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Serum biomarkers in the diagnosis of periprosthetic joint infection: consolidated evidence and recent developments

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Abstract. Periprosthetic Joint Infection (PJI) represents one of the leading causes of revision prosthetic surgery, accounting for 25% of failed Total Knee Replacement (TKR) and 15% of failed Total Hip Replacement (THR). The search for a biomarker that, together with clinical and radiological findings, could improve the management of such a kind of patients is currently a big challenge for orthopaedic surgeons.

This review aims (1) to assess the accuracy and the limitations of the traditional (Serum Erythrocytes Sedimentation Rate, C-reactive Protein, Procalcitonin, Interleukin 6, Tumor Necrosis Factor alpha), (2) and to analyse the emerging serum biomarkers (Presepsin, Toll-like Receptor 2, soluble urokinase-type Plasminogen Activator Receptor, Chemokine Ligand 2 and Osteopontin) in the diagnosis of PJI.

A special attention will be given to the emerging serum biomarkers, that could play an important role as first-line investigations, in the screening of PJI in a close future.

Key Words
Periprosthetic joint infections, Total hip replacement, Total knee replacement, ESR, CRP, PCT, IL-6, TNF-alpha, Presepsin, TLR-2, suPAR, CCL-2, Osteopontin.

Introduction

Periprosthetic Joint Infection (PJI) is a fearsome complication of joint arthroplasty which accounts for 25% of failed Total Knee Replacement (TKR) and 15% of failed Total Hip Replacement (THR), in the US[1,2].

PJI currently represents one of the leading causes of revision prosthetic surgery[3]. Nonetheless, a substantial increase in the number of patients affected by PJI is expected in the next years, because of the increasing volume of Total Joint Replacements (TJRs) performed internationally[4,5].

The orthopaedic research, therefore, is turning a great attention to the study of PJI, in order to better understand and manage this dreadful disease. It is remarkable that in the last years the trend of published works concerning PJI is increasing: in 2008, only 30 articles on this topic were recorded in PubMed database, whereas 269 articles were indexed in 2016 and 364 articles in 2017[6].

The diagnosis of PJI, however, remains difficult, due to its heterogeneous clinical manifestation and to the poor standardized diagnostic criteria[7].

Moreover, in the treatment of PJI, there are still lots of unanswered questions, including the diagnostic value of serum biomarkers, synovial fluid analysis, radiological and nuclear medicine imaging.

There is also no consensus on the timing of surgery, the usefulness of prolonged antibiotics assumption, as well as the optimal timing to perform the antibiotic-loaded spacers implants removal and the final reimplantation of a revision total joint prosthesis[7,8].

Decision making in patients with a suspected PJI is never easy; consequently, the search for a biomarker that, together with clinical and radiological findings, could improve the management of such a kind of patients is currently a big challenge for orthopaedic surgeons.

This review aims (1) to assess the accuracy and the limitations of the traditional (Serum Erythrocytes Sedimentation Rate, C-reactive Protein, Procalcitonin, Interleukin 6, Tumor Necrosis Factor alpha) (Table I) (2) and to analyse the emerging serum biomarkers (Presepsin, Toll-like Receptor 2, soluble urokinase-type Plasminogen Activator Receptor, Chemokine Ligand 2 and Osteopontin) in the diagnosis of PJI.

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Table I. Strengths and limitations of the traditional serum biomarkers used in the diagnosis of PJI.

Biomarker	Strengths	Limitations
ESR	1. Inexpensive and reproducible test 2. Its performance could be improved with ROC analysis	1. It is non-specific 2. It is increased up to 6 weeks after surgery 3. It is influenced by systemic antibiotics 4. If normal, a PJI cannot be ruled out 5. It is useful only when other MSIS criteria are met
CRP	1. Inexpensive and reproducible test 2. Short half-life 3. It is the most accurate biomarkers in the diagnosis of PJI	1. It is non-specific 2. It is increased up to 2 weeks after surgery 3. It is influenced by systemic antibiotics 4. If normal, a PJI cannot be ruled out 5. It is useful only when other MSIS criteria are met
PCT	1. Inexpensive and reproducible test 2. Very short half-life 3. PCT peaks more rapidly than CRP 4. In one trial27, PCT resulted in more accurate than CRP in the diagnosis of septic arthritis	1. It is non-specific for the diagnosis of PJI 2. Its role in the diagnosis of PJI is controversial
IL-6	1. IL-6 peaks and normalizes more rapidly than CRP 2. It can be useful if assessed in association with other serum biomarkers	1. It is non-specific for the diagnosis of PJI 2. It can moderately increase in aseptic loosening
TNF-alpha		1. TNF alpha is an unstable biomarker 2. TNF alpha is not as sensible as IL-6 and CRP 3. It should not be used in the diagnosis of PJI

Particular attention will be given also to the cost of the new laboratory tests described, in order to assess which tests might be useful in the current management of PJI.

The Ideal Biomarker in the Diagnosis of PJI

The ideal biomarker for the diagnosis of PJI should be reliable and reproducible in different settings, and it should be able to identify, as soon as possible, a PJI[9]. It should also provide a risk stratification, in order to suggest the appropriate therapeutic treatment, and have a prognostic value in the aftercare[9]. Unfortunately, such a kind of biomarker has not been discovered yet.

Several diagnostic tests have been proposed, but most of them lack scientific evidence, have a poor sensibility or specificity and are not available in all laboratories[10].

Serum biomarkers could represent a favourable diagnostic tool, compared with synovial fluid markers. In fact, they can be easily obtained from a blood sample and could be periodically assessed, thus monitoring the long-term outcome of a surgical procedure[4].

Currently, the only serum biomarkers recommended by the American Academy of Orthopaedic Surgeons (AAOS), as the first line of diagnostic evaluation in suspected PJI, are Serum Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP)[5]. These biomarkers, however, are non-specific since they are elevated with any type of infection or inflammation[4].

Serum Biomarkers Currently Used in the Diagnosis of PJIs

Serum erythrocyte sedimentation rate (ESR)

Serum Erythrocyte Sedimentation Rate (ESR), originally described by Dr. Edmund Faustyn Biernacki in 1897, constitutes the rate at which erythrocytes settle in an anticoagulated blood specimen over a one-hour period[11]. ESR is measured in millimeters/hour (mm/h); its reference interval is usually defined in male as "age in years divided by 2" and for female, as "age in years plus 10.9"[11,12].

Red Blood Cells (RBCs) membranes are negatively charged; therefore, these cells tend to repulse each other[11]. Nonetheless, the presence of positively charged acute phase proteins, i.e., fibrinogen and immunoglobulins, increases RBCs aggregation thus their ESR[11].

An increased ESR could be depicted in several medical conditions, including inflammation and inflammatory arthritis; infection; systemic autoimmune disease; trauma; infarction and neoplasm[11].

ESR is usually increased up to six weeks after a surgical procedure, thus in this time-lapse ESR should be not assessed if a PJI is suspected[4]. It is reported that ESR has a sensitivity of 91% and specificity of 72% in detecting PJI[4].

Shiha et al[13], in a level III study, have recently observed that the previous administration of systemic antibiotics may influence the ESR values, thus seriously affecting the likelihood of diagnosing an infection in patients who have PJI. Consequently, a normal ESR value could not rule out a PJI. Furthermore, ESR serum levels are influenced by innumerable factors, including patient's unmodifiable risk factor – i.e., age and sex –, obesity, comorbidities, drugs assumption, smoking status severity, stage of inflammation, and other unknown factors[9].

Nonetheless, the use of Receiver Operating Characteristic (ROC) analysis could improve the ESR test performance in the diagnosis of PJI.

Alijanipour et al[9], in a retrospective level III study on septic and aseptic revision knee or hip replacements, have recently shown that ESR thresholds were similar in both joints in early-postoperative PJI, while in late-chronic PJI are higher in hips than knees.

Currently, however, high ESR values could predict a PJI only when the other Musculoskeletal Infection Society (MSIS) criteria are met.

C-reactive protein (CRP)

C-Reactive Protein (CRP) is a pentameric protein discovered by Tillet and Francis in 1930 in patients with pneumococcal pneumonia. In such a kind of patients, they noticed this protein interacted with the C-polysaccharide of *Streptococcus pneumoniae* cell wall, hence the term C-reactive protein[11].

CRP is a nonspecific acute phase protein, member of the pentraxin family, and is an integral part of the innate immune system[11].

CRP is produced and synthesized in the liver in response to inflammatory cytokines, such as IL-6, IL-1, TGF-beta, and TNF alpha. It takes part in complement binding and in macrophagic phagocytosis[11,14].

CRP concentration is generally expressed in mg/dl and its level tends to be proportional to the intensity of the inflammatory process[11,14]. Once inflammation subsides, CRP values fall quickly because of its short half-life (4 to 7 hours)[11,14-15].

Nonetheless, CRP level remains high up to two weeks post-operatively[4,15], then it begins lowering in both PJI and non-infected patients[16].

CRP specificity in the PJI diagnosis is 68.13±0.78%, while its sensibility is 92.31±0.95%[15]. Its poor specificity can be explained considering that CRP values are influenced by so many factors such as inflammation, autoimmune systemic diseases, rheumatic diseases, tissue injury, necrosis, neoplasm, smoking status and obesity[11,17].

Moreover, in low-grade PJI caused by *Propionibacterium acnes* or coagulase-negative *Staphylococcus*, normal levels of CRP can be found; thus, normal serum CRP values cannot rule out a PJI[18,19].

Synovial CRP has recently shown a greater sensitivity and specificity in diagnosing PJI, compared with serum CRP[20]. Synovial CRP assessment, however, cannot be easily repeated in the aftercare; therefore, it could be useful in PJI diagnosis, rather than in its clinical monitoring[21].

Currently, CRP is the most accurate serum biomarker in the diagnosis of PJI, with the highest specificity and sensibility, but it is useful in predicting a PJI only when the other MSIS criteria are met[4].

Procalcitonin (PCT)

Procalcitonin (PCT) is a 116 amino-acids protein, member of the calcitonin superfamily, normally expressed in thyroid C cells and, to a small extent, in neuroendocrine cells[22]. Physiologically, all the PCT produced in thyroid C cells are converted to calcitonin. The PCT level in healthy subjects is very low (0.05 ng/mL)[22].

Serum PCT level is elevated in the presence of bacteria, when it rises more rapidly than CRP levels, peaking within very short time, within 6-24 h[4,22]. Moreover, if the patient responds appropriately to the treatment, the PCT level returns to normal range faster than CRP, thanks to its short half-life of 25 to 30 hours[22,23].

Botner et al[24], in a prospective study on 78 patients undergoing TKR or THR revision surgery for PJI, observed that PCT levels (> 0.3 ng/mL) were very specific (98%) in the diagnosis of PJI, but they had a low sensitivity (33%).

Worthington et al[25], in a prospective case-control study on 46 patients undergoing THR for septic or aseptic loosening, found that PCT is useful in diagnosing PJI.

Similar data were reported by Drago et al[26], in a prospective study on 52 patients undergoing THR or TKR for PJI or aseptic loosening.

On the other hand, Hügle et al[27], in a prospective study on 42 patients with septic or aseptic arthritis, reported that PCT, cut-off 0.25 ng/ml, was more sensible (93%) and specific (75%) than CRP in detecting septic arthritis.

These data may be explained, as suggested by Shahi and Parvizi[4], considering that PCT is secreted by monocytes when stimulated by lipopolysaccharide.

PCT accuracy in detecting PJI, however, seems to be very low; hence, currently, this biomarker should not be used in the diagnosis of PJI. It may have a role in the differential diagnosis of bacterial arthritis or other causes of joint inflammation[4].

Interleukin 6 (IL-6)

Interleukin-6 (IL-6) is a pleiotropic cytokine produced by different immune cells, mainly monocytes and macrophages during the acute phase of inflammation[28]. IL-6 triggers the synthesis of CRP and is also implicated in the regulation of metabolic, regenerative, and neural processes[28].

IL-6 cut-off value for the clinical diagnosis of inflammation is 1 pg/ml. IL-6 levels, however, could be also increased in patients with chronic inflammatory diseases, Paget disease, immunodeficiency syndromes[29].

Wirtz et al[29] reported that IL-6 is a better indicator for postoperative inflammatory response in patients undergoing Total Joint Replacement (TJR), compared with CRP, since it peaks and normalizes faster than CRP[24,29,30].

In the diagnosis of PJI, IL-6 revealed more accurate than CRP and ESR[31-32]. Botner et al[25] observed a significantly higher serum IL-6 concentration in patients with PJI, compared with patients affected by aseptic loosening (p=0.0001).

However, serum IL-6 levels should be assessed together with synovial IL-6, if possible, and with the measurement of CRP and ESR.

Tumor necrosis factor-alpha (TNF-alpha)

Tumor Necrosis Factor-alpha (TNF-alpha) was originally identified as a factor that causes a rapid necrosis of transplantable tumours in mice[33]. Currently, it is considered a pro-inflammatory cytokine, involved in the innate immune response[33].

Currently, little is known about the value of TNF-alpha in the diagnosis of PJI. Stahelova et al[33], in a prospective study on 303 patients, found no association between PJI and polymorphisms in the genes coding for TNF-alpha.

Botner et al[24] reported that TNF-alpha is not as sensitive as CRP and interleukin-6 in the diagnosis of PJI. According to these authors, moreover, PCT is more specific than TNF-alpha in the diagnosis of PJI[24]. It is important to note that TNF-alpha is an unstable biomarker, but the analytic process requires more than two hours each sample[24].

Based on these findings, TNF-alpha is not useful in assessing patients with a failed total joint replacement[25]. It should be not used as a serum biomarker of PJI because it has a lower sensibility than CRP and IL-6 and a lower specificity than Procalcitonin.

Emerging Serum Biomarkers in the Diagnosis of PJI

Presepsin

Presepsin is a biomarker, originally described by Yaegashi et al[34] in 2004. It is currently used in the diagnosis and evaluation of sepsis[34].

From a molecular point of view, presepsin is the soluble cluster of differentiation 14-SubType (sCD14-ST). Two different forms of the cluster of differentiation 14 (CD14) have been characterized: a membrane-bound CD14 (mCD14) and a soluble CD14 (sCD14)[34].

mCD14 is mainly expressed on cellular membranes of monocytes, macrophages, and neutrophils, where it acts as a high-affinity receptor for the lipopolysaccharide-binding protein complex (LPS-LBP)[34-35]. It can also bind to peptidoglycan and other surface molecules, expressed in both Gram-negative and Gram-positive bacteria, thus triggering the acquired immune response[35-36].

sCD14, on the other hand, enhances the immune and inflammatory responses, by mediating the activation of CD14-negative cells, namely epithelial and endothelial cells, in the presence of microbes.

sCD14 is then cleaved in smaller fragments by plasma proteases; presepsin is a specific N-terminal 13 kDa glycoproteic fragment of CD14[34,36].

Since 2004, several studies have investigated the role of presepsin in the diagnosis of systemic inflammatory response syndrome (SIRS), sepsis and neonatal sepsis[37].

Other papers have evaluated the role of presepsin in the prognosis of severe acute pancreatitis, in detecting infections in patients with haematological malignancies, in the risk stratification and diagnosis of severe community-acquired pneumonia, in the risk stratification in cardiac surgery patients, in the diagnosis of pacemaker and implantable cardioverter defibrillator (ICD) pocket infections and in polytrauma patients[37].

It is reported that if presepsin concentration is lower than 300 pg/ml, there is no risk of systemic infection, whereas a value of presepsin higher than 530 pg/ml may suggest a septic state[38].

In the field of orthopaedic surgery, presepsin could be helpful in the diagnosis and management of patients with PJI.

In a recent preliminary prospective study from our Institution, Vicenti et al[37] assessed the normal perioperative plasmatic levels of presepsin, in 117 patients undergoing primary cementless THR or primary cemented TKR, for primary osteoarthrosis of the hip or of the knee respectively[37]. Presepsin was found to increase until 72 hours postoperatively, when it reaches its maximum, and starts decreasing at 96 hours after surgery[37]. Moreover, presepsin resulted in more accurate than CRP in the assessment of post-operative inflammation[37]. Based on these data, the authors suggested assessing routinely the plasmatic presepsin concentration in patients undergoing at three different moments: at 24 hours before surgery, at 72 hours postoperatively and at 96 hours postoperatively, when a decrease of presepsin levels should be found[37].

Marazzi et al[39], in a prospective multicentre study on 100 patients undergoing TJR for PJI or aseptic loosening, observed that presepsin levels in PJI were higher than in aseptic loosening. Presepsin showed, in this study, a linear correlation with CRP and IL-6 levels, thus confirming that presepsin increases because of the inflammatory process in response to infection[39].

Furthermore, in patients with PJI, presepsin significant lowered at 48 hours postoperatively and reached values comparable to control patients at one month postoperatively.

Ulla et al[40] showed that presepsin cost-effective and able to distinguish septic patients in a complex population presenting to the Emergency Department with Systemic Inflammatory Response Syndrome (SIRS). However, before performing this test, it should be considered that a presepsin assessment might cost about 2400 euros.

Presepsin could be a useful first-line biomarker in patients with a suspected PJI, even if it is currently a quite expensive test.

Toll-like receptor 2 (TLR-2)

Toll-like Receptors (TLRs) are a class of receptors, usually expressed on antigen presenting cells, which play a critical role in the early innate immune response to microbes[41,42].

Among TLRs, TLR-2 is essential to recognize a variety of Pathogen-Associated Molecular Patterns (PAMPs), including bacterial lipoproteins, lipomannan, and lipoteichoic acids[41].

Galliera et al[42] have recently described a specific involvement of the soluble form of TLR-2 in PJI, where it is involved in the recognition and response to Gram-positive bacteria. A close interaction has been also found between sCD14 and TLR-2, thus suggesting a possible mechanism of action of presepsin in response to Gram-positive bacterial infection.

Marazzi et al[39] observed that TLR-2 slowly decreases up to 48 hours after surgery and reaches values comparable to non-infected patients at one-month follow-up.

Soluble urokinase plasminogen activator receptor (suPAR)

The receptor for urokinase Plasminogen Activator (uPA) is a glycoprotein, which has been characterized into two forms: a membrane-bound form – i.e., urokinase Plasminogen Activator Receptor (uPAR) – and a soluble form – i.e., soluble urokinase Plasminogen Activator Receptor (suPAR) –.

uPAR is expressed on different cells type, i.e., lymphocytes, neutrophils, macrophages, tumor cells and endothelium, and its production is enhanced by chemokines[43,44]. uPAR, together with its ligand uPA, binds to β-integrins, thus promoting the migration and adhesion of leukocytes.

suPAR originates from the cleavage of uPAR from the cell membrane and can be detected in blood and other organic fluids – including urine, cerebrospinal fluid, synovial fluid, and bronchoalveolar fluid[43,44]. It has a key role in several immune functions, including cell migration and adhesion, chemotaxis, immune activation, tissue remodeling, and invasion[44,45].

In healthy subjects, suPAR serum levels are low and quite stable, while they significantly increase in the presence of an immune activation[44,46]. Currently, suPAR is an emerging diagnostic and prognostic biomarker in the management of sepsis, where it seems to be also able to discriminate the different grades of sepsis severity[44,47].

The role of suPAR in the field of PJI has been recently investigated by Galliera et al[44], in a prospective trial on 80 patients undergoing TJR for aseptic loosening or PJI. These authors found that suPAR has a good diagnostic value in the detection of PJ[44]. Indeed, the area under the curve (AUC) of the ROC curve of serum suPAR was significantly higher than CRP and IL-6 ones, in patients who

suffered for PJI[44]. suPAR levels were also found to correlate with the same inflammatory cytokines involved in the sCD14-mediated response (CRP, TNF alpha, IL-1, IL-6, and CCL2), thus suggesting that suPAR and presepsin might act together in the inflammatory host response to infection[44].

Marazzi et al[39] have observed that post-operatively suPAR has the same trend of presepsin: its levels lower significantly at 48 hours postoperatively, compared with baseline values, and reach values close the control patients at one month postoperatively.

suPAR, in association with routine inflammatory parameters such as CRP, may have a high diagnostic potential in the diagnosis of PJI[44].

Chemokine ligand 2 (CCL2)

Chemokine ligand 2 (CCL2) is a monomeric protein, belonging to the CC chemokine family, produced by monocytes/macrophages and dendritic cells[44]. After its cleavage, performed by MMP-12, CCL2 becomes active and starts recruiting monocytes, memory T cells, and dendritic cells to the sites of inflammation[44].

Galliera et al[44] observed that CCL2 values were significantly higher in patients affected by PJI, compared to control patients. Of note, CCL2 levels were found to be strongly related to serum suPAR concentration, thus underlining the diagnostic potential of this biomarker in the diagnosis of PJI.

Marazzi et al[39] confirmed that the serum levels of CCL2 were significantly higher in patients undergoing TJR for PJI, compared with aseptic patients. Moreover, ROC analysis showed that CCL2 gives good diagnostic values in PJI. In PJI patients, similarly to presepsin, CCL2 significantly decreases at 48 hours postoperatively and reaches values comparable to aseptic patients at one-month follow-up[44].

Osteopontin (OPN)

Osteopontin (OPN) is a phosphoprotein, with signalling and adhesive functions, involved in cell-cell and cell-matrix interactions[48]. It can act as either an extracellular matrix component in mineralized tissues or a soluble cytokine in inflamed tissues and serum[48]. OPN has a crucial role in inflammation, and its levels are found to be related with suPAR[39].

In severe sepsis, plasmatic levels of OPN are significantly higher in non-survivors than survivors; hence, OPN appears to be associated with a greater inflammatory response and an increased mortality[48-49].

In the field of PJI, Marazzi et al[39] reported that OPN is significantly higher in PJI, compared with aseptic TJR loosening. ROC analysis revealed OPN has good diagnostic values in PJI[39]. Furthermore, OPN has also shown a post-operative trend comparable to presepsin.

Conclusions

The traditional serum biomarkers currently used in the diagnosis of PJI have shown several limitations; thus, they can be useful only when the other MSIS criteria are met.

The ideal biomarker for the diagnosis of PJI, unfortunately, have been not discovered yet. However, a series of new biomarkers have been recently proposed in the diagnosis and management of PJI. If the preliminary data are confirmed in future studies, the emerging biomarkers – i.e., presepsin, TLR2, suPAR, CCL-2, and OPN – could become useful tools, as first-line investigations, in patients with suspected PJI.

Because of the recent introduction of these serum biomarkers, the cost-effectiveness analysis data are not available at the moment. Consequently, further level-I evidence are eagerly awaited, before introducing the use of these biomarkers in clinical practice.

Conflict of Interests

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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