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Orthopaedics & Traumatology Surgery & Research

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Original article

# Diagnostic accuracy of intra-articular C-reactive protein assay in periprosthetic knee joint infection – a preliminary study

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## A R T I C L E   I N F O

## A B S T R A C T

*Background:* Periprosthetic joint infection often raises diagnostic challenges, as the published criteria are heterogeneous. New markers for predicting periprosthetic infection have been evaluated. Here, we assessed one of these markers, C-reactive protein (CRP), in joint fluid.
*Hypothesis:* We hypothesised that intra-articular CRP levels would perform better than serum CRP concentrations in diagnosing knee prosthesis infection.
*Patients and methods:* We prospectively included 30 patients including 10 with native-knee effusions, 11 with prosthetic-knee aseptic effusions, and 11 with prosthetic-knee infection defined using 2011 Musculoskeletal Society criteria. Serum CRP was assayed using turbidimetry or nephelometry and intra-articular CRP using nephelometry. Appropriate statistical tests were performed to compare the three groups; P values < 0.05 were considered significant.
*Results:* Serum and intra-articular CRP levels were 5- to 16-fold higher in the group with periprosthetic infection than in the other two groups. Although the areas under the ROC curves were not significantly different, the likelihood ratios associated with the selected cut-offs suggested superiority of intra-articular CRP: a value > 2.78 mg/L suggested possible infection (100% sensitivity and 82% specificity) and a value > 5.37 mg/L probable infection (90% sensitivity and 91% specificity).
*Discussion:* Our findings suggest a possible role for intra-articular CRP assay in diagnosing knee prosthesis infection and perhaps periprosthetic infection at any site.
*Level of evidence:* Level III, diagnostic study, development of a diagnostic criterion in consecutive patients comparatively to a reference standard.

## 1. Introduction

Periprosthetic joint infection places a huge medical and economic burden on public health [1,2]. This potentially severe complication occurs in about 1 to 4% of knee prostheses and 0.5 to 2% of hip prostheses [3–7]. The diagnosis rests on a set of clinical, laboratory, histological, and microbiological criteria [8–10]. However, published diagnostic criteria are heterogeneous [11]. Microbiological studies play a crucial role in diagnosing periprosthetic infection but cannot be used alone as they are negative in 7 [11] to 23% [12] of confirmed cases. In addition, the presence of a potential contaminant (e.g., coagulase-negative *Staphylococcus*) in a single specimen is not sufficient to establish the diagnosis of periprosthetic infection. Parvizi et al. recently developed a set of

diagnostic criteria that is now widely accepted [13]. Nevertheless, these criteria are not perfect, and their absence does not completely rule out periprosthetic infection.

The inadequate diagnostic performance of conventional criteria has prompted a search for new markers capable of predicting periprosthetic infection. Examples include leukocyte-esterase activity, inflammatory cytokine levels, and growth factor levels in intra-articular fluid from prosthetic joints [14,15]. The most promising marker to date may be C-reactive protein (CRP) [16].

Here, our objective was to assess the diagnostic accuracy of intra-articular CRP in knee prosthesis infection. Our working hypothesis was that intra-articular CRP performed better than serum CRP in diagnosing knee prosthesis infection.

## 2. Patients and methods

Specific ethics committee approval was not required, as no specific interventions were required for the study.

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**Table 1**
Baseline patient characteristics.

| | Native knee $n = 10$ | Prosthesis, aseptic effusion $n = 11$ | Prosthesis, infection $n = 10$ | |
|---|---|---|---|---|
| Age (years) | 69.8 (52–87) | 79.8 (67–89) | 74.3 (55–88) | NS |
| % females | 80 | 54.5 | 70 | NS |
| Body weight (kg) | 85.6 (63–101) | 79.9 (51–105) | 93.9 (60–144) (DM 1) | NS |
| Height (m) | 1.65 (1.58–1.80) (DM1) | 1.66 (1.45–1.85) (DM 1) | 1.65 (1.55–1.83) (DM 1) | NS |
| Body mass index (kg/m$^2$) | 31.78 (26.91–40.46) (DM 1) | 29.66 (24.26–36.57) (DM 1) | 34.76 (22.09–56.96) (DM 1) | NS |

The data are median (range). NS: non-significant.

Between February and August 2012, we prospectively included 31 patients seen at the orthopaedic surgery and rheumatology departments of the Strasbourg university hospital, Strasbourg, France. Among them, 10 had an aseptic effusion in a native knee, 11 an aseptic effusion in a prosthetic knee, and 10 a knee prosthesis infection. Among patients with knee prostheses, aseptic effusion and infection were distinguished based on 2011 Musculoskeletal Infection Society criteria [13].

We collected the following baseline data: age, sex, body mass index, risk factors for infection (diabetes, smoking, anti-thrombotic therapy), and time since prosthesis implantation.

Joint fluid was obtained by aspiration of the joint cavity during either an outpatient visit or a surgical procedure. Intra-operative aspiration was performed before opening the capsule, to avoid contamination with blood. In everyday practice, microbiological studies are obtained routinely and cytological studies as deemed necessary by the physician. Residual joint fluid, in a volume of at least 1 mL, was placed in an SST gel tube and used to assay CRP. Blood was drawn at the same time for a serum CRP assay.

Biochemical assays were performed at the biochemistry laboratory of the biology technical platform of the Strasbourg university hospital. Serum CRP was assayed using turbidimetry or nephelometry. Nephelometry provides accurate CRP quantification when the CRP level is below the threshold detectable by turbidimetry (ultrasensitive CRP, usCRP). Intra-articular CRP was assayed by nephelometry; the time and cost needed for this test were similar to those of the serum usCRP assay. Results are reported in mg/L.

### 2.1. Statistics

Serum and intra-articular CRP levels in the three groups were compared using the Kruskal-Wallis test. Pairwise comparisons were then performed using the Mann-Whitney test corrected according to the Steel-Dwass-Critchlow-Fligner procedure.

Within-patient comparisons of serum and intra-articular CRP levels were performed with the Wilcoxon test for paired data. Spearman's test was used to assess correlations. This analysis was conducted in the overall population and in each of the three groups.

To determine the best cut-offs for serum and intra-articular CRP levels, we determined the area under the receiver-operating characteristics curves (AUC-ROC). The AUC-ROC values for serum and intra-articular CRP were compared using the Delong test. The cut-offs associated with the optimal compromise between sensitivity and specificity were identified and their likelihood ratios (LRs) were computed.

Values of $P < 0.05$ were considered significant.

## 3. Results

### 3.1. Baseline patient characteristics

At baseline, the groups did not differ significantly regarding age, body weight, height, body mass index, or risk factors for infection.

In the native-knee group, two patients had conditions likely to affect inflammation marker levels (inflammatory joint disease and chronic viral hepatitis, respectively). Mean time since prosthesis implantation was 10.6 years in the group with aseptic effusion and 3.8 years in the group with prosthesis infection. None of the patients had had the knee prosthesis implanted within 1 month before collection of the study samples (Table 1).

### 3.2. CRP values

Serum CRP levels differed significantly across the three groups. In the group with prosthetic infection, the serum CRP level was five times higher than in the prosthesis-aseptic effusion group and 16 times higher than in the native-knee group ($P < 0.05$ and $P < 0.001$, respectively; Fig. 1), (Table 2).

Intra-articular CRP levels also differed significantly across the three groups ($P < 0.001$). The value in the group with prosthetic infection was six times higher than in the prosthesis-aseptic effusion group and 12 times higher than in the native-knee group ($P < 0.01$, Fig. 2). Intra-articular CRP levels were not significantly different between the prosthesis-aseptic effusion group and the native-knee group.

### 3.3. Pairwise comparisons of serum and intra-articular CRP levels overall and in each group

We found a strong correlation between serum and intra-articular CRP levels in the overall population (rho = 0.90, $P < 0.001$, Fig. 3). The two values correlated significantly with each other in the native-knee group (rho = 0.95; $P < 0.001$) but not in the prosthesis-aseptic effusion group (rho = 0.61; $P = 0.07$) or prosthetic infection group (rho = 0.67; $P = 0.06$).
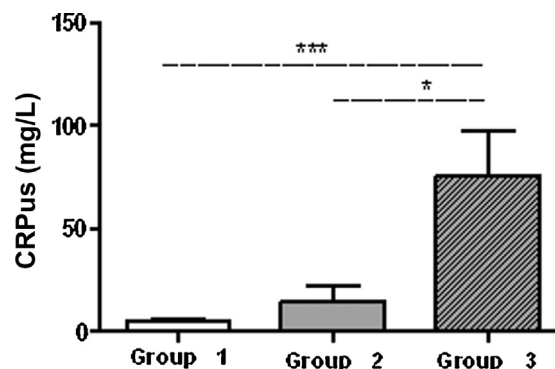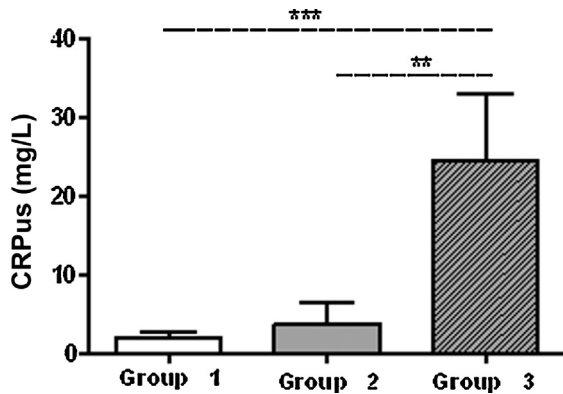


**Fig. 1.** Serum CRP in mg/L (mean ± SD). Group 1: native knee, $n = 10$; group 2, knee prosthesis, aseptic effusion, $n = 11$; group 3, knee prosthesis infection, $n = 10$. *$P < 0,05$; ***$P < 0.001$.

**Table 2**
C-reactive protein (CRP) levels.

| | Native knee $n = 10$ | Prosthesis, aseptic effusion $n = 11$ | Prosthesis, infection $n = 10$ | |
|---|---|---|---|---|
| Serum CRP (mg/L) | 4.53 (0.39–15.20) | 4.69 (0.94–66.50) | 52.00 (19.50–225.00) | *** |
| Intra-articular CRP (mg/L) | 1.25 (0.27–7.60) | 0.69 (0.17–30.80) | 13.95 (4.39–92.10) | *** |

The data are median (range). ***$P < 0.001$.



**Fig. 2.** Intra-articular CRP in mg/L (mean ± SD). Group 1: native knee, $n = 10$; group 2, knee prosthesis, aseptic effusion, $n = 11$; group 3, knee prosthesis infection, $n = 10$. **$P < 0.01$; ***$P < 0.001$.
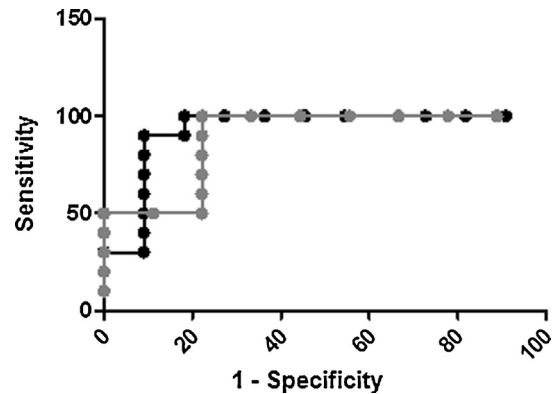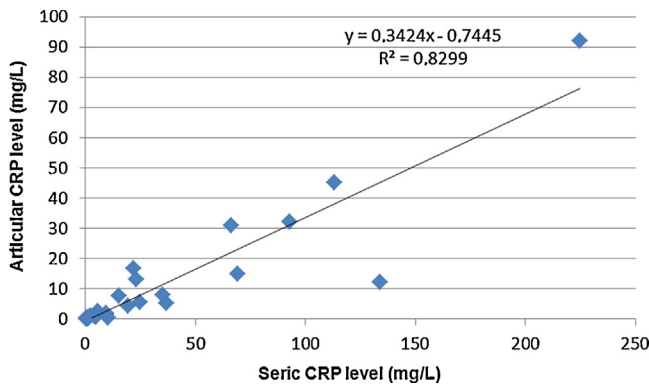


**Fig. 3.** Correlation between serum and intra-articular CRP levels.

### 3.4. Serum and intra-articular CRP cut-offs for diagnosing periprosthetic infection

The ROC curve analysis identified two intra-articular CRP cut-offs, with different intrinsic characteristics, for the diagnosis of periprosthetic infection (Fig. 4). The 2.78 mg/L cut-off was 100% sensitive and the 5.37 mg/L cut-off was 90.91% specific (Table 3). The positive likelihood ratios were 5.5 and 9.9 for these two intra-articular CRP cut-offs compared to 4.5 and 4.09 for the two serums CRP cut-offs (Table 4), indicating better diagnostic performance of intra-articular CRP.

**Table 3**
Cut-offs for intra-articular C-reactive protein (CRP) values.

| Cut-off (mg/L) | Sensitivity (%) | 95%CI | Specificity (%) | 95%CI | Positive likelihood ratio |
|---|---|---|---|---|---|
| >2.780 | 100 | 69.2–100 | 81.82 | 48.2–97.7 | 5.5 |
| >5.365 | 90 | 55.5–99.8 | 90.91 | 58.7–99.8 | 9.9 |

95%CI: 95% confidence interval.



**Fig. 4.** ROC curves for serum and intra-articular CRP levels. The curves were plotted using the intra-articular CRP levels measured in the group with knee prosthesis and aseptic effusion ($n = 9$) and the group with infected knee prosthesis ($n = 10$).

**Table 4**
Cut-offs for serum C-reactive protein (CRP) values.

| Cut-off (mg/L) | Sensitivity (%) | 95%CI | Specificity (%) | 95%CI | Likelihood ratio (LR+) |
|---|---|---|---|---|---|
| >14.95 | 100 | 69.2–100 | 77.78 | 40.0–97.2 | 4.5 |
| >51.75 | 50 | 18.7–81.3 | 88.89 | 51.8–99.8 | 4.5 |

95%CI, 95% confidence interval.

## 4. Discussion

In this study, intra-articular CRP performed better than serum CRP in diagnosing knee prosthesis infection.

CRP is a protein released by the liver, in amounts that increase during systemic inflammatory processes. Other cells may be able to produce CRP, for instance within atheroma plaques [17], but no evidence of production by the synovial membrane has been reported. Given that CRP activates the complement cascade, higher CRP levels would be expected at the initial site of infection, i.e., within the joint in the case of periprosthetic infection [18]. There is consequently a rationale for using intra-articular CRP assay as a diagnostic tool for periprosthetic infection.

CRP was initially evaluated in synovial fluid samples from native joints. Zamani et al. found a mean level of 12.72 mg/L in patients with inflammatory arthritis and 2.36 mg/L in those with mechanical joint effusions [19]. Parvizi et al. measured intra-articular CRP levels in 59 patients with joint prostheses, including 25 with periprosthetic infections, and found significantly higher values in the group with infection (22.49 mg/L *versus* 1.19 mg/L in the group without infection) [6]. Our data confirm the considerable CRP elevation in synovial fluid from joints with periprosthetic infection and the low CRP values in synovial fluid from native joints or uninfected prosthetic joints.

Parvizi et al. determined that 9.5 mg/L was the best cut-off for diagnosing periprosthetic infection, with 85% sensitivity and 95% specificity [20]. Our results suggest that two cut-offs should be considered: intra-articular CRP levels greater than 5.37 mg/L indicate probable infection and those greater than 2.78 mg/L possible infection. When the intra-articular CRP level is lower than 2.78 mg/L,

periprosthetic infection can be ruled out. Nevertheless, comparisons of diagnostic cut-offs should be viewed with circumspection, as the assay methods vary across studies. Standardisation of the techniques and cut-offs would be helpful.

Thus, the intra-articular CRP assay may perform better for the diagnosis of periprosthetic infection than the serum CRP assay. The AUC-ROC was better for intra-articular CRP, although the difference was not statistically significant. Nevertheless, the likelihood ratios associated with the cut-offs identified in our study support the superiority of intra-articular CRP.

Our study has several limitations. Among patients with knee prosthesis, those with and without infection were separated using the criteria developed by Parvizi et al. [13], which have well-known limitations. Given these diagnostic difficulties and the absence of a pathognomonic criterion for periprosthetic infection, longer-term follow-up data on our patients are needed to look for delayed symptoms of previously latent chronic periprosthetic infection. Our sample size was limited, and a larger sample might have produced different results; however, the differences were evaluated using statistical tests that provide valid information even for small samples. CRP is found in blood and can therefore be reliably assayed in joint fluid only in the absence of bleeding. To minimise this potential source of bias, joint aspiration was performed before opening the capsule in patients with knee prostheses.

Despite these limitations, our study identified two intra-articular CRP cut-offs of potential usefulness for diagnosing knee prosthesis infection. However, the AUC-ROC curves for intra-articular and serum CRP were not significantly different. Nevertheless, the likelihood ratios seem to support the superiority of intra-articular CRP.

Our results suggest that intra-articular CRP assay may be useful for diagnosing knee prosthesis infection and perhaps more broadly periprosthetic infection at any site. A multicentre study in a larger sample size is being designed.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

## Acknowledgements

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