of pre-operative history and elevated serum markers, 16 out of 21 patients would have been correctly detected as septic. This means that five patients would have been missed. Four of these five missed patients were correctly diagnosed using synovial CRP.

Discussion

General inflammatory blood markers, which include elevated serum CRP and ESR, are readily available and are used in clinical practice as screening tests for periprosthetic joint infections. Both serum CRP and ESR have shown to provide good sensitivity > 90%, but results for specificity are mixed, ranging from 20% to 80%.[13-15] These findings are more or less consistent with our results, showing signif-

Table I. Synovial CRP, serum CRP, ESR, WBC and %PMN for the septic and aseptic groups. Values are given as means; 95% confidence intervals (CI) are given in parentheses

	Septic (n = 21)	Aseptic (n = 59)	p-value (*t*-test)
Synovial CRP (mg/l)	15.5 (7 to 21)	1.2 (0 to 2)	< 0.001
Serum CRP (mg/l)	51.3 (33 to 78)	8.7 (6 to 13)	< 0.001
ESR (mm/h)	66 (50 to 82)	26 (22 to 81)	< 0.001
Synovial WBC cells/µl	20253 (10574 to 29932)	1592 (784 to 2399)	< 0.001
Synovial %PMN	85 (79 to 91)	35 (28 to 41)	< 0.001

CRP, C-reactive protein, ESR, erythrocyte sedimentation rate; %PMN, percentage of polymorphonuclear neutrophils; WBC, white blood cell

Table II. Thresholds, sensitivities, specificities and area under the curve (AUC) for synovial CRP, serum CRP, ESR, WBC and %PMN. 95% confidence intervals (CI) are given in parentheses

	Threshold	Sensitivity (%)	Specificity (%)	AUC
Synovial CRP	2.5 mg/l	*95.5* (86.7 to 99.9)	*93.3* (84.3 to 99.9)	0.96 (0.90 to 0.99)
Serum CRP	9.5 mg/l	*78.3* (65.8 to 87.9)	*86.4* (65.1 to 97.1)	0.87 (0.79 to 0.95)
ESR	29 mm/h	*76.7* (63.9 to 86.6)	*90.9* (70.8 to 98.9)	0.90 (0.83 to 0.97)
WBC	3089 cells/µm^3	*85.0* (73.4 to 92.9)	*86.3* (65.1 to 97.1)	0.92 (0.89 to 0.99)
PMN	72.1	*90.0* (79.5 to 96.2)	*90.1* (70.8 to 98.9)	0.94 (0.89 to 0.99)

CRP, C-reactive protein, ESR, erythrocyte sedimentation rate; %PMN, percentage of polymorphonuclear neutrophils; WBC, white blood cell

icant differences in the serum CRP and ESR of patients undergoing revision arthroplasty for septic or aseptic reasons. To improve diagnostic accuracy, different molecular serum markers have been identified. Two studies showed an excellent sensitivity and specificity for IL-6,[6,13] whereas one study[16] revealed good specificity but poor sensitivity. The strength of both procalcitonin and TNF-α is their high specificity, making it possible to rule out infections.[6] However, the number of these studies is limited and the diagnostic strength of these new markers does not significantly exceed that of serum CRP and ESR. This is mainly because these are unspecific inflammatory markers. Moreover, they are frequently not readily accessible and are more expensive.[17] A general drawback of all known serum markers is that they are not specific for periprosthetic joint infection and may be easily influenced by concomitant infections. Their analyses in joint aspirates have been considered to be more promising, as synovial fluid is in direct contact with the infection site. Aspirate analyses such as synovial WBC and %PMN already belong to the standard procedures exceeding the diagnostic value of serum markers,[18-23] which is supported by our data for WBC and %PMN.

The assessment of synovial fluid biomarkers is an interesting new approach. Different studies have evaluated a series of experimental inflammatory proteins, some of them yielding approximately ideal sensitivity and specificity.[7-9] However, further investigations with larger numbers are required to confirm these results. The analysis of CRP in synovial fluid has been performed in both natural joints and prosthetic joints. In normal joints, differentiation between inflammatory and non-inflammatory arthritis was possible. However, there was no significant difference in the synovial CRP levels among all types of inflammatory arthritis, and infection could not be excluded.[24]

In arthroplasties, elevated synovial CRP levels were associated with periprosthetic joint infection. In different studies Parvizi et al[10,11] evaluated the role of synovial CRP in prosthetic joint infections. In their first study they showed a superior diagnostic accuracy of synovial CRP compared with serum CRP. Furthermore, different assays for the measurement of synovial CRP were evaluated.[10] In their second study, Parvizi et al [11] showed that a synovial CRP of 9.5 mg/l has a sensitivity of 85% and specificity of 95% for diagnosing periprosthetic joint infection. However, periprosthetic joint infection was defined solely on the basis of the AAOS guidelines using serum CRP, ESR, synovial WBC and %PMN, whereas in our study we also included clinical and culture findings. Parvizi et al[11] investigated both acute and chronic joint infections, whereas we focused only on chronic hip infections. Despite these differences, we can confirm their findings, thereby highlighting the fact that synovial CRP is an appropriate marker for all kind of periprosthetic joint infections. In our study there was high sensitivity and specificity for synovial CRP, and it exceeded those of the other parameters displayed by the AUC. However, our threshold was much lower than that of Parvizi et al,[11] which may be because we included only chronic infections, and chronic infections typically do not produce such an increase in serum CRP as do acute infections. The diagnostic values of synovial markers such as WBC, %PMN and synovial CRP were superior to those of the serological markers serum CRP and ESR. Considering the high confidence intervals, the increased AUC of synovial CRP was not significantly different from those of WBC and %PMN.

However, synovial CRP appears to be a useful adjunct and carries more weight than serum CRP. Assuming infection only on the basis of elevated serum markers, five patients would have been missed in our cohort. Four of these five missed patients were correctly diagnosed using synovial CRP, thereby supporting the value of this test.

The strength of our study is that we investigated a homogeneous group of chronic periprosthetic hip infections, but nevertheless it had limitations. The sample size was relatively small, but serological and synovial fluid findings were significantly different in the septic and aseptic groups. A further limitation is that the nephelometric method failed to measure samples with very high viscosity, leading to the exclusion of some patients.

In conclusion, as CRP assays are standard tests in medical laboratories, the measurement of synovial CRP may be easily transferred into clinical practice, expanding the diagnostic battery for chronic periprosthetic hip infections.

Author contributions

M. Omar: Literature search, Data collection, Data analysis and interpretation, Drafting and writing manuscript.
M. Ettinger: Data analysis and interpretation, Tables and figures, Drafting manuscript.
M. Reichling: Data collection, Data analysis.
M. Petri: Data collection, Manuscript revision.
D. Guenther: Data collection, Manuscript revision.
T. Gehrke: Study design, Data interpretation, Manuscript revision.
C. Krettek: Study design, Data interpretation, Manuscript revision.
P. Mommsen: Literature search, Study design, Data analysis and interpretation, Manuscript revision.

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