Serum procalcitonin, interleukin-6, soluble intercellular adhesin molecule-1 and IgG to short-chain exocellular lipoteichoic acid as predictors of infection in total joint prosthesis revision

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ABSTRACT

The diagnosis of prosthetic joint infection and its differentiation from aseptic loosening remains problematic. The definitive laboratory diagnostic test is the recovery of identical infectious agents from multiple intraoperative tissue samples; however, interpretation of positive cultures is often complex as infection is frequently associated with low numbers of commensal microorganisms, in particular the coagulase-negative staphylococci (CNS). In this investigation, the value of serum procalcitonin (PCT), interleukin-6 (IL-6) and soluble intercellular adhesion molecule-1 (sICAM-1) as predictors of infection in revision hip replacement surgery is assessed. Furthermore, the diagnostic value of serum IgG to short-chain exocellular lipoteichoic acid (sce-LTA) is assessed in patients with infection due to CNS. Presurgical levels of conventional serum markers of infection including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white blood cell count (WBC) is also established. Forty-six patients undergoing revision hip surgery were recruited with a presumptive clinical diagnosis of either septic (16 patients) or aseptic loosening (30 patients). The diagnosis was confirmed microbiologically and levels of serum markers were determined. Serum levels of IL-6 and sICAM-1 were significantly raised in patients with septic loosening ($P=0.001$ and $P=0.0002$, respectively). Serum IgG to sce-LTA was elevated in three out of four patients with infection due to CNS. In contrast, PCT was not found to be of value in differentiating septic and aseptic loosening. Furthermore, CRP, ESR and WBC were significantly higher ($P=0.0001$, $P=0.0001$ and $P=0.003$, respectively) in patients with septic loosening. Serum levels of IL-6, sICAM-1 and IgG to sce-LTA may provide additional information to facilitate the diagnosis of prosthetic joint infection.

KEY WORDS: Biological markers.
Diagnosis.
Hip prosthesis.
Infection.
Reoperation.

Introduction

The clinical and laboratory diagnosis of septic prosthetic joint loosening and its differentiation from aseptic loosening is complex as currently used diagnostic tests lack sensitivity and specificity and underlying rheumatological disease can lead to periprosthetic inflammatory changes in tissue.[1,2] Furthermore, interpretation of positive microbiological cultures from samples taken prior to or during surgery is often difficult because infection is frequently associated with low numbers of commensal microorganisms, particularly skin organisms including coagulase-negative staphylococci (CNS) and *Propionibacterium acnes*; insufficient or inappropriate intraoperative samples may be taken during surgery; and microbial contamination during sample collection or processing may occur.[2–4]

To improve the microbiological diagnosis of septic loosening, Atkins *et al*.[5] undertook a prospective study to assess the significance of positive cultures and number of positive samples in reliably diagnosing infection. The study demonstrates that recovery of indistinguishable microorganisms from multiple intraoperative samples is highly predictive of infection. This has been used as the definitive test for the diagnosis of septic loosening in the present study.

The host response to bacterial infection results in the release of a wide range of inflammatory mediators, some of which may be used to facilitate the diagnosis of infection[6–16] or interpretation of complex positive microbiological cultures. Within the past decade, a large number of serological markers have been suggested as sensitive and specific indicators of bacterial infection.[6–16] Levels of serum markers including procalcitonin (PCT)[6–8] interleukin-6 (IL-6)[9–11] and human soluble intercellular adhesion molecule-1 (sICAM-1)[10] have been evaluated and used to facilitate diagnosis of infection and/or sepsis. Furthermore, serum IgG antibodies to short-chain exocellular lipoteichoic acid (sce-

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LTA; previously termed lipid S)[13] produced by CNS have been shown to be a valuable diagnostic marker in patients with intravascular device-related infection[15,16] and septic loosening[12] due to CNS.

The aim of the present study is to establish whether or not serum levels of PCT, IL-6 and sICAM-1 in patients with well-defined septic and aseptic loosening can facilitate a differential diagnosis and offer useful additional information alongside conventional predictors (i.e., C-reactive protein [CRP], erythrocyte sedimentation rate [ESR] and white blood cell count [WBC]). Furthermore, the potential value of serum IgG to sce-LTA as a marker for septic loosening due to CNS is also assessed.

Materials and methods

Patient recruitment

A prospective case-control study of 46 patients undergoing revision hip surgery under a single surgeon was conducted. Ethical committee approval was obtained prior to commencement of the study. Patients were recruited following informed consent. Strict inclusion criteria were adopted and any patient who had a history of possible infection remote from the hip within the previous six months was excluded from the study. Patients with co-morbidities including psoriasis, inflammatory bowel disease and malignancy were also excluded.

Preoperative clinical evaluation of each patient was undertaken. Preoperative anteroposterior and true lateral radiographs of the pelvis were also obtained. In addition, CRP, ESR and WBC were determined seven to 21 days prior to surgery.

Surgery was performed by a single surgeon in an operating suite with vertical laminar airflow. Based on results of presurgical patient assessment and intraoperative clinical findings, patients were given a presumptive clinical diagnosis of septic or aseptic loosening.

Preoperative serum markers

Preoperative results of CRP, ESR and WBC were determined by standard laboratory methods.

Intraoperative tissue samples and blood collection

Patients receiving antibiotics had their treatment stopped two weeks prior to surgery. Immediately prior to surgery, 5-mL blood was obtained from each patient for estimation of serum levels of PCT, IL-6, sICAM-1 and IgG to sce-LTA. A standard set of clinical samples[5] for microbial culture was taken during surgery and comprised a swab of hip joint fluid, femoral tissue, capsular tissue, acetabular tissue, bone and/or cement, and the prosthetic hip.

Microbiological culture

Clinical samples were processed using standard microbiology methods. Briefly, 5-mL sterile phosphate buffered saline (PBS) was added to each of the acetabular, capsular, femoral tissue and bone/cement samples together with 10 sterile glass beads and were vortex-mixed for 2 min. Aliquot samples were then inoculated on two blood agar plates and one chocolate agar plate. One blood agar plate was incubated in 5% CO_2 and the other anaerobically. The chocolate plate was incubated in 5% CO_2. All plates were incubated at 37°C for up to seven days. Aliquot samples were also inoculated in Robertson's cooked meat broth and incubated at 37°C. Broths that became turbid were subcultured, as described previously. Broths showing no turbidity had a terminal subculture after five-days' incubation. The hip prosthesis was cultured by removing clinical debris from the device (premoistened with sterile saline) with a sterile scalpel and then culturing, as described previously.

Microorganisms recovered from clinical samples were identified by standard microbiological methods. Strain similarity of isolates recovered from multiple samples was based on phenotypic characteristics including biotype and antibiogram as determined by British Society for Antimicrobial Chemotherapy (BSAC) methodology.[17] A definitive diagnosis of septic or aseptic loosening was established using criteria including presurgical imaging data, elevated presurgical serum CRP and/or ESR, positive microbiology cultures yielding indistinguishable microorganisms from two or more clinical samples.

Serum levels of PCT, IL-6 and sICAM-1

Serum levels of PCT, IL-6 and sICAM-1 at the time of surgery were determined using commercially available kits in accordance with the manufacturers' instructions (PCT, B.R.A.H.M.S PCT-Q, Hennigsdorf, Germany; IL-6 and sICAM-1, R&D Systems Europe, UK).

Serum IgG to sce-LTA

Serum IgG to sce-LTA was determined by enzyme-linked immunosorbent assay (ELISA), as previously described by Worthington *et al*.[15]

Diagnostic parameters of serum markers

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of serum markers demonstrating the potential to facilitate diagnosis of septic loosening were determined. Routinely used cut-off values of 10 mg/L and 30 mm/h were applied for CRP and ESR, respectively. Diagnostic parameters for IL-6 and sICAM-1 were established over a series of cut-off points and the best predictors of septic loosening determined.

Statistical analysis

The Mann-Whitney U test was used to determine the significance of differences between levels of serum markers in patients with septic and aseptic loosening. Serum values of CRP, ESR, WBC, IL-6 and sICAM-1 were expressed as the median. All tests were two-sided and $P<0.05$ was considered significant.

Results

Patient demographics

Forty-six patients (25 male, 21 female; mean age: 72 years [range: 50–90]) requiring revision hip surgery due to prosthetic joint loosening were recruited to the study. Based on presurgical patient assessment, a presumptive clinical diagnosis was made by the same surgeon. Thirty (65%) patients were diagnosed clinically as having aseptic loosening of their hip prosthesis, while 16 (35%) were suspected of having septic loosening.

Patients with aseptic loosening
Results of microbiological culture of intraoperative tissue samples from the 30 patients with a clinical diagnosis of aseptic loosening are shown in Table 1. Nineteen (63%) generated sterile cultures while 11 (37%) yielded microorganisms from their intraoperative samples. Of the 11 patients yielding positive cultures, nine (82%) yielded only one positive culture from six intraoperative samples. The remaining two (18%) patients yielded three or more positive samples out of six intraoperative samples, all of which grew heavily mixed microorganisms. As initial criteria to confirm infection were based on the criteria of Atkins *et al.*,[5] these mixed positive culture results were regarded as sample contamination and therefore non-significant. All 11 patients with positive microbiology were followed up for evidence of infection for a mean of 33 months. None re-presented with signs of infection. As they had undergone direct exchange revision surgery, this provides further evidence to support the correct classification as aseptic loosening. This cohort of patients was then investigated further for serum levels of PCT, IL-6, sICAM-1.

Patients with septic loosening
Sixteen patients with a clinical diagnosis of septic loosening based on presurgical patient assessment yielded identical microorganisms (based on phenotypic characteristics) from two or more samples (Table 2). Further evaluation of these patients for serum levels of PCT, IL-6, sICAM-1 was undertaken.

Presurgical results of CRP and ESR, and WBC
Presurgical results for CRP, ESR and WBC are shown in Table 3. There was a significant difference in levels of CRP ($P<0.0001$), ESR ($P<0.0001$) and WBC ($P=0.03$) between patients with septic and aseptic loosening.

Serum levels of PCT, IL-6, sICAM-1 and IgG to sce-LTA
Serum levels of PCT, IL-6, sICAM-1 and IgG to sce-LTA in patients with septic loosening are given in Table 2.

Procalcitonin
All patients with aseptic loosening had non-detectable serum levels of PCT (<0.5 ng/mL). Fifteen (94%) out of 16 patients with septic loosening had serum levels <0.5 ng/mL. One patient who yielded a pure culture of *Proteus mirabilis* from all six intraoperative samples had an elevated serum level >2.0 ng/mL. Based on these results, the diagnostic parameters of PCT as a serum marker for diagnosis of septic loosening were not determined.

Interleukin-6
The median serum concentration of IL-6 in patients with aseptic loosening was 2 pg/mL (range: 0–114), while the median in those patients with septic loosening was 24 pg/mL (range: 5–288). There was a significantly higher serum IL-6 concentration in patients with septic loosening of the hip prosthesis ($P=0.0001$).

Soluble intercellular adhesion molecule-1
The median serum sICAM-1 concentration in patients with aseptic loosening was 180 ng/mL (range: 104–434), while the median in those patients with septic loosening was 330 ng/mL (range: 136–1050). There was a significantly higher serum sICAM-1 concentration in patients with septic loosening of the hip prosthesis ($P=0.0002$).

Diagnostic parameters of CRP, ESR, IL-6 and sICAM-1
The sensitivity, specificity, PPV, NPV and accuracy of CRP, ESR, IL-6 and sICAM-1 for the diagnosis of septic loosening are shown in Table 4. Cut-off values of 9 pg/mL and 250 ng/mL for IL-6 and sICAM-1, respectively, demonstrate the optimum sensitivity and specificity. Nineteen (63%) out of 30 patients with aseptic loosening had serum levels of IL-6 and sICAM-1 below the optimum cut-off points, while 13 (81%) out of 16 patients with septic loosening had elevated serum levels of IL-6 and sICAM-1.

IgG to sce-LTA
No patient with aseptic loosening of their hip prosthesis had a detectable serum IgG to sce-LTA level. No patient with septic loosening caused by microorganisms other than CNS recovered from intraoperative samples had an elevated serum IgG to sce-LTA level. No patients with up to two positive intraoperative samples yielding identical strains of CNS had an elevated serum IgG to sce-LTA level. Four (25%) patients with septic loosening of their hip prosthesis yielded identical strains of CNS from three or more intraoperative samples and three (75%) of these patients had elevated serum IgG to sce-LTA levels (mean: 4250 EIU; range: 4000–6800). One patient had a pure culture of CNS recovered from three out of six intraoperative tissue samples, while single strains of CNS were recovered from five out of six samples from the remaining two patients.

Table 1. Number of positive samples and microorganisms recovered from 30 patients with aseptic loosening of the hip.

Number of patients	Number of positive cultures	Microorganisms recovered	PCT (ng/mL)	IL-6 (pg/mL)	sICAM-1 (ng/mL)
19	0	NG	<0.5	8 (0–114)	210 (104–376)
6	1	CNS	<0.5	7 (0–22)	211 (130–286)
1	1	*Propionibacterium acnes*	<0.5	2.0	232
1	2	Mixed CNS, non-haemolytic *Streptococcus* species	<0.5	13.0	110
1	2	CNS, *Corynebacterium* species	<0.5	50.0	130
1	3	Mixed CNS	<0.5	1.0	130
1	5	Mixed CNS, *P. acnes*, non-haemolytic *Streptococcus*	<0.5	2.0	434

CNS: coagulase-negative staphylococci
NG: No growth

Discussion

Accurate distinction between septic and aseptic loosening of joint prostheses is complex but important as the revision plan and patient management differs in each case.[1,2] Routine tests currently used to facilitate the diagnosis are non-specific and lack sensitivity. Furthermore, confirmatory microbiological culture of intraoperative tissue samples frequently yields positive results that are difficult to interpret. In a search for additional predictors of septic loosening to support current diagnostic methods, this study investigated the potential serum markers PCT, IL-6, sICAM-1 and IgG to sce-LTA in patients with well-defined septic or aseptic loosening.[2,5]

Procalcitonin is a 13 kDa polypeptide that has frequently been reported to facilitate the diagnosis of systemic bacterial infection.[6–8,18] In the present study, serum PCT did not discriminate between infectious and non-infectious causes of prosthetic hip loosening. Serum PCT concentrations in healthy individuals are reported to be <0.1 ng/mL, with little or no rise in patients with viral or localised infections, or infections without systemic manifestation.[18] Indeed, the most potent stimulus for PCT induction is systemic bacterial infection.[19] Previous studies have reported serum PCT levels to be elevated in the range 6–53 ng/mL in patients with severe systemic infection,[18] 0.5–5240 ng/mL in patients with severe sepsis[20] and 0.3–1.5 ng/mL in patients with localised infection.[18] The low serum PCT levels detected in the study patients reported here are therefore not entirely surprising and do not rule out a localised infection.

It is well accepted that pathogen-associated molecular patterns (PAMPs), including LTA and sce-LTA, induce the immune and inflammatory response by binding to specific cellular receptors.[21] Serum levels of the inflammatory markers IL-6 and sICAM-1 in the study patients with septic loosening were significantly raised, suggesting that these serum markers may offer a useful adjunct to current tests, and provide supporting clinical information to facilitate a diagnosis. Furthermore, the diagnostic parameters of IL-6 and sICAM-1 compared favourably with other markers currently used to discriminate septic and aseptic loosening.

Interleukin-6 is considered to be one of the three major pro-inflammatory cytokines produced during inflammation; however, it is not a specific marker for bacterial infection as levels are often elevated after physical trauma.[18,22] While the normal range of serum IL-6 in adults is 0.2–4.5 pg/mL, cut-off ranges vary considerably between studies.[9,23,24] Applying a cut-off level of 9 pg/mL in this study yielded sensitivity,

Table 2. Serum levels (PCT, IL-6, sICAM-1 and IgG to sce-LTA) and number of positive samples yielding identical microorganisms from ≥2 intraoperative samples (n=6) from 16 patients with septic loosening of the hip.

Patient	Number of positive samples (out of 6)	Number of positive cultures with identical microorganism (and second identical microorganism)	Microorganisms recovered	PCT (ng/mL)	IL-6 (pg/mL)	sICAM-1 (ng/mL)	IgG to sce-LTA (EIU)
1	3	2	*P. acnes*	<0.5	5	428	ND
2	3	2	α-haemolytic *Streptococcus* species	<0.5	288	350	ND
3	3	3	*Corynebacterium* species	<0.5	8	136	ND
4	3	3	CNS	<0.5	15	1050	4000
5	4	3 (2)	*Staphylococcus aureus* (3) *Morganella morganii* (2)	<0.5	287	266	ND
6	5	4 (2)	*Corynebacterium* species (4) *S. aureus* (2)	<0.5	15	310	ND
7	5	5 (2)	CNS 1 (5) CNS 2 (2)	<0.5	9	300	6200
8	5	3 (2)	*Escherichia coli* (3) *Enterococcus faecalis* (2)	<0.5	65	530	ND
9	5	5 (2)	CNS 1 (5) CNS 2 (2)	<0.5	60	400	6800
10	5	4	CNS	<0.5	25	432	ND
11	5	5	*Citrobacter koseri*	<0.5	23	260	ND
12	6	6 (6)	*Streptococcus agalactiae* (6) α-haemolytic *Streptococcus* species (6)	<0.5	36	280	ND
13	6	6	*E. faecalis*	<0.5	17	216	ND
14	6	6 (4)	*E. faecalis* 1 (6) *E. faecalis* 2 (4)	<0.5	6	270	ND
15	6	6	*S. aureus*	<0.5	38	386	ND
16	6	6	*Proteus mirabilis*	>2.0	84	390	ND

CNS: coagulase-negative staphylococci

ND: IgG to sce-LTA not detected

Table 3. Presurgical results of CRP, ESR and WBC in patients with septic and aseptic loosening.

Patient group	Median CRP (mg/L)	Median ESR (mm/h)	Median WBC (x10^9/L)
Septic loosening (n=16)	39.5 (9–208)	48.5 (13–129)	8.5 (4.8–12.4)
Aseptic loosening (n=30)	3.0 (3–154)	10.0 (4–29)	7.2 (4.0–11.5)
Mann-Whitney	P=0.0001	P=0.0001	P=0.003
Range in parentheses			

specificity, PPV, NPV and accuracy of 81%, 77%, 65%, 50% and 78%, respectively. In a recent study undertaken by Di Cesare *et al.*,[11] elevated serum IL-6 levels correlated positively with periprosthetic infection, generating diagnostic sensitivity and specificity of 100% and 95%, respectively. These results support the current findings and further advocate the use of serum IL-6 as a potential diagnostic marker of periprosthetic infection.

Intercellular adhesion molecule-1 is an integral membrane protein that is critical for leucocyte extravasation into inflamed tissue, the level of which is up-regulated during inflammation by a variety of cytokines. In bone, ICAM-1 is expressed at the surface of the osetoblasts.[25] Interestingly, sICAM-1, which is present in serum, cerebrospinal fluid and bronchoalveolar lavage, and arises from cleavage of ICAM-1, has been relatively understudied as a predictor of infection compared with many inflammatory markers. The results presented here demonstrate that sICAM-1 level is significantly raised in patients with septic loosening of their prosthetic hip compared to those with mechanical loosening. Soluble ICAM-1, if used in addition to, and in combination with, IL-6 may therefore serve as a valuable serological marker to discriminate septic and aseptic loosening of prosthetic joints. Applying a cut-off figure of 250 ng/mL, sensitivity, specificity, PPV, NPV and accuracy of 94%, 74%, 65%, 65% and 80%, respectively, were achieved.

Microorganisms most commonly associated with septic loosening of prosthetic joints are CNS, in particular *Staphylococcus epidermidis*, and account for approximately half of the cases.[2] Serum markers which not only predict infection but give an indication to this aetiological agent may therefore facilitate both diagnosis and potentially influence patient management. Serum IgG antibody to sce-LTA has been shown to be of diagnostic value in patients with infections due to CNS including prosthetic joint infection.[12,14,15] Surprisingly, in this study only four (25%) patients had septic loosening due to CNS, which limited the analysis of the value of sce-LTA in predicting septic loosening due to these microorganisms. However, of these four patients with well-defined septic loosening due to CNS (i.e., recovered from three or more intraoperative samples[5]) three (75%) had elevated serum IgG to sce-LTA levels (Table 2) and supports previous findings.[12]

Based on the results of this study, serum levels of IL-6, sICAM-1 and sce-LTA may predict infection in patients with prosthetic hip loosening and provide useful adjuncts to current diagnostic markers. As a serum sample for CRP, ESR and WBC is obtained routinely from patients as a part of presurgical assessment, serum levels of IL-6, sICAM-1 and IgG to sce-LTA could also be established at this stage of patient management, providing supporting diagnostic clinical information. Prospective studies of larger patient populations are required to assess further the clinical value of these serum markers, and perhaps additional serum markers, in aiding the diagnosis of septic loosening of prosthetic hips. □

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Table 4. Diagnostic parameters of CRP, ESR, IL-6 and sICAM-1 in patients with septic loosening of the hip.

Serum marker	Cut-off values	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CRP	10 mg/L	94	97	94	50	96
ESR	30 mm/H	81	100	100	39	93
IL-6	9 pg/mL	81	77	65	50	78
sICAM-1	250 ng/mL	94	74	65	65	80

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