Synovial pH Is As Specific As Synovial Leukocyte Count But Less Sensitive For The Diagnosis of Chronic Prosthetic Joint Infection

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Abstract

Synovial fluid markers have been shown to be most accurate in diagnosing prosthetic joint infection (PJI). An inverse correlation for synovial leukocyte count and synovial pH is known assuming that leukocyte metabolism causes synovial fluid acidosis. This study analysis synovial pH as a potential marker for PJI. We prospectively included 92 patients who presented with painful total joint arthroplasty (TJA) of the hip (THA; n = 25) or knee (TKA, n = 67). Joints were diagnosed as infected (n = 30) or aseptic (n = 62) based on the Musculoskeletal Infection Society criteria of 2018. An ideal cut-off value for synovial pH and the sensitivity and specificity were calculated. Additionally, the sensitivity and specificity were calculated for synovial white blood cell (WBC) count (cut-off > 3000 leukocytes) and percentage of neutrophils (PMN%, cut-off > 80%). The median synovial pH level was significantly lower in the group with chronic PJI (7.09 vs. 7.27; $p < 0.001$) compared to implants with aseptic failure. The calculated optimal cut-off value was 7.11 (AUC 0.771) with a sensitivity of 53% and specificity of 89%. However, the sensitivity and specificity of synovial WBC count were 90% and 88% and for synovial PMN% 73% and 98%, respectively. Synovial pH may be a cost-effective parameter to diagnose chronic PJI.

Introduction

Periprosthetic joint infection (PJI) is one of the most feared complications that can occur after total joint arthroplasty (TJA) of the hip (THA) or knee (TKA) [1, 2]. Its incidence after primary TJA around 1–2% [3], but due to the increasing number of performed joint replacements, the number of revision arthroplasties due to PJI will continue to rise in the coming years [4–6]. Timely and accurately diagnosing of PJI – especially in low grade cases - is still challenging in daily clinical practice and since to date no optimal, universal test is available [6, 7].

Currently, the diagnosis of PJI is usually established using the criteria published by the Musculoskeletal Infection Society (MSIS) and by the International Consensus Meeting (ICM) proceedings [8, 9]. Beside the clinical findings as well as serum and microbiological testing, both definitions include synovial white blood cell (WBC) count and percentage of synovial polymorphonucleocytes (PMN%). Synovial fluid analysis appears to be most reliable at the moment[10, 11] but it still has no perfect diagnostic accurary and the optimal threshold for different joints and organisms are debated [9, 12, 13].

The potential role of synovial fluid pH as a biomarker to differentiate identify joint with inflammatory joint disease and those with normal joints was investigated (n = 16) as early as 1966 [14]. Generally, the pH is a scale used to specify the acidity or basicity of an aqueous solution[15] and acidic solutions (solutions with higher concentrations of H^+ ions) are measured to have lower pH values than alkaline solutions. A previous study on synovial fluid pH in native joints[14] showed a significantly lower synovial pH value in cases of inflammatory joint disease than in non-inflammatory joints (7.223 vs. 7.434). Later research (n = 22) found a close correlation for an increasing synovial WBC count and an associating decreasing synovial pH in septic native joint arthritis [16]. The demonstrated inverse correlation of WBCs and pH supports the suggestion that white blood cell metabolism is responsible for synovial fluid acidosis.

Considering that PJI is associated with an increased synovial WBC count [8, 9], this study evaluates synovial pH in patients undergoing revision arthroplasty of the hip or knee as a potential synovial biomarker for chronic PJI and compares its accuracy with synovial WBC count and PMN%.

Methods

Prior to this prospective investigation approval of the institutional review board of the authors' institution was obtained (ethics committee of the University of Muenster, ref. no. 2019-666-f-S) and it was registered in the German Clinical Trials Register (Registration number: DRKS00021038; date of registration: 18/03/2020). Written consent was obtained from all participants and the study was conducted according to the principles of the World Medical Association Declaration of Helsinki. No specific source of funding was required for this study.

All patients who presented to our tertiary centre for revision arthroplasty with a potential indication for revision either for chronic PJI or for aseptic causes routinely undergo tests of serum, synovial and microbiological parameters prior to rule out PJI. For this study we added a synovial pH-test to the diagnostic preoperative algorithm and analyse the preliminary findings of data collected between August 2019 and October 2020. Synovial fluid was collected in safePICO syringes (Radiometer GmbH, Krefeld, Germany) with a built-in mixing ball and dry electrolyte-balanced heparin, helping to minimize the risk for clot formation and measured by potentiometry on a commercial blood gas analyser (ABL 90 FLEX PLUS, Radiometer GmbH, Krefeld, Germany).

In our practice all patients undergo analysis of serum c-reactive protein (CRP), serum interleukin-6 (Il-6), serum and synovial WBC count, differentiation of synovial WBCs including PMN% and synovial microbiology culture. Patients who had surgery within the last 4 weeks, those with chronic systemic inflammation such as rheumatoid arthritis, those with confirmed inflammatory diseases of other organs such as pneumonia and urinary tract infection, those with malignancies were not screened using synovial pH testing. For patients that underwent revision arthroplasty (n = 62), either for chronic PJI (n = 30) or aseptic failure (n = 32), a minimum of five intraoperative tissue samples for microbiology cultures were taken additionally to the synovial fluid, and another tissue sample was taken for histological again applying the criteria by the MSIS. All taken tissue and synovial fluid samples were cultured for a minimum of 14 days on Columbia blood agar, chocolate agar and Schaedler agar for microbiological testing. Furthermore, 34 patients were evaluated preoperatively, but did not undergo surgery so far because they declined surgery at this point or a non-operative management has been recommended, resulting in a total of 96 patients who were eligible for analysis. Participants meeting the study's inclusion criteria were prospectively evaluated and classified as infected (n = 30), not-infected (n = 62) or inconclusive (n = 4) as defined in the ICM proceedings 2018. Those with an inconclusive score were excluded from the statistical analysis. In total 92 patients (25 THA, 67 TKA, 46 male, median age 69 (IQR 60–76) were included in this study. Thirty patients (19 TKA, 11 THA) were assigned to the PJI group, while the remaining 62 patients were not considered infected (48 TKA, 14 THA).

Statistical analysis

Excel (Microsoft Corporation, Redmont, Washington, USA) and Statistical Package for the Social Sciences Statistics for Windows version 25 (IBM Corporation, Armonk, NY, USA) were used for statistical analysis of pseudonymized patient data. The Shapiro–Wilk test and descriptive statistics were used to analyse distribution of data. For parametric data the means and ranges were calculated; the medians and 25–75% interquartile ranges (IQRs) were obtained for non-parametric data. The non-parametric analyses were performed using the Mann–Whitney U test and frequencies were given for categorical variables that were compared in contingency tables using the chi-squared test.

Receiver operating characteristics (ROC) analyses with presentation of the area under the curve (AUC) with 95% confidence interval (CI) were used for statistical evaluation. To determine the optimal cut-off value for synovial pH the Youden's index was used. Based on the determined cut-off value for synovial pH and the given cut-off values for WBC count (> 3000/µl) and PMN% (> 80%) [8, 9], sensitivities and specificities were calculated for each biomarker from contingency tables. Statistical significance was set at $p \leq 0.05$.

Results

The median synovial pH level was significantly lower in the patients diagnosed with chronic PJI (7.09 (IQR, 6.98–7.26)) compared to the patients with aseptic failure (7.27 (IQR, 7.17–7.32) ($p < 0.001$).

The ROC curve analysis revealed the lowest AUC for synovial pH, at 0.771 (95% confidence interval (95% CI), 0.664–0.878). Using Youden's index, the optimal cut-off value was 7.11 for synovial pH discriminating between chronic PJI and aseptic failure. Fifty-five of 62 not infected samples had a synovial pH value below 7.11 and 16 of 30 infected samples had a synovial pH above 7.11. Applying this threshold, a specificity of 89% and sensitivity of 53% were calculated. The positive predictive value to correctly identify chronic PJI was 69% and the negative predictive value was 79% (Table 1).

Table 1
Results for synovial pH value, synovial white blood cell (WBC) count and percentage of synovial neutrophils (PMN%) in diagnosing prosthetic joint infection (PJI).

Markers	Used cut-off values	Sensitivity (%)	Specificity (%)	PPV	NPV
pH	< 7.11	53	89	0.6956	0.7971
WBC count	> 3000/µl	90	88	0.7941	0.9464
PMN%	> 80%	73	98	0.8529	0.8787

In comparison, the median level of synovial WBC count (14905 (IQR, 6692–28898) vs. 660 (IQR, 310–1422), $p < 0.001$) and synovial PMN% (90.6% (IQR, 76.6–94.6%) vs. 26.9% (IQR, 19.5–45.3%), $p < 0.001$) were significantly higher in patients with chronic PJI compared to patients with aseptic failure.

The highest AUC was shown for synovial PMN% with 0.962 (95% CI, 0.911–1.000), followed by synovial WBC count with 0.936 (95% CI, 0.880–0.993). Using the given cut-off values, the sensitivity and specificity of synovial WBC count were 90% and 88% and 73% and 98% for synovial PMN%, respectively.

In 25 of 30 cases (83.3%) with chronic PJI a causative bacterium was identified (Table 2), while five (16.7%) patients had culture-negative infection and four (13.3%) presented with a polymicrobial infection. In case of the five culture-negative patients one patient had a fistula and the other cases each had an elevated CRP, elevated synovial WBC count and elevated synovial PMN%. There were no unexpected positive cultures in the group that was considered not infected preoperative.

Table 2
List of the identified bacteria for the 25 patients the PJI group.

Culture organism	Frequency [%]
Staphylococcus lugdunensis	3.8
Enterobacter cloacae complex	5.8
Corynebacterium	3.8
Staphylococcus epidermidis	17.2
Escherichia coli	3.8
Streptococcus agalactiae	3.8
Enterococcus faecalis	7.7
Staphylococcus caprae	3.8
Staphylococcus aureus	3.8
Staphylococcus capitis	7.7
Streptococcus dysgalactiae	3.8

Discussion

PJI continues to affect a remarkable number of patients who undergo TJA but the accurate diagnosis is still challenging in daily clinical practise and the search for potential serological and synovial biomarkers is ongoing [17–19]. This study evaluates synovial pH as a potential novel marker for chronic PJI. Using the calculated cut-off value of 7.11, synovial pH showed good potential to diagnose chronic PJI with a high specificity (89%), however it had a poor sensitivity (53%). Despite the low sensitivity, we were able to show a significant difference for the pH value of the chronic septic and aseptic cases after TJA of the knee or hip.

A high synovial WBC and the leukocytes metabolism is responsible for decreasing synovial pH [8]. Furthermore, the presence of bacteria leads to high synovial lactate concentrations and this correlates with a drop of synovial pH [20]. For the present cohort culture negative infection was rare and four patients had polymicrobial infection and in general 11 different organisms were detectable which poses the question if and to what extent [20], different bacteria result in varying synovial pH value as it has been reported for native joint infections [20]. Furthermore, previous studies have discussed and proposed different thresholds for leukocyte count and differential depending on the type of infection (low-grade or high-grade) or even individual species. This may also be the case for synovial pH and should be answered in further investigations with larger numbers.

In addition to the other possible influencing factors such as gender, age, affected joint[21] or comorbidities, the size of the implanted endoprosthesis can be of relevance and needs further investigations. Milošev et al.[21] observed a small but statistically significant difference in the pH of synovial fluid between natural joints with degenerative diseases and joints with metal implants. It has been hypothesized that the release for metal ions from joint implants may lead to a decrease in synovial pH. Therefore it is possible that the pH may be influenced by implant size with megaprosthesis potentially leading to a lower synovial pH and potentially lower diagnostic thershold. Furthermore, a long-lasting TJA may have released more metal ions over time due to mechanical wear which might also lower the synovial pH. However, the usefulness of synovial cell count and differential has been generally questioned in this context when a form of metallosis or adverse local tissue reactions is present. Nonetheless, to our knowledge the effect of implant size on synovial leukocyte count and differentiation has not been explored to the author's knowledge although a difference is possible. Therefore, future studies should also investigate synovial pH if increased metal ion release is present (metal-on-metal bearing, metallosis, megaprostheses, long-lasting implants) in conjunction with synovial leukocytes.

The combination of microbiological long-term incubation, leukocyte count and leukocyte differentiation is the current gold standard analysis of synovial fluid [12]. Especially WBC count and PMN% provide high sensitivities and specificities as demonstrated in numerous studies [8, 9, 12]. While this is the first study to investigate synovial pH for chronic PJI, synovial WBC count and PMN% have already been examined in numerous previously studies but there is still disagreement among orthopaedic surgeons about the optimal threshold [22]. For our investigation we used the thresholds given by MSIS 2018[8] and ICM proceedings[9] to determine the sensitivity and specificity. For our cohort the specificity of WBC count (88%) and PMN% (98%) was as high as for pH (89%), whereas the sensitivity was best for WBC count (90%), but lower for PMN% (73%) and pH (53%). However, other institutions[12] or authors[23] recommend lower cut-off values to detect low-grade infections due to the fact, that the change of synovial fluid parameters depends on the virulence of bacteria[12] and may be as low as 1500 leukocytes and 65% PMN which must also be considered when interpreting synovial pH testing and the sensitivity reported here.

In conclusion, synovial pH can help to diagnose chronic PJI of lower extremity arthroplasty given its very good specificity, however in this preliminary cohort it showed poor sensitivity and therefore must be

combined with other serum and synovial biomarkers.

Declarations

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Author's contributions

TA review of literature, conception and design, acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript; JS review of literature acquisition of data, analysis and interpretation of data, statistical analysis, critical revision of the manuscript; GG conception and design, critical revision of the manuscript; TSB critical revision of the manuscript, conception and design; BM and SK conception and design, critical revision of the manuscript; CT drafting of the manuscript, analysis and interpretation of data, administrative support, conception and design. All authors read and approved the final manuscript.

Competing interests

The author's declare no competing interests.

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