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Published in:
Journal of Arthroplasty

DOI:
10.1016/j.arth.2017.11.006

Publication date:
2018

The Journal of Arthroplasty 33 (2018) 1149–1153

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Complications - Infection

Synovial Calprotectin: An Inexpensive Biomarker to Exclude a Chronic Prosthetic Joint Infection

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ARTICLE INFO

Article history:
Received 23 September 2017
Received in revised form
1 November 2017
Accepted 3 November 2017
Available online 13 November 2017

Keywords:
prosthetic joint infection
calprotectin
chronic
diagnosis
biomarker

ABSTRACT

Background: To diagnose or exclude a chronic prosthetic joint infection (PJI) can be a clinical challenge. Therefore, sensitive and specific biomarkers are needed in the diagnostic work-up. Calprotectin is a protein with antimicrobial properties and is released by activated neutrophils, making it a specific marker for infection. Because of its low costs and ability to obtain a quantitative value as a point of care test, it is an attractive marker to use in clinical practice. In addition, the test is already used in routine care in most hospitals for other indications and therefore easy to implement.
Methods: Between June 2015 and June 2017 we collected synovial fluid of all consecutive patients who underwent revision surgery of a prosthetic joint because of chronic pain with or without prosthetic loosening. Synovial calprotectin was measured using a lateral flow immunoassay. A PJI was defined by the diagnostic criteria described by the Musculoskeletal Infection Society.
Results: Fifty-two patients with chronic pain were included. A PJI was diagnosed in 15 of 52 (29%) patients. The median calprotectin in the PJI group was 859 mg/L (interquartile range 86-1707) vs 7 mg/L (interquartile range 3-25) in the control group ($P < .001$). With a cut-off value of 50 mg/L, synovial calprotectin showed a sensitivity, specificity, positive predictive value, and negative predictive value of 86.7%, 91.7%, 81.3%, and 94.4%, respectively.
Conclusion: Synovial calprotectin is a useful and cheap biomarker to use in the diagnostic work-up of patients with chronic pain, especially to exclude a PJI prior to revision surgery.

To diagnose a chronic prosthetic joint infection (PJI) can be a clinical challenge. Especially in low-grade infections, inflammatory parameters in serum and leucocyte count including leucocyte esterase test in synovial fluid are false negative in a subset of patients [1–3]. In addition, most diagnostic tests measure an inflammatory response and are not specific for infection. For this reason, multiple biomarkers—like alpha-defensin, interleukins, procalcitonin, tumor necrosis factor alpha, toll-like receptors, and many more—have been introduced in orthopedic surgery over the last couple of years to aid in the diagnosis [4–9]. Although several of these biomarkers are promising concerning its diagnostic accuracy, an important limitation of the most sensitive ones are the relatively high costs and its poor applicability in clinical practice. Calprotectin, a protein that is present in the cytoplasm of neutrophils, might be an alternative biomarker to use. Calprotectin has been established for decades in the diagnostic work-up for inflammatory bowel disease [10]. As a lateral flow immunoassay, the test can be used as a point of care test and, because its measurement is already applied in most hospitals, it is easy to implement. Upon neutrophil activation, calprotectin is excreted from the cell at the site of the infection and exhibits antimicrobial properties by binding to zinc and manganese—important transition metals for bacterial survival. This process of chelation of

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2017.11.006.

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https://doi.org/10.1016/j.arth.2017.11.006
0883-5403/

nutrient metals is called nutritional immunity and is an important innate defense strategy of the host to limit pathogenicity during infection [11–14]. Because of these characteristics, calprotectin might be a specific biomarker for infection. Indeed, recent studies show its diagnostic accuracy to distinguish between inflammation and several bacterial infections [15–17]. Recently, we have shown in a pilot study the potential value of synovial calprotectin in diagnosing acute and chronic PJIs [18]. Our preliminary data indicated that synovial calprotectin might be useful in the diagnostic work-up of patients with a painful prosthetic joint, especially to exclude a PJI. Based on these results, we extended the study and exclusively analyzed calprotectin values in patients who were suspected of a chronic PJI. We performed an additional analysis in a smaller cohort of patients to analyze whether calprotectin is predictive for positive intraoperative cultures during reimplantation of the prosthesis as a second step in a 2-stage exchange procedure.

Materials and Methods

Study Design and Inclusion Criteria

From all consecutive cases between June 2015 and June 2017, synovial fluid was collected during revision surgery in patients who presented with chronic pain (defined as symptoms persisting for >4 weeks) at the site of the prosthetic joint with or without radiological signs of aseptic loosening. Knee, hip, and shoulder arthroplasties were included in the study. The recruitment of patients was an extension of our pilot study [18]: 9 patients with a chronic PJI and 15 control patients without a PJI that were part of the pilot study, were also included in the current analysis. The measurement of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in serum was part of the diagnostic work-up in these patients. Nuclear imaging was performed in a subset of patients if there was doubt about the presence of an infection (using 3-phase ^{99m}Tc-methylene diphosphonate bone scintigraphy and, if positive, an additional ^{99m}Tc-labeled hexamethylpropylene amine oxime white blood cell [WBC] scintigraphy). The definitive diagnosis of a PJI was based on the diagnostic criteria defined by the Musculoskeletal Infection Society: (1) presence of a sinus tract communicating with the prosthesis; or (2) a pathogen isolated by culture from at least 2 separate tissue or fluid samples obtained from the affected prosthetic joint; or (3) 4 of the following 6 criteria: elevated serum ESR and serum CRP concentration, elevated synovial leukocyte count, elevated synovial neutrophil percentage, presence of purulence in the affected joint, isolation of a microorganism in one culture of periprosthetic tissue or fluid, or greater than 5 neutrophils per high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at 9400 magnification [19]. In case no PJI was present, an alternative diagnosis, generally diagnosed during revision surgery, was noted. Several patient baseline characteristics were collected, including medical history, use of immune suppressive drugs or antibiotics, microorganism(s) causing the infection, and onset of symptoms after primary arthroplasty. After revision surgery, patients were followed at outpatient clinic at regular intervals. To determine whether a positive calprotectin level (eg, >50 mg/L) was predictive for positive intraoperative cultures at reimplantation, synovial fluid was also collected in a small cohort of patients who underwent the second stage of a 2-stage exchange procedure. During revision surgery, 5 intraoperative biopsies and 1 synovial fluid aspiration were obtained for culture. Each sample was cultured for 9-11 days on blood and chocolate agar under aerobic conditions (with 5% CO_2) and on brucella blood agar under anaerobic conditions. In addition, all samples were cultured in fastidious broth. All broths were subcultured on blood and brucella blood agar after 7 days of incubation. Subcultures were incubated for 2 days.

Measurement of Calprotectin

We used the rapid Calprotectin High Range Quantum Blue lateral flow assay to measure synovial calprotectin, which is commercially available (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland). We used the test off-label for synovial calprotectin by using the standard operating procedure that is provided by the company for measuring fecal calprotectin. We centrifuged the synovial fluid for 5 minutes with 3000 rpm and used 50 μL of synovial fluid in a 1:100 dilution in chase buffer (QB reagent provided in the QB kit). Eighty microliters of this sample was loaded on the test cassette and incubated for 15 minutes. The quantitative result of the test band was measured on the Quantum Blue reader and calculated to mg/L, like previously described [14]. Ten synovial fluids were tested before and after centrifugation; the median difference between the 2 samples was 1.9 mg/L (range 0-7). For this reason, all additional samples were tested without the centrifugation step. The Quantum Blue rapid assay was validated for fecal and serum calprotectin and compared to values measured using the Calprotectin enzyme-linked immunosorbent assay (BÜHLMANN) [20].

Statistical Analysis

Because of a non-Gaussian distribution of our data, a 2-tailed Mann-Whitney U-test or Kruskal-Wallis test was used to calculate the difference between patient groups. A *P*-value <.05 was considered as statistically significant. The Fisher's exact test was used to calculate the confidence intervals for the sensitivity, specificity, positive predictive value, negative predictive value (NPV), and likelihood ratios (LR). Statistics was performed using Prism 7 for Mac OS X (1994-2016 GraphPad Software, Inc).

Results

A total of 52 patients with chronic pain were included. Overall, 29% (15/52) of patients were diagnosed with a PJI according to the Musculoskeletal Infection Society criteria, which was considered as the gold standard for this study. The median calprotectin levels in patients diagnosed with a PJI (n = 15) were 859 mg/L (interquartile range [IQR] 86-1707) vs 7 mg/L (IQR 3-25) in the control group without an infection (n = 37) (*P* < .001) (Fig. 1). The median follow-up of patients was 11 months (IQR 6-19). Based on our previous study, a cut-off value of 50 mg/L showed the highest diagnostic accuracy (area under the curve of 0.94), and was therefore maintained as a threshold [14].

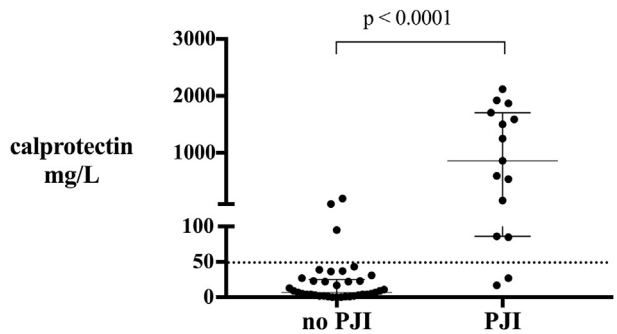

Fig. 1. Synovial calprotectin in patients with chronic pain and/or (a) septic loosening. Definitive diagnosis of a PJI was based on the diagnostic criteria defined by the Musculoskeletal Infection Society. No PJI, n = 37; PJI, n = 15. Error bars are presented as median ± interquartile range.

Table 1
Diagnostic Accuracy of Synovial Calprotectin (Cut-Off Value 50 mg/L), Serum CRP (Cut-Off Value 10 mg/L), and ESR (Cut-Off Value 30 mm/h) for Diagnosing a PJI.

	Synovial Calprotectin	Serum CRP	Serum ESR	Serum CRP and ESR
Sensitivity	86.7% (95% CI 59.5-98.3)	66.7% (95% CI 38.8-88.2)	72.7% (95% CI 39.0-93.9)	63.7% (95% CI 30.8-89.1)
Specificity	91.7% (95% CI 78.1-98.3)	70.4% (95% CI 49.8-86.3)	69.6% (95% CI 47.1-86.8)	75.0% (95% CI 50.9-91.3)
PPV	81.3% (95% CI 59.0-92.9)	55.6% (95% CI 38.7-71.2)	53.3% (95% CI 35.8-70.1)	58.3% (95% CI 36.7-77.2)
NPV	94.4% (95% CI 82.3-98.4)	79.2% (95% CI 64.1-89.0)	84.2% (95% CI 66.2-93.6)	80.0% (95% CI 62.3-89.5)
PLR	10.9 (95% CI 3.6-32.2)	2.3 (95% CI 1.1-4.5)	2.4 (95% CI 1.2-4.9)	2.6 (95% CI 1.1-6.1)
NLR	0.14 (95% CI 0.04-0.53)	0.47 (95% CI 0.2-1.0)	0.4 (95% CI 0.1-1.1)	0.5 (95% CI 0.2-1.1)

PPV, positive predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; CI, confidence interval.

Diagnostic Value of Synovial Calprotectin in Excluding a PJI

Synovial calprotectin showed a high accuracy in excluding a PJI, with specificity, NPV, and negative LR of 91.7%, 94.4%, and 0.14, respectively (Table 1). From the patients with a false positive synovial calprotectin (3/37), all patients were diagnosed with aseptic loosening of the hip. Fifteen patients with aseptic loosening were correctly diagnosed as noninfected (15/18, 83.3%) (Table 2). As depicted in Table 1, serum CRP and ESR were false positive in around 30% of patients. In all these patients, synovial calprotectin was true negative in excluding a PJI. In addition, WBC scintigraphy was false positive in 2 of 15 patients without a PJI; in both false positive cases, synovial calprotectin was true negative.

Diagnostic Value of Synovial Calprotectin in Diagnosing a PJI

Synovial calprotectin showed a sensitivity, positive predictive value, and positive LR of 86.7%, 81.3%, and 10.9, respectively, in diagnosing a PJI (Table 1). Two patients had a false negative synovial calprotectin (2/15). One of these patients, with an infection due to *Enterococcus faecalis*, was using antibiotics at the time of synovial fluid analysis and had a draining fistula, which might have suppressed the inflammatory response. The other patient with a false negative result was a patient with a PJI caused by coagulase-negative staphylococci (CoNS). The remaining 4 patients with an infection caused by CoNS were correctly diagnosed (4/5, 80%); the median calprotectin level in these patients was 1727 mg/L (IQR 518-2056). The patient with a false negative result did had an increased CRP and ESR preoperatively and positive synovial fluid culture, but was using non-steroid inflammatory drugs (NSAID) at the time of analysis. None of the other patients in our study were using NSAIDs. There were no major differences concerning the number of positive intraoperative cultures with CoNS between the patients with true positive and false negative results. Serum CRP was false negative in 37% of patients, but was correctly diagnosed as an infection by synovial calprotectin. In 4 of 6 patients with a PJI, WBC scintigraphy was false negative. In all of these 4 cases, calprotectin values were true positive in diagnosing the infection. In addition, calprotectin adequately diagnosed an infection in 7 of 8 patients in whom (preoperative) synovial fluid was culture negative.

Table 2
Characteristics of Patients With False Positive and False Negative Values of Synovial Calprotectin (Cut-Off Value 50 mg/L) for Diagnosing or Excluding a PJI.

	No PJI (n = 37)		PJI (n = 15)	
	True Negative (n = 34)	False Positive (n = 3)	True Positive (n = 13)	False Negative (n = 2)
Joint				
Hip	21	3	8	0
Knee	12	0	3	2
Shoulder	1	0	2	0
Rheumatoid arthritis	2	0	2	0
Malignancy bone	4	1	0	0
Use of antibiotics	0	0	2	1
Use of immunosuppressive drugs	3	0	2	0
Fistula	0	0	1	1
Onset of symptoms				
Early (<3 mo after arthroplasty)	4	0	2	0
Delayed (3-24 mo after arthroplasty)	6	0	3	1
Late (>24 mo after arthroplasty)	24	3	8	1
Microorganism causing the infection				
Staphylococcus aureus			0	0
Coagulase-negative staphylococci			4	1
Gram negatives			2	0
Streptococcus species			1	0
Enterococcus species			0	1
Propionibacterium acnes			2	0
Corynebacterium species			0	0
Polymicrobial			3	0
Culture negative			1	0
Alternative diagnosis				
Aseptic loosening	15	3		
Metallosis	7	0		
Luxation	3	0		
Fracture	3	0		
Patella problem	2	0		
Other/unknown	4	0		

Diagnostic Value of Synovial Calprotectin During Reimplantation

In 12 patients, calprotectin was measured during the second stage of a 2-stage exchange procedure (at reimplantation) after a median antibiotic holiday of 12 weeks (IQR 8-20). In 2 of 12 patients (17%), 2 or more intraoperative tissue cultures were positive, indicative for a persisting infection or reinfection. In both these patients, preoperative CRP, ESR, intraoperative histology, and calprotectin of synovial fluid were false negative (calprotectin levels of 2 and 10 mg/L). None of these 2 patients used immunosuppressive drugs at the time of the analysis. The median calprotectin levels of patients with negative intraoperative cultures were 8 mg/L (IQR 4-42).

Discussion

Our data show that synovial calprotectin is a sensitive and specific biomarker to aid in the diagnosis of a chronic PJI. With a specificity of 92% and an NPV of 94%, calprotectin is especially useful to exclude a PJI in patients with chronic pain. Even in patients with increased serum inflammatory parameters due to other causes, synovial calprotectin correctly ruled out a PJI, showing its high specificity for infection. Furthermore, calprotectin showed a good sensitivity (87%) to diagnose a PJI, also in patients with negative synovial fluid cultures. However, calprotectin may still be false negative in a minority of patients with a low grade infection, which was the case in 2 of 15 patients in our study. This finding is also illustrated in our reimplantation analysis, showing negative calprotectin levels in patients with positive intraoperative cultures during reimplantation. Because low inocula of bacteria are often present in case of persisting infection of the bone after antibiotic treatment or during infection of the spacer, calprotectin may not be sensitive enough to detect this. For this reason, our preliminary data indicate that calprotectin should probably not be used to monitor treatment response before deciding to reimplant the prosthesis. Although analysis in a larger cohort of patients is necessary to confirm these findings, recent studies with highly sensitive biomarkers suggest the same conclusion [21].

The main features that makes synovial calprotectin an attractive biomarker to use in clinical practice compared to other available biomarkers are: (1) the low costs (20 euro per sample), (2) the possibility to obtain a quantitative value, (3) the use of a lateral flow assay with the possibility to use it as a point of care test (easy to apply and results are obtained within 15 minutes), and (4) its availability, as it is already used in routine care for other indications in most hospitals [17,22]. To the best of our knowledge, lateral flow immunoassays are only available for interleukin-6 and alpha-defensin as biomarkers for PJI [5,23]. Although these tests show excellent diagnostic accuracy, these tests are relatively expensive, and in addition, not routinely available in most hospitals. Other proposed diagnostic tests mostly use an enzyme-linked immunosorbent assay–based method [4,7], which is more labor intensive and again more expensive when applied for only one sample. With the high NPV of calprotectin, additional costs from using more expensive diagnostic methods (eg, advanced nuclear imaging) and unnecessary empirical antibiotic treatment during revision surgery may be avoided.

A limitation of our study is the inability to compare calprotectin with synovial leucocyte counts, which was predominantly due to insufficient amounts of synovial fluid. However, a recent study performed in 327 patients with chronic joint pain that underwent revision surgery of the hip showed lower specificities for synovial leucocyte counts than demonstrated for synovial calprotectin in our study. Even with the proposed new cut-off values for solely chronic PJIs, specificity of synovial leucocyte count varies between 82.1% and 94.2%, depending on the degree of suspicion of an infection preoperatively [19]. Specificity was even lower for the percentage of polymorphonuclear cells. Therefore, because of its antimicrobial properties, calprotectin may be more specific for an infection than merely the presence of leucocytes in synovial fluid. Future studies should focus on the added value of calprotectin in patients with an even lower suspicion of infection than currently studied (ie, patients with negative synovial fluid culture and low leucocyte counts in synovial fluid) to rule out or diagnose a PJI. A second limitation of our study is the relatively small sample size, which inhibits the possibility to perform important subanalyses. The numbers of patients should be expanded in future studies in order to analyze the difference in diagnostic accuracy between different microorganisms and to analyze the effect of immunosuppressive drugs, NSAIDs, and/or antibiotics. In addition, higher cut-off levels of calprotectin may be necessary in patients with other inflammatory conditions. To illustrate, Abildtrup et al [24] showed in a recent meta-analysis that the mean synovial calprotectin value in patients with rheumatoid arthritis is ±110 mg/L, which is above the cut-off value of 50 mg/L in our study. This should be further explored.

In conclusion, we propose to use synovial calprotectin in the diagnostic work-up of patients with a clinical suspicion of a chronic PJI and/or aseptic loosening. With its high NPV, a PJI can be excluded prior to revision arthroplasty in the majority of cases.

Acknowledgments

This study was supported by a Stipendium/Grant from the Noyons Foundation of the Dutch Society for Clinical Chemistry and Laboratory Medicine.

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