Is Synovial C-reactive Protein a Useful Marker for Periprosthetic Joint Infection?

Matthew W. Tetreault MD, Nathan G. Wetters MD,
Mario Moric MS, Christopher E. Gross MD,
Craig J. Della Valle MD

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Abstract

Background Serum C-reactive protein (CRP) is a general marker of inflammation, and recent studies suggest that measurement of CRP in synovial fluid may be a more accurate method for diagnosing periprosthetic joint infection (PJI).

Questions/purposes We aimed to (1) determine if there is a correlation between serum and synovial CRP values, (2) establish cutoff values for diagnosing infection based on serum and synovial CRP, and (3) compare the utility of

measuring CRP in synovial fluid versus serum for the diagnosis of PJI using standard assay equipment available at most hospitals.

Methods Between February 2011 and March 2012, we invited all 150 patients scheduled for revision TKA (84) or THA (66) to participate in this prospective study, of whom 100% agreed. Data ultimately were missing for 31 patients, leaving 60 patients undergoing revision TKA and 59 undergoing revision THA (71% and 89% of the original group, respectively) for whom CRP level was measured in serum and synovial fluid samples. Patients were deemed to have a PJI (32) or no infection (87) using Musculoskeletal Infection Society criteria. Serum and synovial CRP levels were assayed using the same immunospectrophotometer and the correlation coefficient was calculated. Receiver operating characteristic curve analyses were performed to compare utility in diagnosing PJI, which included area under the curve, diagnostic threshold, and test sensitivity, specificity, predictive values, and accuracy. In 22 of 150 patients (14.7%), synovial CRP could not be measured because the sample was too viscous or hemolyzed.

Results In the analyzed 119 samples, there was a strong correlation ($r = 0.76$; $p < 0.001$) between synovial and serum CRP. The area under the curve was 0.90 both for the synovial fluid (95% CI, 0.82–0.97) and serum (95% CI, 0.84–0.96) CRP assays. The diagnostic thresholds were 6.6 mg/L for synovial fluid and 11.2 mg/L for serum. Sensitivities, specificities, positive predictive value, negative predictive value, and accuracies were similar for synovial fluid and serum assays.

Conclusions Although recent studies have suggested a superiority of synovial fluid CRP over serum CRP for the diagnosis of PJI, we found that measurement of CRP in synovial fluid rather than serum using readily available

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M. W. Tetreault, N. G. Wetters, C. E. Gross,
C. J. Della Valle (✉)

Department of Orthopaedic Surgery, Rush University Medical Center, 1611 West Harrison Street, Suite 300, Chicago, IL 60612, USA
e-mail: craigdv@yahoo.com

M. Moric
Department of Anesthesia, Rush University Medical Center, Chicago, IL, USA

assay equipment does not offer a diagnostic advantage in detection of PJIs.

Level of Evidence Level II, diagnostic study. See the Instructions to Authors for a complete description of levels of evidence.

Introduction

Diagnosis of periprosthetic joint infection (PJI) remains challenging. Although evidence-based recommendations for standardizing the diagnosis exist [9, 23, 27], there is no gold standard for diagnosis [2, 24, 36]. Efforts are ongoing to elucidate novel methods for detecting PJI, such as sonication of implants [32], molecular techniques [1, 4, 19, 20], and analysis of circulating cytokines [5, 12, 29]. However, many of these new diagnostic measures are costly, require special equipment, or are time-consuming and thus not readily available [2, 24, 36].

C-reactive protein (CRP) currently is assayed in the serum as a common and inexpensive test to screen for the presence of PJI [2, 15, 24]. However, serum CRP concentration is nonspecific for the diagnosis of localized infection as CRP is an acute-phase reactant present in numerous noninfectious inflammatory processes [15]. Recent studies suggest that the measurement of CRP in synovial fluid may serve as a simple and cost-effective means for improving the diagnosis of PJI [25, 26, 33], as local CRP is thought to enhance complement activation and phagocytosis [14]. However, synovial CRP studies to date were limited to small sample sizes, predominantly knees, and assays not available in all centers.

In this study, we thus sought to (1) determine if there is a correlation between serum and synovial CRP values, (2) establish cutoff values for diagnosing infection based on serum and synovial CRP, and (3) compare the utility of measuring CRP in synovial fluid versus serum for the diagnosis of PJI in TKA and THA revisions for all causes using standard assay equipment currently available at most hospitals.

Patients and Methods

Before beginning this study, we obtained Institutional Review Board approval for collection of all patient samples. Between February 2011 and March 2012, we invited all patients scheduled for revision TKA (84) or THA (66) to participate in this prospective study. All patients agreed to participate. Thirty-one patients (20.7%) ultimately were excluded for missing data: six (4.0%) secondary to insufficient synovial fluid aspirate, three (2.7%) because a serum

Table 1. Demographic data

Patient-specific characteristic	Infected (n = 32)	Aseptic (n = 87)	p value
Age (years)	60.2 (40–88)	59.8 (32–82)	0.86
BMI (kg/m ²)	31.8 (21.6–47.8)	30.9 (17.8–46.1)	0.54
Gender (% males)	53	46	0.54
Joint type (% knees)	53	49	0.84
Inflammatory arthritis (%)	12.5	8.0	0.48
Charlson index	1.0 (0–5)	0.74 (0–5)	0.22

Mean values are shown with ranges in parentheses.

CRP assay was not performed, and 22 (14.7%) because the synovial fluid sample was too viscous (20; 13%), clotted (1; 0.7%), or grossly hemolyzed (1; 0.7%) for CRP to be assayed. Inflammatory arthritis was not considered an exclusion criterion [8]. This left 119 study patients (60 knees and 59 hips; 71% and 89% of the original group, respectively) for whom CRP level was measured in serum and synovial fluid samples. The group consisted of 57 men and 62 women with an average age of 59.9 years (range, 32–88 years) at the time of revision surgery.

Patients were divided into two groups based on the presence (32) or absence (87) of infection at the time of revision surgery using modified Musculoskeletal Infection Society (MSIS) criteria [27]; the modification was to exclude elevated serum CRP from the criteria to avoid confounding our analysis. Acute infection was defined as presentation within 6 weeks of an index procedure [3, 10, 13, 28, 30, 34] and any infection beyond that time was classified as chronic. The patients in the infected and noninfected groups had similar demographics [7] (Table 1).

All synovial fluid aspirates were collected either preoperatively or in the operating room at the time of revision surgery. The synovial fluid samples were analyzed for CRP in addition to the synovial fluid white blood cell (WBC) count, differential, and culture. To assess CRP levels, a minimum of 1 mL of synovial fluid was placed in a red top tube (BD Vacutainer®, Becton, Dickinson and Company, Franklin Lakes, NJ) and transported to the hospital laboratory for measurement using the same assay equipment used for serum CRP at our institution (ARCHITECT™ ci8200 Integrated System, Abbott Diagnostics, Saint-Laurent, Québec, CA). This equipment uses an automated turbidimetric method that reacts anti-CRP antibody and patient CRP antigen to form sedimentation complexes. Blood samples were obtained preoperatively for measurement of erythrocyte sedimentation rate (ESR) and CRP in the serum; serum CRP was assessed using the same equipment as described above. A minimum of three deep

Table 2. Serum and synovial fluid markers

Marker	Infected (n = 32)	Aseptic (n = 87)	p value
Erythrocyte sedimentation rate (mm/hour)	56.7 (44.1–69.3)	23.3 (18.5–28.0)	< 0.001
Serum CRP (mg/L)	93.0 (55.4–130.6)	13.3 (6.2–20.4)	< 0.001
Synovial white blood cells (cells/ μ L)	49,929 (29,103–70,756)	1002 (0–1280)	< 0.001
Synovial neutrophil percentage	90 (87–93)	39 (33–45)	< 0.001
Synovial CRP (mg/L)	40.6 (25.7–55.5)	2.7 (0.59–4.2)	< 0.001

Mean values are shown with 95% CI in parentheses; CRP = C-reactive protein.

tissue specimens was obtained intraoperatively for culture, and tissue also was obtained for all patients for intraoperative frozen sections and permanent histopathologic examination. The incubation periods for cultures at our institution are: aerobic = 3 days, anaerobic = 7–10 days, fungal = 1 week (preliminary)/4 weeks (final).

Statistical Methods

Continuous data values were compared for statistical significance with univariate unpaired, 2-tailed Student's t-tests with an α level of .05 as the data were normally distributed. Proportions were compared using Fisher's exact test. When considering serum and synovial fluid CRP values, any value less than the calibrated sensitivity of the machinery (< 5 mg/L) was standardized at a value of 0 for the purpose of statistical analysis. Correlation coefficients (r^2) were examined to determine any linear correlation between serum and synovial fluid CRP concentration. We used receiver operating characteristic (ROC) curve analyses, with Wald CIs, to assess the ability of serum and synovial fluid CRP concentration to determine the presence of PJI. Youden's J statistic was used to determine optimum cutoff values for the diagnosis of infection. We calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for the two CRP assays evaluated. Area under the curve (AUC) values were compared between synovial and serum CRP analysis using an approach proposed by DeLong et al. [11]. McNemar's test was used to compare sensitivity and specificity between the two assays. Statistical significance was considered a probability less than 0.05. All statistical analyses, including the generation of ROC curves, were performed using SAS[®] version 9.2 (SAS Institute Inc,

Table 3. Summary of CRP assay results

Variable	Synovial CRP	Serum CRP	p value
Area under the curve			
Aggregate	0.90 (0.82–0.97)	0.90 (0.84–0.96)	0.860
Hips	0.88 (0.78–0.99)	0.92 (0.85–0.99)	0.483
Knees	0.91 (0.81–1.00)	0.89 (0.79–0.99)	0.804
Threshold (mg/L)			
Aggregate	6.6	11.2	–
Hips	8.5	11.2	–
Knees	14.1	21.2	–
Sensitivity (%)			
Aggregate	88 (82–93)	97 (94–100)	–
Hips	87 (78–95)	100 (100–100)	–
Knees	82 (73–92)	88 (80–96)	–
Specificity (%)			
Aggregate	85 (79–91)	76 (68–84)	–
Hips	86 (78–95)	84 (75–93)	–
Knees	93 (87–99)	84 (74–93)	–
Positive predictive value (%)			
Aggregate	68 (60–77)	60 (51–68)	–
Hips	68 (57–80)	68 (56–80)	–
Knees	82 (73–92)	68 (56–80)	–
Negative predictive value (%)			
Aggregate	95 (91–99)	99 (96–100)	–
Hips	95 (89–100)	100 (100–100)	–
Knees	93 (87–99)	95 (89–100)	–
Accuracy (%)			
Aggregate	86 (79–92)	82 (75–88)	–
Hips	86 (78–95)	88 (80–96)	–
Knees	90 (82–98)	85 (76–94)	–

95% CI are provided in parentheses; CRP = C-reactive protein.

Cary, NC). Post hoc power analysis based on McNemar's test determined that our sample of 119 subjects, given a power of 80%, alpha of .05, and observed correlation of 0.7, would detect a difference in sensitivity or specificity of 7.2% between synovial fluid and serum CRP testing.

Results

A strong positive correlation existed between synovial fluid CRP and serum CRP ($r = 0.76$; $p < 0.001$). Compared with the aseptic group, the infected group showed greater serum and synovial fluid markers (Table 2).

There was no difference in the AUC between synovial fluid and serum CRP (Table 3). The AUC was 0.90 for the synovial and serum CRP assays at an optimal threshold of 6.6 mg/L for synovial fluid (Fig. 1A) and 11.2 mg/L for serum (Fig. 1B).

Fig. 1A–B ROC curves are shown for (A) synovial fluid CRP and (B) serum CRP for the diagnosis of PJI.

Comparing synovial versus serum CRP assay, diagnostic performance was similar for sensitivity, specificity, PPV, NPV, and accuracy (Table 3). When hips and knees were considered separately, there remained minimal difference in diagnostic performance for synovial versus serum CRP (Table 3). Interestingly, infected synovial fluid samples were less likely to be too viscous or hemolyzed for CRP analysis; infected samples accounted for 4.5% (one of 22) of too viscous or hemolyzed samples versus 27% (32 of 119) of assayable samples ($p = 0.026$).

Discussion

Serum CRP, an indicator of systemic inflammation, has long been an important biomarker for the diagnosis of PJI. Recent studies have suggested that CRP concentration in synovial fluid might hold promise as a superior diagnostic marker for PJI [25, 26]. However, these studies were limited to small sample sizes, predominantly knees, and assays not available at all centers. The purpose of our study was to compare the utility of measuring CRP in synovial fluid versus serum for the diagnosis of PJI in TKAs and THAs using standard assay equipment currently available at most hospitals.

The primary limitation of this study is that the sample size was relatively small, however, our sample size was more than double those of the three prior studies that evaluated the utility of synovial CRP in the diagnosis of PJI [25, 26, 33]. Using standard parameters, our sample was adequately powered to detect a less than 10% difference in sensitivity and specificity, which we think is a clinically

relevant difference; therefore it does not appear that the measurement of synovial CRP offers a real advantage to the clinician. Given the cost of the CRP assay (approximately USD 105 per test at our institution) and because nearly one of six samples was unable to be read (ie, too viscous, hemolyzed, or clotted), we did not think that additional data collection to expand our sample size was warranted; a post hoc power analysis was used when analyzing our data. Second, we acknowledge the possibility of bias secondary to uninterpretable tests, but we think that the likelihood of exclusion bias is low and this more represents a limitation of the testing modality. Third, while we used well-accepted criteria for the diagnosis of PJI, some patients may have been incorrectly categorized as having an infection, although this likely would have changed the results for the serum and synovial CRP. Finally, patients with inflammatory arthritis were included in our analysis but this was unlikely to affect results as they were a small and equally distributed subgroup, CRP values were within the median range of the corresponding septic or aseptic cohorts, and again, both types of CRP likely would have been affected.

In corroboration with prior studies, we found a strong positive correlation between serum and synovial fluid CRP ($r = 0.76$) levels. Parvizi et al. [26] reported a high correlation coefficient ($r^2 = 0.72$) between these two CRP assays in the setting of total joint arthroplasty while Catterall et al. [6] reported a positive correlation in patients with acute knee trauma. Catterall et al. [6] postulated that diffusion of serum CRP into the joint could be responsible for an elevated synovial fluid CRP when elevated systemically. Parvizi et al. [26] applied this to PJI and theorized that synovial permeability caused by local

Table 4. Summary of studies assessing utility of synovial CRP in the diagnosis of periprosthetic joint infection

Study	Fluid	Assay (number; infected, uninfected)	Area under the curve	Threshold (mg/L)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	Too viscous or hemolyzed (%)
Parvizi et al. [25]	SF	Individual ELISA (15; 10, 5)	0.84 (0.64–1.04)	0.06	70.0	100.0	100.0	62.5	80.0	N/A
		Multiplex ELISA (59; 25, 34)	0.91 (0.82–0.99)	3.7	84.0	97.1	95.5	89.2	91.5	N/A
	Serum	Immunoturbidimetric assay (55; 25, 30)	0.88 (0.77–0.98)	16.5	76.0	93.3	90.5	82.4	85.5	0
Parvizi et al. [26]	SF	Immunoturbidimetric assay (63; 20, 43)	0.92	9.5	85.0	95.2	NR	NR	NR	4.8
Vanderstappen et al. [33]	SF	Immunoturbidimetric assay*	0.98 (0.94–1.00)	1.8	100 (71.5–100)	84.9 (68.1–94.9)	68.8 (41.3–89)	100 (87.7–100)	88.6 (75.4–96.2)	45.3
		(95; 11, 33)**								
Current study	Serum	Immunoturbidimetric assay (24; 7, 17)	0.98 (0.94–1.00)	2.8	90.9 (58.7–99.8)	93.9 (79.8–99.3)	83.3 (51.6–97.9)	96.9 (83.8–99.9)	93.2 (81.3–98.6)	45.3
	SF	Immunoturbidimetric assay (141; 33, 108)	0.90 (0.82–0.97)	6.6	88 (82–93)	85 (79–91)	68 (60–77)	95 (91–99)	86 (79–92)	14.7
	Serum	Immunoturbidimetric assay (141; 33, 108)	0.90 (0.84–0.96)	11.2	97 (94–100)	76 (68–84)	60 (51–68)	99 (96–100)	82 (75–88)	0

* Two optimal cutoff points identified (1.8 mg/L and 2.8 mg/L); **infection status not specified for 51 excluded cases (43 for too viscous fluid, 8 for inadequate sample volume); 95% CI in parentheses when reported; SF = synovial fluid; ELISA = enzyme-linked immunosorbent assay; N/A = not applicable; NR = not reported.

inflammation may allow for high levels of serum CRP to diffuse into the joint, thus increasing synovial CRP. Because CRP is believed to play a role in complement activation and phagocytosis [14], there is a potential functional explanation for why synovial fluid CRP level in an inflamed or infected joint often mimics the serum CRP level.

Our diagnostic cutoff points for synovial CRP and serum CRP were similar to those reported in the two prior studies to evaluate immunoturbidimetric assays of these markers (Table 4). Our cutoff of 6.6 mg/L for synovial fluid was between the cutoffs identified by Vanderstappen et al. [33] (1.8 mg/L and 2.8 mg/L) and Parvizi et al. [26] (9.5 mg/L). Similarly, our cutoff of 11.2 mg/L for serum CRP was near the cutoff of Parvizi et al. [26] of 16.5 mg/L determined using immunoturbidimetry, the assaying method readily used in most hospitals. Our synovial fluid cutoff was slightly greater than the cutoff determined by Parvizi et al. [25] using ELISA (individual = 0.06 mg/L, multiplex = 3.7 mg/L). This may suggest that the cutoff point of synovial CRP analysis depends on the assay rather than being an absolute value [33]. Nevertheless, because there is still some overlap in CRP values between septic and aseptic cases (Table 2), PJI should not be excluded on the basis of serum or synovial CRP results alone [18, 33].

Measurement of CRP in synovial fluid using assay equipment currently available in our hospital did not offer a distinct advantage over serum CRP in the diagnosis of PJI in hips or knees. Meanwhile, prior studies evaluating the utility of synovial-fluid CRP measurement were promising but not convincing of superiority relative to serum CRP in the diagnosis of PJI (Table 4). Zamani et al. [35] initially showed that CRP level in synovial fluid measured using ELISA can be used to differentiate between inflammatory and noninflammatory primary arthritis. Parvizi et al. [25, 26] adapted this idea to evaluate the utility of synovial fluid CRP assays in differentiating infected versus noninfected revision arthroplasties. A study of nearly 60 revision knee arthroplasties found suggestive (although not statistically significant) evidence that a multiplex ELISA assay of synovial fluid CRP may be more accurate in diagnosing PJI than the standard serum CRP assay [25]. Parvizi et al. [26] performed a followup study of 63 patients (51 knees and 12 hips) to evaluate measurement of synovial fluid CRP using the same automated turbidimetric method that is used regularly to measure serum CRP in most hospital laboratories. Test parameters (sensitivity, specificity, and AUC) for synovial CRP were deemed favorable to serum CRP test parameters previously reported [15, 17]. However, ROC curve analysis for serum CRP was not performed for direct comparison of test utility in this cohort of patients. Meanwhile, a more recent, direct comparison found similarly high diagnostic strengths between synovial fluid and

serum CRP immunoturbidimetric analysis in 44 cases of presumed PJI of the knee [33]. Using a significantly larger sample size and including hips and knees, we similarly did not observe statistical superiority in any testing parameters, including AUC, sensitivity, specificity, PPV, NPV, and accuracy.

In 15% of cases, the synovial fluid was too viscous or hemolyzed to be assayed. This was threefold greater than the percentage reported (4.8%) by Parvizi et al. [26] in the first study to evaluate synovial CRP using the same immunoturbidimetric method routinely used to measure serum CRP in diagnosing PJI. Vanderstappen et al. [33] reported an even higher rate of excessively viscous samples (45.3%) using immunoturbidimetric assay. We think this is important because purported advantages of assaying synovial CRP are its ease of use, its relatively rapid turnaround time, and its low cost [26]. To date, the one test that showed superiority of synovial CRP over serum CRP in a head-to-head comparison was a multiplex ELISA that required the synovial fluid be shipped to an outside laboratory on dry ice; wait-time for the return of results was not noted [25].

To justify the cost and utilization of synovial fluid sample, we believe that measurement of synovial CRP should enhance our ability to diagnose PJI compared with present modalities. We found no advantage to the use of synovial-fluid CRP over serum CRP in the diagnosis of PJI; moreover, in 15% of patients, the synovial-fluid test could not be performed, perhaps making it of even lower utility. Thus, collected synovial fluid is best used to obtain a cell count with a differential and cultures [3, 10, 16, 21, 22, 27, 28, 31, 32]; diverting the sample for the measurement of CRP does not appear warranted at this time.

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