HK22: Is there a role for synovial calprotectin in the diagnosis of periprosthetic joint infection (PJI)?

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Response/Recommendation: Yes. Synovial calprotectin (CLP) serves as a promising biomarker for diagnosing chronic PJI of the hip and the knee.

Level of Evidence: Strong

Delegate Vote:

Rationale:
Calprotectin (CLP) is a zinc and calcium-binding heterodimer, produced primarily by granulocytes and monocytes[1]. CLP is released by these cells at the site of inflammation or infection. The role of this novel marker in the diagnosis of PJI has been explored [2-4]. Generally, there are two available methods for quantifying CLP in synovial fluid. The CLP ELISA immunoassay is based on colorimetric detection using monoclonal and polyclonal antibodies against CLP. In contrast, the calprotectin lateral flow test (LFT) is a quantitative detection of synovial CLP, which has the advantage of immediate availability of results, making it useful for prompt intraoperative diagnosis of PJI. Recently, five meta-analyses evaluated the accuracy of CLP for diagnosing PJI and collectively concluded that CLP exhibits a high level of diagnostic sensitivity and specificity, confirming its potential utility as a reliable biomarker in the clinical assessment of PJI [4-8].

This systematic literature review was conducted independently by two researchers using the PubMed/Medline and Scopus databases. A total of 15 original studies were included based on the selected MeSH terms related to CLP and the diagnosis of PJI. Among these, six studies investigated laboratory methods, including five utilizing the enzyme-linked immunosorbent assay (ELISA) [9-13] and one employing the immunoturbidimetric method [14]. The LFTs were investigated in 11 studies, including six studies dedicated to chronic PJI (Lyfstone® Calprotectin) [12, 15-19], and five studies for off-label use on synovial fluid samples [3, 9, 20-22]. For the diagnosis of PJI, eight studies referenced the 2018 International Consensus Meeting (ICM) criteria [23], three adhered to the European Bone and Joint Society (EBJIS) 2021 criteria [24], and four studies utilized older diagnostic criteria.

A comprehensive analysis was conducted utilizing pooled data from 1,161 patients, as sourced from the original studies. The joint samples included 372 hips, 722 knees, and 12 samples from shoulder joints. Notably, one study did not specify the joint distribution [21]. 399 were diagnosed with PJI, 749 experienced aseptic failures, and in 13 cases, the diagnosis was inconclusive. Subsequent analyses included only four studies with groups larger than 100 patients [12, 17, 19, 20]. The cut-off values for definitive positive PJI diagnosis varied among the studies and the applied quantification method, ranging from 1.5 to 173 mg/L (area under the curve [AUC] ranging between 0.71 and 0.996). The most frequently used threshold across seven studies was 50 mg/L (AUC = 0.926 - 0.996) [3, 9, 10, 12, 19, 20, 22]. Across all cohorts, sensitivity varied from 60 to

100%, specificity from 61 to 100%, positive predictive value (PPV) from 40 to 100%, and negative predictive value (NPV) from 78 to 100%. The LFT presented sensitivity from 60 to 100% and specificity from 61 to 98.5%, comparable with the ELISA method (87.5 to 100% and 76.9 to 100%, respectively).

Warren et al. reported 98.2% sensitivity and 98.5% specificity using a dedicated LFT [19], applying a threshold proposed by the test manufacturer (50 mg/L) and the ICM 2018 diagnostic standard, although only including total knee arthroplasty PJIs. Conversely, a smaller study by Lazic et al. analyzing patients who have implant loosening revealed sensitivity and specificity of 60 and 61%, respectively [16]. Despite using the EBJIS diagnostic standard, they could not establish a correlation between the extent of osteolysis and the test performance. Furthermore, the same group showed that CLP has a favorable diagnostic performance when other causes of intra-articular inflammation are present, e.g., in the early postoperative phase. However, larger studies are required to define accurate threshold values in such circumstances. Concerning LFT dedicated to diagnosing PJI, there is a need to remember that for reading the result, a smartphone application is required. Lighting conditions, different resolutions, and camera parameters can influence the obtained results.

Several authors evaluated different POC spell outtests with specific analyzers dedicated to fecal samples with off-label use in synovial fluid samples with excellent results. Wouthuyzen-Bakker et al. used the Quantum Blue® fCAL assay on 61 synovial fluid samples from patients to exclude PJI, achieving 89% sensitivity and 90% specificity [3]. A similar test was employed by Bottagisio et al. [21] and Alkadhem et al. [20] with comparable accuracy. However, it is essential to note that these tests are validated for solid samples rather than liquids, necessitating a recalibration of results from µg/g to mg/L.

The potential limitations of laboratory methods include higher costs, reduced availabilities, and longer turnaround times due to the need for sample delivery to the laboratory. Salari et al. demonstrated excellent accuracy in their study of 76 patients, categorizing them into PJI and aseptic groups according to the ICM 2018 definition [10]. With a cut-off of 50 mg/L (AUC = 0.996), they achieved 100% sensitivity and 95% specificity. Warren et al. investigated lateral flow and ELISA tests on the same cohorts [12]. They received the same results of sensitivity (98.1%) and specificity (95.7%) for both methods. Similar results were obtained by Grassi et al., with the results of sensitivity and specificity for the LFT (97.4 and 94%, respectively) and for the ELISA method (92 and 100%, respectively) [9]. The only study comparing different laboratory methods was conducted by Grzelecki et al. [14]. They used the immunoturbidimetric technique and found sensitivities and specificities of 95.6 and 96%, respectively, and the results were equivalent to the ELISAspell out method.

Both laboratory and LFT methods dedicated to the detection of CLP in synovial fluid are promising for diagnosing chronic PJIs. Despite some limitations emphasized by prior studies, such as the concern with small sample size, application of different diagnostic standards, the influence of blood contamination on the obtained results, and the need for validation when synovial fluid samples are used, the excellent accuracy of this biomarker encourages its use in clinical practice.

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