



Supportive Diagnostics for Periprosthetic Joint Infection

**The Contribution of Nuclear Imaging
and Alpha-Defensin Testing**

Steven J. Verberne

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**SUPPORTIVE DIAGNOSTICS FOR PERIPROSTHETIC JOINT
INFECTION**

The Contribution of Nuclear Imaging and Alpha-Defensin Testing

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General Introduction and Thesis Outline

INTRODUCTION

In the Netherlands, a total number of 36,707 total hip prostheses and 26,708 total knee prostheses were implanted in the year 2022 (LROI) and is increasing over time. Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) remain excellent surgical treatment options for patients with functionally limiting joint pain. In the United States, based on data from 2000 to 2014, the number of THA and TKA procedures is projected to increase by 71% and 85%, respectively, by 2030¹.

Despite the overall success of these procedures, up to 27% of THA patients and 44% of TKA patients report persistent postoperative pain²⁻⁴. The most common underlying causes include (low-grade) infection, mechanical loosening, instability, malposition, and periprosthetic fracture⁵. A comprehensive, multimodal approach is essential for the clinical evaluation of pain following total joint arthroplasty (TJA), as the treatment strategy strongly depends on the underlying cause^{6,7}.

PERIPROSTHETIC JOINT INFECTION

One of the most serious complications after TJA is periprosthetic joint infection (PJI), with an overall incidence of 1–2%. In revision arthroplasty, this number increases significantly, with approximately 20% of cases attributed to PJI⁸. PJI is considered one of the most devastating of prosthesis-related complications⁹ and can result in substantial morbidity and a decline in functional outcomes¹⁰. Unfortunately, the incidence of this complication is increasing over time¹¹. The economic burden of PJI in the United States is projected to reach USD 1.85 billion by 2030¹².

Timely identification and accurate localization of a PJI, particularly differentiation from mechanical loosening, is essential for initiating appropriate medical and surgical management¹³. A delay in the diagnosis and treatment of a PJI can have a critical impact on maintaining the prosthesis and joint function. The timing and presentation of PJI can vary considerably. Infections are typically classified as:

- Early: ≤3 months post-operatively
- Delayed: 3–24 months
- Late: >24 months

Early infections are most often acquired intraoperatively or perioperatively, while late acute infections are usually hematogenous in origin. Acute joint inflammation suggests the presence of intra-articular free-living bacteria, whereas chronic infections are associated

with the formation of biofilm at the bone–cement or bone–prosthesis interface. The clinical signs of acute PJI (or acute on chronic PJI) are often more obvious with a presentation of acute joint pain and/or acute unwell with systemic signs of sepsis. However, patients with an implant compromised from a chronic (or low grade) PJI can have symptoms similar to those from an aseptically loose implant ^{14, 15}. In fact, a significant proportion of ‘aseptic loosening’ revisions may be (low-grade) infected ¹⁶.

DIAGNOSTIC CRITERIA FOR PERIPROSTHETIC JOINT INFECTION (PJI)

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In the diagnostic workup of a painful TJA, a thorough history and physical examination remains a critical start. A variety of combined diagnostic tests have been described and investigated in order to improve the recognition and diagnosis of PJI. Serum biomarkers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are frequently used in conjunction with synovial fluid and histological analyses, including:

- Synovial white blood cell (WBC) count
- Polymorphonuclear cell (PMN) percentage
- Synovial CRP
- Leukocyte esterase
- Calprotectin
- Alpha-defensin (AD)
- Aerobic and anaerobic cultures

These tests help to detect PJI, but their diagnostic accuracy varies significantly, and no single test has emerged as a universally accepted gold standard for diagnosing PJI

Plain radiographs are a standard first-line diagnostic imaging modality and often sufficient to determine malpositioned joint implants or fractures. However, radiographs lack the sensibility to identify subtle (a)septic loosening ^{6, 7, 20-22}. Additional diagnostic imaging could be used in order to exclude or diagnose the presence of a (low grade) PJI.

The assessment of suspected PJI has not (yet) been standardized in a universally accepted diagnostic protocol. Multiple diagnostic guidelines, by various orthopaedic and infectious disease societies, have been reported in an attempt to improve the early detection and treatment of PJI ¹⁷⁻¹⁹. The first PJI studies reported a diagnosis of PJI as a result of (multiple) positive culture results, or when per-operative pus was found ²³. However, an underestimation of PJI numbers was reported which resulted in the incorporation of

histopathology, the presence of a sinus tract and the sonication of the prosthesis in the criteria for PJI ^{24,25}.

In 2011, the Musculoskeletal Infection Society (MSIS) published a new definition of PJI (MSIS criteria) that was adopted by the majority of authors in the following years ²⁶. These criteria were renewed after the first worldwide consensus meeting in 2014 ²⁷. In 2018, the criteria were modified at the second International Consensus Meeting (ICM). The criteria system consists of cumulative (validated) points (Table 1) ¹⁷.

Table 1: PJI (periprosthetic joint infection) scoring system, as agreed upon by consensus at the International Consensus Meeting 2018 (ICM 2018 Criteria); CRP C-reactive protein; ESR erythrocyte sedimentation rate; white blood cell count; PMN polymorphonuclear neutrophils.

A. Major Criteria		Decision	
two or more positive periprosthetic cultures with phenotypically identical organisms			
a sinus tract communicating with the joint			Infected
	Score	Points	
B. Preoperative Diagnosis / Minor Criteria			
serum: elevated CRP or D-Dimer	2	>6	
serum: elevated ESR	1	2-5	Infected
synovial: elevated WBC count or LE	3	0-1	Possibly infected*
synovial: positive alpha-defensin	3		Not Infected
synovial: elevated synovial PMN (%)	2		
synovial: elevated synovial CRP	1		
C. Intraoperative Diagnosis / Inconclusive pre-op score* or dry tap			
intraoperative: positive histology	3	>6	Infected
intraoperative: positive purulence	3	4-5	Inconclusive
intraoperative: single positive culture	2	0-3	Not infected

The European Bone and Joint Society (EBJS) developed a different set of criteria because a number of (low) grade PJI were probably missed when using the MSIS criteria ²⁸. In 2021, the EBJS published the most recent classification system and allocated the patients in three groups: infection unlikely, infection likely and infection confirmed as shown in table 2. The EBJS criteria retained parts of the MSIS, IDSA, and ICM definitions, which are validated in multiple publications. However, the EBJS definition included a novel middle 'infection likely' group, which is developed to direct clinicians to (re)consider cases which traditionally would not be classed as infected, but which may be. Another important difference with the MSIS criteria is the incorporation of nuclear imaging as a reflection of the increasing knowledge in the field and the wider availability of the nuclear imaging modalities ²⁹.

DIAGNOSTIC BIOMARKERS

For diagnosing PJI, numerous novel diagnostic biomarkers have been developed and investigated recently³⁰. One of the best-described biomarkers in recent years has been alpha-defensin (AD), a protein secreted by activated neutrophils in the synovial fluid. Elevated AD levels indicate a local immune response to infectio³¹. AD levels can be measured in a laboratory-based enzyme-linked immunosorbent assay (ELISA). As a fast alternative, a point-of-care lateral flow (LF) device was developed which gives a result within 10 minutes. Both the MSIS and EBJIS criteria have incorporated AD testing in their most recent definitions of PJI. However, differences in diagnostic accuracies between various joints have been reported. According to the many meta-analyses performed in the last few years, the ELISA test performs extremely well (sensitivity 95% to 100%, specificity 95% to 97%)^{30,32-38}, whereas the LF test appears not to be as good (sensitivity 71% to 85%, specificity 89% to 96%). However, most of the reported meta-analyses included multiple studies that seemed to count the same patients more than once, used different criteria to diagnose PJI, and included retrospective studies, which are generally more prone to bias. Furthermore, several relevant new studies have been published, suggesting that a repeat meta-analysis may be necessary³⁹⁻⁴³. Another relevant limitation is that most studies combined THA and TKA populations, without performing separate analyses. Therefore, potential differences in diagnostic accuracy between THA and TKA remain unclear. In particular, there is a lack of specific evidence regarding the diagnostic performance of the AD-LF test in patients with chronic painful THA, and it remains uncertain in which subgroups the test may underperform.

Table 2: EBJIS criteria for the diagnosis of clinically-suspected periprosthetic joint infection.

		Infection Unlikely (all findings negative)	Infection Likely (two positive findings) ^a	Infection Confirmed (any positive finding)
Clinical and blood workup				
Clinical features	Clear alternative reason for implant dysfunction (e.g. fracture, implant breakage, malposition, tumour)		1) Radiological signs of loosening within the first five years after implantation 2) Previous wound healing problems 3) History of recent fever or bacteraemia 4) Purulence around the prosthesis ^b	Sinus tract with evidence of communication to the joint or visualization of the prosthesis
C-reactive protein			> 10 mg/l (1 mg/dl) ^c	
Synovial fluid cytological analysis ^d				
Leukocyte count ^c (cells/ μ l)	$\leq 1,500$	> 1,500		>3,000
PMN (%) ^c	$\leq 65\%$	> 65%		> 80%
Synovial fluid biomarkers				
Alpha-defensin ^e				Positive immunoassay or lateral-flow assay
Microbiology ^f				
Aspiration fluid			Positive culture	
Intraoperative (fluid and tissue)	All cultures negative	Single positive culture ^g		$\geq$ two positive samples with the same microorganism
Sonication ^h (CFU/ml)	No growth	> 1 CFU/ml of any organism ^g		> 50 CFU/ml of any organism
Histology ^{c,i}				
High-power field (400x magnification)	Negative	Presence of $\geq$ five neutrophils in a single HPF		Presence of $\geq$ five neutrophils in $\geq$ five HPF Presence of visible microorganisms
Others				
Nuclear imaging	Negative three-phase isotope bone scan ^c	Positive WBC scintigraphy ^j		

- a. Infection is only likely if there is a positive clinical feature or raised serum C-reactive protein (CRP), together with another positive test (synovial fluid, microbiology, histology or nuclear imaging).
- b. Except in adverse local tissue reaction (ALTR) and crystal arthropathy cases.
- c. Should be interpreted with caution when other possible causes of inflammation are present: gout or other crystal arthropathy, metallosis, active inflammatory joint disease (e.g. rheumatoid arthritis), periprosthetic fracture, or the early postoperative period.
- d. These values are valid for hips and knee periprosthetic joint infection (PJI). Parameters are only valid when clear fluid is obtained and no lavage has been performed. Volume for the analysis should be > 250 µL, ideally 1 ml, collected in an EDTA containing tube and analyzed in <1h, preferentially using automated techniques. For viscous samples, pre-treatment with hyaluronidase improves the accuracy of optical or automated techniques. In case of bloody samples, the adjusted synovial WBC = synovial WBC observed – [WBC blood / RBC blood x RBC synovial fluid] should be used.
- e. Not valid in cases of ALTR, haematomas, or acute inflammatory arthritis or gout.
- f. If antibiotic treatment has been given (not simple prophylaxis), the results of microbiological analysis may be compromised. In these cases, molecular techniques may have a place. Results of culture may be obtained from preoperative synovial aspiration, preoperative synovial biopsies or (preferred) from intraoperative tissue samples.
- g. Interpretation of single positive culture (or < 50 UFC/ml in sonication fluid) must be cautious and taken together with other evidence. If a preoperative aspiration identified the same microorganism, they should be considered as two positive confirmatory samples. Uncommon contaminants or virulent organisms (e.g. *Staphylococcus aureus* or Gram negative rods) are more likely to represent infection than common contaminants (such as coagulase-negative staphylococci, micrococci, or *Cutibacterium acnes*).
- h. If centrifugation is applied, then the suggested cut-off is 200 CFU/ml to confirm infection. If other variations to the protocol are used, the published cut-offs for each protocol must be applied.
- i. Histological analysis may be from preoperative biopsy, intraoperative tissue samples with either paraffin, or frozen section preparation.
- j. WBC scintigraphy is regarded as positive if the uptake is increased at the 20-hour scan, compared to the earlier scans (especially when combined with complementary bone marrow scan).

NUCLEAR IMAGING

Nuclear imaging has been utilized for the diagnosis of musculoskeletal infections since the 1970s⁴⁴. In the early studies investigating the use of nuclear imaging, heterogeneous data have been described, which led to difficulty incorporating nuclear imaging modalities into diagnostic algorithms. In the current diagnostic protocols for diagnosing PJI, various orthopaedic and infectious disease societies (including the AAOS, ICM and MSIS), did not incorporate the routine use of nuclear imaging for diagnosing PJI. Moreover, the American Academy of Orthopedic Surgeons (AAOS) clinical practice guidelines have provided limited support for the use of nuclear medicine imaging modalities⁴⁵. On the contrary, the EBJS classification system did incorporate the use of three-phase bone scintigraphy and leukocyte scintigraphy for diagnosing PJI in 2021²⁸.

Imaging of joint prostheses remains a specific competence of radiologists and nuclear medicine physicians. In nuclear medicine procedures, radionuclides are combined with pharmaceutical compounds to form radiopharmaceuticals. When administered, these radiopharmaceuticals converge in specific organs and in cellular clusters with increased bioactivity. Nuclear techniques image the extent of a pathological process in the body, based on the cellular function and physiology, rather than relying on physical changes in tissue anatomy. Radionuclide imaging is not hampered by metallic artifacts in the evaluation of periprosthetic activity, in contrast to conventional imaging. However, periprosthetic uptake can be the result of a variety of pathological conditions, including infection, inflammation, mechanical loosening, metallosis, trauma and/or tumor activity. Periprosthetic uptake can also be the result of physiological bone remodeling after the implantation of the prosthesis. Therefore, interpretations may be conducted in collaboration with the orthopedic surgeon, who is knowledgeable about the type of implant, implantation technique, time since surgery, use of antibiotics, and clinical status of the patient. These variables can influence the interpretation and the outcome for the nuclear imaging diagnosis.

A variety of nuclear imaging techniques can contribute in the evaluation of PJI. The use of nuclear imaging has been intensively investigated and each imaging modality and radiopharmaceutical is characterized by specific diagnostic accuracy, drawbacks, and added value in diagnosing PJI. The choice of the most accurate imaging technique and optimal radiopharmaceutical depends on its effectiveness in each phase (and diagnostic goal) of the diagnostic algorithm of PJI. In the evaluation of painful joint replacements, nuclear imaging can be valuable in diagnosing PJI and differentiation with aseptic loosening. However, the exact role of nuclear imaging in the diagnostic algorithm of PJI remains a subject of debate. Although intensively investigated, there is no true consensus regarding the gold standard technique for the most accurate radionuclide modality⁴⁶⁻⁴⁸.

The most used imaging techniques for diagnosing PJI are bone scintigraphy (BS), leukocyte scintigraphy (LS), combined leukocyte-bone marrow scintigraphy (LS-BMS) and fluorodeoxyglucose positron emission tomography (FDG-PET). These imaging modalities can be combined with Positron Emission Tomography (PET, single-photon emission computed tomography (SPECT) and/or computer tomography (CT) to improve interpretation through a more precise localization and characterization of periprosthetic radiopharmaceutical uptake. These hybrid imaging techniques are more capable of accurate anatomical as well as precise information of the extent of the infection, which could improve the accuracy of diagnosing PJI and the intra- and interobserver reliability^{49,50}. An extended and detailed overview of all available imaging modalities that can contribute

in diagnosing PJI is provided in Chapter 2. In this thesis introduction, we shortly outline the most commonly used nuclear imaging modalities.

Bone Scintigraphy

The first and most extensively investigated radionuclide procedure used for imaging joint arthroplasty is bone scintigraphy (BS). This technique is widely available at low costs, is easily performed, and rapidly completed. This technique is based on the skeletal uptake of phosphates and labeled phosphates with ^{99m}Tc , the “bone-seeking” tracers. Any cause of accelerated bone turnover induces increased periprosthetic activity on images, including pathological conditions such as fracture, heterotopic ossification, mechanical loosening⁵¹⁻⁵⁵, and periprosthetic infection. An important limitation of using BS in PJI is the postoperative physiological bone remodeling after implantation which induces accumulation of the radiopharmaceutical with uptake patterns in asymptomatic prostheses up to 2 and 5 years for THA and TKA, respectively⁵⁶. Although no consensus is reached in the literature regarding the interpretation criteria for BS, it is universally accepted that normal findings (no increased perfusion or blood pool, no periprosthetic uptake in the late phase) is considered strong evidence against the presence of PJI^{57, 58, 59-61}. The assessment of knee prostheses with BS is considered more complex than that of hip prostheses and several studies confirmed low diagnostic accuracy in diagnosing infection⁶². However, BS is a sensitive diagnostic tool for detecting periprosthetic bone changes in both joints. The clinical advantage is excluding any form of loosening, although of limited value in the first postoperative years. The clinical usefulness of BS in the assessment of painful prosthetic joints is limited in differentiating PJI with other causes of prosthetic failure while, in the diagnostic algorithm of PJI, investigation with more specificity is often needed.

Labeled leukocyte scintigraphy

In vitro radiolabeling of autologous peripheral leukocytes is a more specific method for imaging of periprosthetic infection⁶³. An important difference from BS is that labeled leukocytes do not accumulate at sites of increased bone turnover or remodeling in the absence of infection. Leukocytes are labeled with ^{99m}Tc -hexamethyl propyleneamine oxime (HMPAO) or ^{111}In -oxine (^{111}In) and migrate to sites of infection and inflammation. Since circulating neutrophils are predominantly radiolabeled and neutrophils are present at the site of PJI, in theory LS should be accurate in diagnosing PJI and differentiation of inflamed aseptic loosening in which neutrophils are generally absent. No significant differences have been reported regarding the use of leukocytes labeled with ^{99m}Tc -HMPAO or ^{111}In -oxine^{62, 64-67}. Unfortunately, several investigations reported unsatisfactory results and that the value of this technique was a subject of controversy. Primary clinical investigations reported a sensitivity of 100% and specificity of 89% for infected prosthetic joint replacements⁶⁸. Subsequent studies concluded that this technique was specific and

not sensitive for diagnosing PJI, while other authors reported differently. The variability and controversial conclusions in the literature can be attributed to several factors. (1) As for most nuclear imaging techniques, investigated accuracy for diagnosing PJI varies between the different prostheses. This differentiation is often insufficiently investigated or reported. (2) The presence of ectopic bone marrow in the appendicular skeleton is mostly induced by implantation surgery (decrease specificity). (3) Various factors that influence diagnostic accuracy are often not clinically investigated, including the assumed negative influence of administered antibiotics (which decreases sensitivity), the type of infecting organism, time after implantation/surgery (which decreases specificity), and analyses of acute, delayed low-grade infection, along with the presence of biofilm (which also decreases sensitivity)^{69, 70}. (4) There is no universally accepted protocol or standard interpretation criteria for analyzing leukocyte images regarding diagnosing PJI. Clinical studies use different criteria which could explain the heterogeneity of reported diagnostic accuracy.

LS can be performed as routine leukocyte imaging (2–4h) and delayed imaging (24h)^{69, 71, 72}. The importance between both protocols is the difference between the biological basis for recruitment of leukocytes in acute or subacute PJI and chronic, low-grade PJI. Several authors reported that a delayed imaging at 24 h is more preferable in the detection of PJI. The authors concluded increased sensitivity (83% vs. 50% and 100% vs. 87%) and specificity (100% vs. 90% and 82% vs. 77%) for infected hip and knee prostheses respectively by comparing early, routine imaging and late images^{69, 71, 72}.

Another approach to improve specificity for diagnosing PJI is LS combined with BMS. BMS is performed with the tracers ^{99m}Tc-sulfur colloid or ^{99m}Tc-nanocolloid. LS may be less specific in diagnosing PJI due to the accumulation of labeled leukocytes in the bone marrow. During implantation of prostheses, the rasping of the femoral medullary canal and acetabular cup could cause abnormal distribution of normal bone marrow around the prosthesis. This complicates the interpretation of the leukocyte images and makes differentiation between altered of distribution and infectious uptake difficult. The principle of combined LS-BMS is the radiotracer accumulation in the reticuloendothelial system of the marrow, with similar physiological distribution of ^{99m}Tc-sulfur colloid and labeled leukocytes in the bone marrow. However, the accumulation of leukocytes in PJI is stimulated and simultaneously suppresses the uptake of sulfur colloid in the bone marrow, resulting in spatially incongruent images. Consequently, discrimination of infection and implantation induced leukocyte accumulation in the bone marrow is possible. Improvement in sensitivity of 83% versus 92% and specificity of 57% versus 98% was reported when LS was combined with BMS in the assessment of periprosthetic hip infection⁶⁷. However, lower sensitivity of 39% and 33% was also reported in diagnosing periprosthetic hip and knee infection, respectively⁷³. Despite these variations of reported

diagnostic accuracy, the combined interpretation of LS-BMS images is highly specific and is for many authors the gold standard for diagnosing PJI⁷⁴. However, the exact role of this technique in the diagnostic algorithm of evaluating suspected infected prostheses remains subject to debate, mainly due to the lack of a universal accepted protocol, different interpretation criteria for PJI and practical limitations in daily practice.

LS is hampered due to practical drawbacks including the laborious preparation of in vitro labeling in sterile conditions with time consuming procedures, the need of appropriate trained staff and a imaging procedure that is time intensive and inconvenienced for the patient. Radiolabeled antigranulocyte antibodies and antibody fragments have been investigated and explored as alternatives for in vitro labeled leukocytes in order to overcome some of these limitations of LS. Considerable efforts have been devoted to developing in vivo methods of labeling leukocytes that resulted in antigranulocyte scintigraphy (AGS), performed with different tracers. Besilesomab (/Granuloscint/ScintimunR) is a murine monoclonal G1 immunoglobulin that binds to normal cross-reactive antigen-95 leukocytes (NCA-95), while Sulesomab (/LeukoScanR) is a fragment antigen binding (Fab') portion of a murine monoclonal G1 immunoglobulin that binds nonspecific cross-reactive antigen-90 (NCA-90) on leukocytes⁷⁵. The protocol is based on injection of a prepared agent into the patient, tracing leukocytes in vitro. However, the results of clinical validation of AGS have been variable. The use of Besilesomab in diagnosing hip PJI demonstrated a sensitivity of 67% and specificity of 75%⁷⁶, while using Sulesomab in diagnosing hip PJI, the reported sensitivity ranges between 75% and 94% and specificity between 47% and 95%⁷⁷⁻⁷⁹. A meta-analysis in 2007 reported a pooled sensitivity of 80% and specificity of 83%⁸⁰. In vivo labeling of leukocytes overcomes practical limitations of the in vitro labeling procedures. However, based on published studies its accuracy varies in diagnosing PJI and may be less sensitive and less specific compared to that of LS, especially in the assessment of hip prostheses. Therefore, this technique may not be the preferred modality at this time and therefore has not gained wide acceptance.

Fluorodeoxyglucose Positron Emission Tomography

The hybrid imaging modality PET/CT with the tracer fluorodeoxyglucose (FDG) has been used in the assessment of periprosthetic infections⁵⁰. 18F-Fluorodeoxyglucose (FDG) is transported into cells via glucose transporters and phosphorylated to 18F-2-FDG-6 phosphate without being metabolized. Compared to conventional radionuclide imaging techniques, FDG-PET/CT has a number of advantages, including a less time-consuming procedure and improved anatomical correlation of areas with increased FDG uptake that improves the accuracy of interpretation. Another important advantage, compared to combined LS-BMS, is that treatment with antibiotics is assumed not to affect the sensitivity

of FDG-PET in delineating sites of infections because FDG does not depend on leukocyte migration⁸¹.

The differentiation between inflammatory reaction of mechanical loosening and periprosthetic infections can be difficult when using FDG as tracer because leukocytes are present in both inflammation and infection. Clinical investigations proposed that site and pattern of FDG uptake is more important than intensity of uptake in the region of interest^{82, 83}. Standardized uptake values-based analysis is assumed as not reliable in differentiating between aseptic loosening and PJI^{84, 85}. Uptake in bone-prosthesis interface of the middle portion of the hip prosthesis is considered specific, while only increased uptake at the tip is assumed nonspecific for periprosthetic hip infection⁷³. Similar to conventional tracers, the postoperative remodeling conditions after implantation result in periprosthetic FDG uptake that remains for months to years. For asymptomatic hip prostheses, this physiological uptake is localized around the head and neck of the prosthesis^{86, 87}. Persistently increased nonspecific FDG uptake following knee arthroplasty has also been reported, however, not yet clinically validated.

Studies that investigated accuracy of FDG-PET in the assessment of PJI reported variable results. Primary investigation on accuracy using FDG-PET for PJI reported sensitivity of 90%, 91% and specificity of 89%, 72% for hip and knee prostheses, respectively^{83, 88}. In subsequently published investigations, sensitivity ranged between 33% and 100% and specificity between 62% and 100%. A meta-analysis concluded significantly higher specificity for hip prostheses compared to knee prostheses (75%)⁴⁷. The lower specificity of FDG-PET in knee prostheses may be related to the relatively limited knowledge about the incidence and pattern of nonspecific FDG uptake. Moreover, some authors reported that FDG-PET is not reliable in differentiating between mechanical loosening and PJI^{46-48, 59, 89-92}. Despite these reported variable results of diagnostic accuracies, FDG-PET can be considered an accurate imaging technique in the assessment of PJI. The inconclusive published clinical results on accuracy in the assessment of periprosthetic infections is most likely due to the lack of uniform interpretation criteria used in the clinical investigations of diagnosing PJI. Further clinical validation, however, is needed in order to confirm the diagnostic accuracy of FDG-PET in the assessment of PJI.

There is ongoing investigation to objectify the most specific imaging technique and optimal radiopharmaceutical for diagnosing PJI. Until now this remains subject to debate

⁴⁶⁻⁴⁸.

AIMS OF THE THESIS

Part 1: The contribution of Nuclear Imaging in diagnosing PJI

Chapter 2. The objective of this chapter is to illustrate and describe the most frequently used imaging modalities and radiopharmaceuticals in the assessment of PJI. We reviewed the literature for all the available imaging techniques, including BS, BS-LS, LS, LS-BMS, AGS and FDG-PET/CT, used to diagnose PJI.

Chapter 3. The objective of this study was to obtain an estimate of the diagnostic accuracy of different imaging modalities used for diagnosing periprosthetic hip infection using a systematic review and meta-analysis.

Chapter 4. The aim of this study was to compare the diagnostic accuracy of different imaging modalities used for diagnosing periprosthetic knee infection using a systematic review and meta-analysis.

Chapter 5. The objective of this study is to systematically review the reproducibility of currently used nuclear imaging modalities in the evaluation of symptomatic hip- and knee arthroplasties.

Chapter 6. The objective of this study is to evaluate the various diagnostic criteria using FDG-PET/CT in diagnosing periprosthetic hip infection. We evaluated the FDG uptake patterns in symptomatic hip prostheses, the diagnostic accuracy and the intra- and interobserver agreement.

Chapter 7. The objective of this study was to evaluate the use of FDG-PET/CT in assessing residual infection after resection arthroplasty and its role in determining the optimal timing of second-stage re-implantation. We evaluated the role of FDG-PET/CT in therapy resistant patients after resection arthroplasty of the hip in the treatment of PJI. Primarily, the FDG uptake in the resection area was analyzed to identify possible specific uptake patterns. Secondary, the effect of the FDG-PET/CT findings on the two-stage revision management - in terms of identifying patients in need of additional medical treatment or delayed re-implantation - were investigated.

Part 2: The contribution of Alpha-Defensin in diagnosing PJI

Chapter 8. The aim of this study was to compare the diagnostic accuracy of the AD LF and AD ELISA test for diagnosing PJI of TKA and THA using a systematic review and meta-analysis of prospective studies only.

Chapter 9. The objective of this study was designed to examine the accuracy of the AD LF test for diagnosis of PJI in chronic painful total hip arthroplasties.

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PART I

The Contribution of Nuclear Imaging in Diagnosing Periprosthetic Joint Infection



2

Imaging of Periprosthetic Joint Infection

Management of Periprosthetic Joint Infections (PJIs)

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1 INTRODUCTION

Imaging of joint prostheses is a specific competence of radiologist and nuclear medicine physicians. However, interpretations are performed in strong collaboration with the orthopedic surgeon who is aware of the type of implant, implantation technique, time after surgery, the use of antibiotics, and clinical status of the patient. The timely identification and localization of a prosthetic joint infection (PJI), including a differentiation from mechanical loosening, is essential to allow the initiation of appropriate medical and surgical therapy. It can make the difference between one-stage or two-stage revision. Unfortunately, assessment of suspected PJI has thus far not been standardized in an universally accepted diagnostic protocol, although efforts are made [1,2]. Despite clinical suspicion, physical examination, multiple diagnostic tests (i.e., laboratory tests, articular biopsy, cultures, and imaging), and complex algorithms, an accurate diagnosis remains challenging. A delay in diagnosing and treatment of a PJI can have a critical impact on loosening or maintaining the prosthesis and joint function.

In the diagnostic work-up, a variety of imaging techniques including radiographs, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, bone-, and leukocyte scintigraphy (LS) and fluorodeoxyglucose positron emission tomography can contribute in the evaluation of PJI. The use of imaging has been intensively investigated and each imaging modality and radiopharmaceutical is characterized by specific diagnostic accuracy, drawbacks, and added value in diagnosing PJI. The choice of the most accurate imaging technique and optimal radiopharmaceutical depends of its effectiveness in each phase of the diagnostic algorithm of PJI. The objective of this chapter is to illustrate and describe the most frequently used imaging modalities and radiopharmaceuticals in the assessment of PJI. This chapter will mainly focus on imaging of the most prevalent joint replacements, the knee and hip.

2 CONVENTIONAL IMAGING

Medical imaging has advanced in remarkable ways since the discovery of plain radiography 120 years ago. In the current clinical setting, conventional imaging is capable of imaging the anatomy of the human body in intricate detail using various modalities. Conventional imaging, including radiographs, ultrasound, CT, and MRI, allows improved screening, diagnosis, and monitoring of pathology, mostly in the context of anatomical changes.

2.1 Plain radiographs

Radiography is the primary imaging method of prosthetic joints. The initial radiographs serve as baseline and reference films for comparison with all future studies. Initial, sequential radiography are the most valuable methods for detecting complications as

dislocations (3%), periprosthetic fracture, proper positioning, and cement extrusion. In the follow-up, radiographs are used in order to detect possible complications including mechanical loosening, particle disease, component wear, dislocation, fracture, heterotopic ossification, and infection (Fig. 1).



Fig. 1 Plain radiograph of a loose total hip prosthesis. This 77-year-old man had right hip replacement 11 months previously. He suffered from increasing pain at rest and on walking 7 months after implantation. Two weeks before the X-ray, bacteremia due to coagulase-negative staphylococci was diagnosed. Besides a loosening line around the stem and a tilting of the cup, a subperiosteal new bone formation (→) suggestive of infection is visible. Biopsies performed during revision grew coagulase-negative staphylococci.

However, most of the clinical studies confirmed that plain radiography is not reliable in diagnosing the exclusion of PJI [3–5]. Radiographic findings such as radiolucency, osteolysis, and migration could be present in both septic and aseptic loosening of prostheses. Although infrequently present, increased periosteal bone formation or an adjacent soft tissue collection are highly suggestive for periprosthetic infection. Radiographic findings in patients with low-grade periprosthetic infection are possibly unremarkable and could mimic mechanical loosening or small particle disease. In PJI with aggressive microorganisms, progression could be rapid with bone destruction and sinus tract formation resulting in possible radiographic findings as ill-defined bone resorption and/or endosteal surface, nonconcentric lucency and absence of sclerotic margin. Although neither sensitive nor specific for diagnosing PJI, plain radiographs should be routinely performed in the assessment of suspected PJI [1,2].

2.2 Ultrasound

The value of ultrasound in assessing painful hip prostheses is limited to identifying the presence of hip joint effusion. In the early postoperative phase, sonography can confirm the presence of effusion when PJI is suspected. In low-grade PJI, ultrasound is capable of identifying both the presence and plot of the sinus tract. Clinical investigation reported sensitivity of 93% and specificity of 83% for sonographic detection of hip effusion [6]. The presence of intra-articular fluid, a straightforward ultrasound diagnosis, is nonspecific and more associated with sign of loosening process and its related inflammation [7]. However, ultrasound is an invaluable technique to guide aspiration of an effusion or collection [8]. In the diagnostic work-up of PJI, ultrasound is mostly useful in PJI in which effusion cannot be clinically diagnosed.

2.3 Computed tomography and magnetic resonance imaging

Computed tomography (CT) is widely known to be accurate in the depiction of soft tissue abnormalities, including infection. Although details of CT imaging in the assessment of PJI is degraded by metal artifacts, clinical investigations reported that it is possible to depict hip prosthesis [9–11]. PJI could be characterized on CT by aggressive osteolysis with an ill-defined margin, associated with osteomyelitis. However, typically PJI with more chronic indolent changes is possibly difficult to differentiate from other forms of osteolysis. Periostitis, indicated by periosteal new bone, on CT appears an highly sensitive (100%) and not very specific (16%) marker of infection [13]. In PJI, the bone may appear normal on CT in 25% of cases. Investigation of the potential use of CT in differentiating mechanical loosening from PJI reported that CT is accurate in the diagnosis of painful infection at the site of a hip prosthesis on the basis of soft tissue findings, whereas periprosthetic bone abnormalities are not useful [12]. Soft tissue abnormalities including joint distension, fluid filled bursae and fluid collections in muscles and perimuscular fat result in a 83% sensitivity, 96% specificity, and 94% accuracy in the evaluation of painful prostheses. However, there is no further published clinical validation of these results for other type of prostheses. MRI is proposed as better imaging modality than CT for demonstrating periprosthetic soft tissues, mainly due to greater resolution [14]. This technique is more accurate at depicting periprosthetic soft tissues around the femoral stem compared to the region of the acetabulum. The signal intensity of infection on MRI is similar to that of fluid with usually ill-defined margin. Moreover, MRI is capable of depicting bone involvement and assess the extent and route of sinus tracts (Fig. 2).

In the evaluation of PJI, CT and MRI are of limited clinical value in the presence of metallic prosthetic implants owing to beam hardening and dephasing artifacts. However, both techniques are useful in detecting soft tissue abnormalities as joint effusion, sinus tracts, soft tissue abscesses, bone erosion, and periprosthetic lucency, especially in the case of total hip arthroplasty.

3 NUCLEAR IMAGING

In nuclear medicine procedures, radionuclides are combined with pharmaceutical compounds, to form radiopharmaceuticals. When administered, these radiopharmaceuticals converge in specific organs and in cellular clusters with increased bioactivity. Nuclear techniques image the extent of a pathological process in the body, based on the

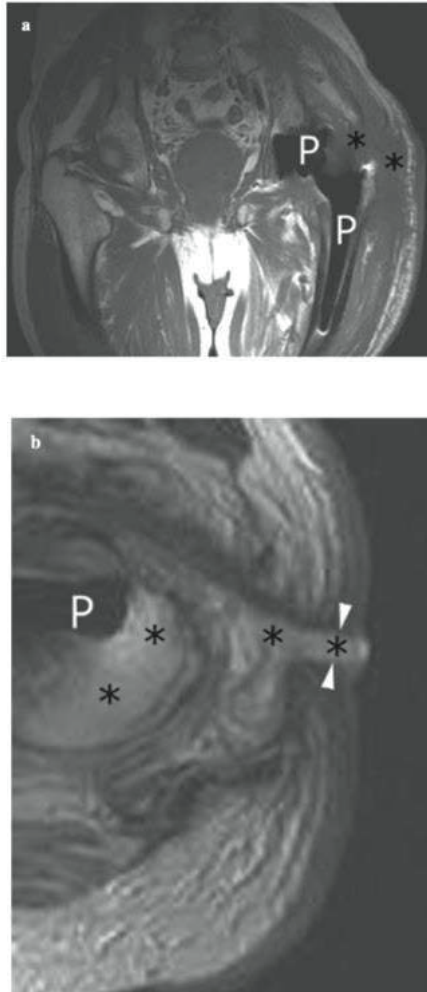


Fig. 2 A 70-year-old man who underwent unilateral total hip arthroplasty. (A) Coronal T1-weighted sequence. Hypointense fluid collection (asterisks) can be seen around the prosthesis (P). Involvement of the skin surface cannot be demonstrated. (B) Axial STIR sequence. The presence of a stula (arrowheads) can be easily demonstrated on this image.

cellular function and physiology, rather than relying on physical changes in tissue anatomy. Radionuclide imaging is not hampered by metallic artifacts in the evaluation of periprosthetic activity, in contrast to conventional imaging. In the diagnostic algorithm of PJI, the exact role of nuclear imaging remains a subject of debate, although intensively investigated and confirmed diagnostic added value. In the evaluation of painful joint replacements, nuclear imaging is most valuable in differentiating aseptic loosening from PJI. However, some partial analogies between the pathophysiological frameworks of these two conditions make nonspecific tracers of inflammation unreliable. There is no true consensus about the gold standard technique since each radionuclide modality has its drawbacks and limitations.

3.1 Bone scintigraphy

The first and most extensively investigated radionuclide procedure used for imaging joint arthroplasty is bone scintigraphy (BS). This technique is widely available at low costs, is easily performed, and rapidly completed (2–4h after radiopharmaceutical injection). The technique is based on the skeletal uptake of phosphates and labeled phosphates with ^{99m}Tc , the “bone seeking” tracers. Accumulation of these tracers depends on the incorporation with the calcium moiety of the amorphous bone mineral matrix forming calcium-phosphate salts that later mature into hydroxyapatite crystals [15].

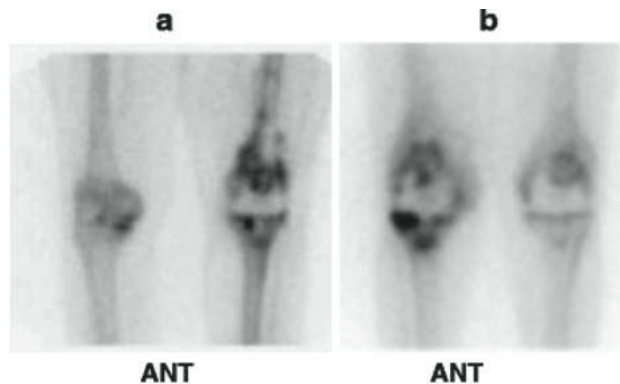


Fig. 3

(a) Aseptically loosened 6-year-old knee prostheses. Note the striking bony uptake around the left knee prosthesis, compared to the right.

(b) One-year-old infected right knee prosthesis. Intraoperative cultures grew *S. hominis*. Periprosthetic uptake pattern is virtually indistinguishable from that in (a).

Incorporation of the radiopharmaceutical into the bone is related to blood flow and rate of new bone formation [16]. Any cause of accelerated bone turnover induce increased periprosthetic activity on images, including pathological conditions such as fracture,

heterotopic ossification, mechanical loosening, and periprosthetic infection (Figs. 3 and 4). Also, the bone seeking tracers accumulate in areas of sterile inflammation, such as osteolysis induced by polyethylene wear debris.

Most of the clinical investigations reported high sensitivity and low specificity in the assessment of PJI (Table 1). The low specificity is caused by increased uptake of the radiopharmaceutical at sites of increased periprosthetic activity in various conditions. Interpretation of images is performed as three-phase scan or only as delayed scan. The first clinical investigations on delayed scans reported that BS was 85% accurate for diagnosing prosthetic hip loosening with limitation of determining the cause of failure [32–34]. Subsequently, several authors investigated the uptake patterns and suggested that focal periprosthetic uptake indicated loosening and diffuse uptake indicated infection (sensitivity 100%, specificity 54%) [35], while others concluded reversely [37]. In order to improve specificity, BS was performed as triple-phase-BS. This implies evaluation of the flow or perfusion phase, immediately followed by the soft tissue or blood-pool phase and the third (bone) phase after 2 and 4h. However, most authors reported low sensitivity, low specificity, or both [4,22,28,29]. Although no consensus is reached in the literature regarding interpretation criteria for BS, it is universally accepted that normal findings (no increased perfusion or blood pool, no periprosthetic uptake in the late phase) is considered strong evidence against the presence of PJI. Regardless of the interpretation criteria used, the diagnostic accuracy in the assessment of complicated hip or knee prostheses is approximately 50–70%. Recent meta-analysis showed a sensitivity of 81% and 75% with specificity of 78% and 55% for hip and knee prostheses, respectively [38,39]. The assessment of knee prostheses with BS is more complex than that of hip prostheses and several studies confirmed low diagnostic accuracy in diagnosing infection [24].

An important limitation of using BS in PJI is the postoperative physiological bone remodeling after implantation which induces accumulation of the radiopharmaceutical with uptake patterns in asymptomatic prostheses up to 12–24 months after implantation. In case of hip prostheses, this partially depends on the time after implantation and the modality of attachment of prosthetic implant. The accumulation of the radiopharmaceutical in the first postoperative 12 months is independent of the presence of cement. After the first postoperative year, 90% of cemented hip prostheses depict normal uptake pattern while 10% present increased periprosthetic uptake. Porous-coated hip prostheses present more frequent increased periprosthetic uptake after the first year. Regarding total knee prostheses, physiological bone remodeling after implantation could present periprosthetic uptake up to 5 years, while 60% of the femoral and 90% of the tibial component present increased periprosthetic uptake in the second postoperative year [40]. Investigators proposed serial scans in order to determine increased periprosthetic uptake, however, significant interpatient variability was observed when periprosthetic activity decreased over time in the first 2 years after implantation [41].

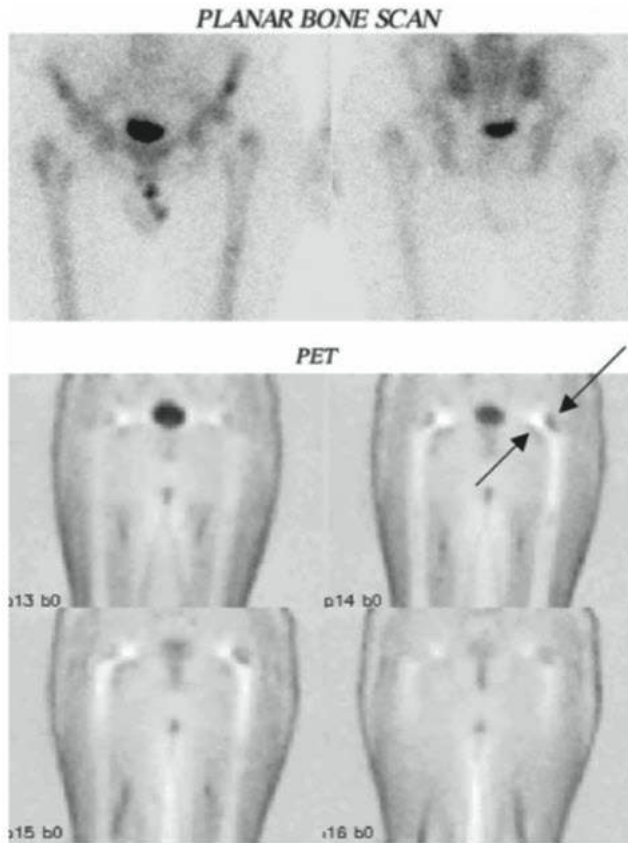


Fig. 4 Normal pattern: a clinically asymptomatic 52-year-old patient with a bilateral hip prosthesis from 1999. PET shows slightly increased ^{18}F -DG accumulation around the femoral neck.

The clinical usefulness of BS in the assessment of painful prosthetic joints is limited in differentiating PJI with other causes of prosthetic failure. However, the scan is a sensitive diagnostic tool for detecting periprosthetic bone changes. The clinical advantage is excluding any form of loosening, although of limited value in the 1–2 years after implantation. In the diagnostic algorithm of PJI, investigation with more specificity is often needed.

Table 1 Diagnostic accuracy of bone scintigraphy in patients with PJI

Study	Prosthetic Joint	Year	No.	Sensitivity (%)	Specificity (%)
Boubaker et al ¹	Hip	1995	88	92	64
Nijhof et al ²	Hip	1997	60	96	15
Itasaka et al ³	Hip	2001	48	83	79
Larikka et al ⁴	Hip	2001	64	92	83
Stumpe et al ⁵	Hip	2004	34	56	88
Reinartz et al ⁶	Hip	2005	92	68	76
Mumme et al ⁷	Hip	2005	70	78	70
Nagoya et al ⁸	Hip	2008	46	88	90
Palestro et al ⁹	Knee	1991	23	67	76
Verlooy et al ¹⁰	Knee	1993	21	100	33
Sacchetti et al ¹¹	Knee	1996	13	88	100
Smith et al ¹²	Knee	2001	75	92	76
Magnuson et al ¹³	Hip/Knee	1988	49	100	18
Levitsky et al ¹⁴	Hip/Knee	1991	72	30	86
Segura et al ¹⁵	Hip/Knee	2004	77	100	0
Love et al ¹⁶	Hip/Knee	2008	150	76	51

3.2 Gallium scintigraphy

In order to overcome important limitations of BS, several techniques have been investigated over the years. One of the earliest techniques to improve diagnostic accuracy was combined bone and gallium scintigraphy (GS). Gallium-67 has been used for localization of infection over the past decades [42]. After renal excretion (24h), approximately 75% of the injected doses is equally distributed among the liver, soft tissue, and skeletal and bone marrow [43]. Gallium-67 has affinity for polymorphonuclear leukocytes and uptake in area of infection is likely due to several factors including vascular membrane permeability at inflammatory sites and bacterial uptake of gallium. An important advantage is the usefulness in immunocompromised patients, despite the few or lack of circulating leukocytes [44]. Imaging is usually performed 2–3 days after injection.

Since both gallium and diphosphonates are bone seeking pharmaceuticals, gallium-67 alone is not accurate enough to diagnose PJI. The combined images are therefore interpreted using standardized criteria comparing congruency of the spatial distribution and intensity [45]. The test is positive for infection when distribution of the two tracers is different or, in case of comparable distribution, the relative intensities of gallium uptake

exceeds the BS uptake. The test is equivocal when the distribution of the two radiotracers is the same, both spatially and in intensity. The test is negative when the gallium images are normal, regardless of the bone scan findings or when the distribution of the two tracers is spatially congruent and the relative intensity of gallium uptake is less than that of the diphosphonate. The diagnostic accuracy of PJI in general ranges between 65% and 95% and provides more specificity in the assessment of PJI than BS alone (Table 12.2) [46,51]. Recent metaanalysis for periprosthetic hip infection reported a sensitivity of 59% (38–70%), and specificity of 97% (90–99%) [19,39,46,48]. Although combined interpretation of BS-GS provides more specificity in diagnosing PJI than BS alone, the clinical use is of limited value due to important drawbacks inherent of 67-Ga-citrate. This technique is hampered by high radiation dose and often equivocal cases [19]. Therefore, the use of this technique has declined over the years and often been replaced by other techniques.

Table 2 Diagnostic accuracy of combined bone and gallium scintigraphy in patients with PJI

Study	Prosthetic Joint	Year	No.	Sensitivity (%)	Specificity (%)
Tehranzadeh et al ¹⁶	Hip	1981	27	100	88
Gómez-Luzuriaga et al ¹⁷	Hip	1988	40	70	90
Aliabadi et al ¹⁸	Hip	1989	44	37	100
Kraemer et al ¹⁹	Hip	1993	43	38	98
Itasaka et al ³	Hip	2001	48	67	99
Reing et al ²⁰	Hip/Knee	1979	79	95	100
McKillop et al ²³	Hip/Knee	1984	15	83	78
Merkel et al ²¹	Hip/Knee	1986	154	66	81

3.3 Leukocyte scintigraphy

The introduction of in vitro radiolabeling of autologous peripheral leukocytes is one of the most important achievement in the radionuclide diagnoses of infection to date and dramatically improved the accuracy of diagnosing PJI [36]. An important difference with BS-GS is that labeled leukocytes do not accumulate at sites of increased bone turnover or remodeling in the absence of infection. Leukocytes are labeled with 99mTc-hexamethyl propyleneamine oxime (HMPAO) or 111In-oxine (111In) and migrate to sites of infection and inflammation. The accumulation of in vitro labeled leukocytes depends on several factors including chemotaxis, the quantity of leukocytes labeled, and the primary cellular response of a given inflammatory response [52]. Since circulating neutrophils are predominantly radiolabeled and neutrophils are present at the site of PJI, in theory LS should be accurate in diagnosing PJI and differentiation of inflamed aseptic loosening in which neutrophils are generally absent. No significant differences have been reported regarding the use of leukocytes labeled with 99mTc-HMPAO or 111In-oxine [24,53–57].

Unfortunately, several investigations reported unsatisfactory results and the value of this technique was a subject of controversy (Table 12.3). Primary clinical investigations reported a sensitivity of 100% and specificity of 89% for infected prosthetic joint replacements [67]. Subsequent studies concluded that this technique was specific and not sensitive for diagnosing PJI, while other authors reported reversely. For lower prosthetic joint replacements, McKillop et al. reported 50% sensitivity and 100% specificity, while other authors reported 100% sensitivity and 45–50% specificity [50,65,66]. Specified for infected hip prostheses, a recent meta-analysis reported pooled sensitivity of 88% (ranges between 81% and 97%) and pooled specificity of 92% (ranges between 57% and 97%). For prosthetic knee infection, Rand et al. reported a sensitivity of 85% and specificity of 83% [68]. In further clinical validations for knee prostheses, sensitivity ranges between 86% and 100% and specificity between 53% and 100% were determined [24,63]. The variability and controversial conclusions in the literature can be attributed to several factors. (1) As for most nuclear imaging techniques, investigated accuracy for diagnosing PJI varies between the different prostheses. This differentiation is often insufficiently investigated or reported. (2) The presence of ectopic bone marrow in the appendicular skeleton is mostly induced by implantation surgery (decrease specificity). (3) Various factors that influence diagnostic accuracy are often not clinically investigated including the assumed negative influence of administrated antibiotics (decrease sensitivity), the type of infecting organism, time after implantation/surgery (decrease specificity) and/or in combination with analyses of acute, delayed low-grade infection, and the presence of biofilm (decrease sensitivity) [20,63]. (4) There is no universally accepted protocol and interpretation criteria for analyzing leukocyte images regarding diagnosing PJI. Clinical studies use different criteria which could explain the heterogeneity of reported diagnostic accuracy.

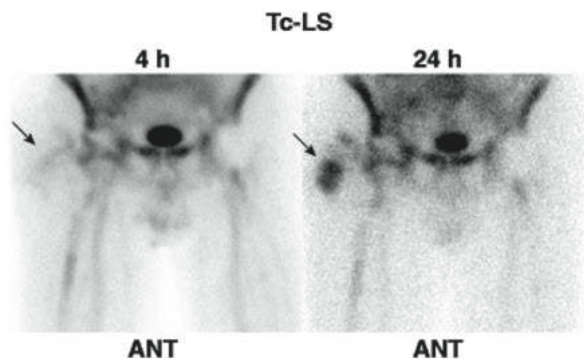


Fig. 5 Infected right hip replacement: 4-h (*left*) and 24-h (*right*) labeled leukocyte images. The abnormal labeled leukocyte activity (*arrows*) is seen clearly only on the later images [36].

In order to improve diagnostic accuracy of LS in diagnosing PJI, several attempts have been made including the introduction of delayed imaging and the combined interpretation of LS with other techniques. (1) LS can be performed as routine leukocyte imaging (2–4h) and delayed imaging (24h), as illustrated in Fig. 5. The importance between both protocols is the difference between the biological basis for recruitment of leukocytes in acute or subacute PJI and chronic, low-grade PJI. In case of early or delayed PJI, bacteria secrete chemotactic factors which continuously recruit leukocytes from peripheral blood to the periprosthetic infected area. In low- grade infections, neutrophils recruitment is less evident due to the biofilm that retards the invasion of labeled leukocytes. Subsequently more time is needed for leukocyte accumulation [69]. Therefore, several authors reported that a delayed imaging at 24 h is more preferable in the detection of PJI. The authors concluded increased sensitivity (83% vs. 50% and 100% vs. 87%) and specificity (100% vs. 90% and 82% vs. 77%) for infected hip and knee prostheses respectively by comparing early, routine imaging and late images [20,60,63,70]. (2) Besides decreased sensitivity of LS in chronic PJI, LS is less specific in diagnosing PJI due to the accumulation of labeled leukocytes in the bone marrow. The distribution of leukocytes in the bone marrow is characterized by significant interindividual variability. The normal bio-distribution alters in case of localized or generalized marrow expansion, prosthetics implantation, and systematic diseases. During implantation of prostheses, the rasping of the femoral medullary canal and acetabular cup could cause abnormal distribution of normal bone marrow around the prosthesis. This complicates the interpretation of the leukocyte images and makes differentiation between alternation of distribution and infectious uptake difficult. In order to overcome this problem, LS is often combined with bone marrow scintigraphy (BMS). This technique is performed with the tracers ^{99m}Tc -sulfur colloid or ^{99m}Tc -nanocolloid. The principle of combined LS-BMS is the radiotracer accumulation in the reticuloendothelial system of the marrow, with similar physiological distribution of ^{99m}Tc -sulfur colloid and labeled leukocytes in the bone marrow. However, the accumulation of leukocytes in PJI is stimulated and simultaneously suppresses the uptake of sulfur colloid in the bone marrow, resulting in spatially incongruent images, as illustrated in Fig. 6 [60]. Consequently, discrimination of infection and implantation induced leukocyte accumulation in the bone marrow is possible. Fuster et al. confirmed improvement in sensitivity of 83% versus 92% and specificity of 57% versus 98% when LS was combined with BMS in the assessment of periprosthetic hip infection. Basu et al. reported lower sensitivity of 39% and 33% in diagnosing periprosthetic hip and knee infection, respectively. Despite some variation in reported diagnostic accuracy (Table 12.3), the combined interpretation of LS-BMS images is highly specific and is the gold standard for diagnosing PJI according to several authors [71]. (3) Another approach in order to improve specificity for diagnosing PJI is the combined interpretation of LS with BS. This did not increase the accuracy of LS for diagnosing knee arthroplasty. For hip prostheses, the added value of this combined technique remains

unclear. Very few investigations reported sensitivity of 60–91% and high specificity of 93–98%. For lower extremity, the largest retrospective study reported lower sensitivity of 64% and moderate high specificity of 78% [72]. In the published investigations, it is proposed that the addition of BS does not improve diagnostic accuracy regarding PJI.

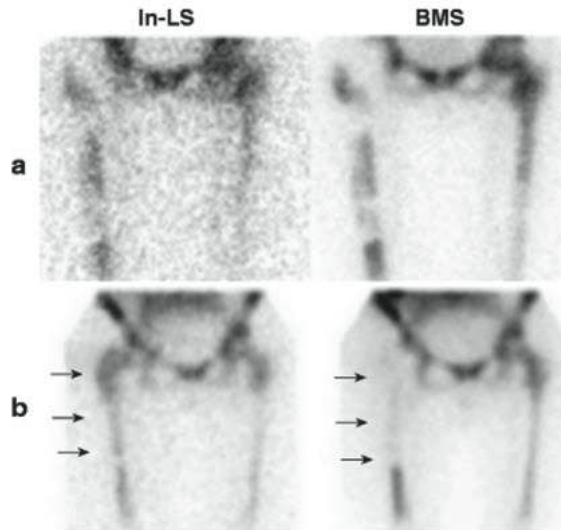


Fig. 6 (A) Aseptically loosened right hip replacement. The distribution of activity around the prosthesis on the labeled leukocyte (*left*) and sulfur colloid (*right*) images is spatially congruent, and the combined study is negative for infection. (B) Infected right hip replacement. There is activity around the femoral component on the labeled leukocyte study (*left*). On the bone marrow image (*right*), however, activity is present only distal to the tip of the prosthesis. The distribution of activity on the labeled leukocyte and sulfur colloid images is spatially incongruent (*arrows*), and the combined study is positive for infection [36].

In daily practice, LS is hampered due to important drawbacks. (1) In vitro labeling requires laborious preparation performed in sterile conditions with complicated and time-consuming procedures and appropriate trained staff. An inherent risk is the possible complication of contamination due to in vitro labeling. (2) From patient's perspective, the 3-day imaging procedure is time intensive and inconvenienced. (3) This technique is not routinely available and not widely used in clinical practice. Moreover, there is poor availability of sulfur colloid in Europe. (4) Leukocyte scintigraphy is limited in the use of immunocompromised patients, in contrast to BS-GS. (5) Imaging quality is not ideal. (6) In case of combined imaging with BMS, there is need to perform another imaging protocol.

In conclusion, most recent investigations reported, with few exceptions, diagnostic accuracy that ranges between 86% and 98% regarding the use of LS in diagnosing PJI. LS, especially combined with BMS, improves specificity compared with BS and/or GS [36].

However, the exact role in the diagnostic algorithm of evaluating suspected infected prostheses remains subject of debate, mainly due to the lack of a universal accepted protocol and interpretation criteria for PJI and significant limitations in daily practice.

3.4 Antigranulocyte scintigraphy

Radiolabeled antigranulocyte antibodies and antibody fragments have been investigated and explored as alternatives for in vitro labeled leukocytes in order to overcome important limitations of LS. Considerable efforts have been devoted to develop in vivo methods of labeling leukocytes that resulted in antigranulocyte scintigraphy (AGS), performed with different tracers. Besilesomab (/Granuloscint/ScintimunR) is a murine monoclonal G1 immunoglobulin that binds to normal cross-reactive antigen-95 leukocytes (NCA-95), while Sulesomab (/LeukoScanR) is a fragment antigen binding (Fab') portion of a murine monoclonal G1 immunoglobulin that binds nonspecific cross-reactive antigen-90 (NCA-90) on leukocytes [58]. The protocol is based on injection of a prepared agent into the patient, tracing leukocytes in vitro. Both tracers are proposed as promising agents for imaging of inflammations and infectious processes in PJI (Fig. 12.8).

However, the results of clinical validation of AGS have been variable. Boubaker et al. investigated the use of Besilesomab in diagnosing periprosthetic hip infection and reported a sensitivity of 67% and specificity of 75% [17]. Using Sulesomab in diagnosing periprosthetic hip prostheses, they reported sensitivity ranges between 75% and 94% and specificity between 47% and 95% [73–76]. Regardless of which tracer was used, recent meta-analyses reported comparable results for infected hip prostheses (sensitivity 80% and 84%, specificity 72% and 75%) and knee prostheses (83% sensitivity and 83% specificity) [39,77].

In conclusion, in vivo labeling of leukocytes overcomes important limitations of the in vitro labeling procedures. However, based on published studies its accuracy in diagnosing prosthetic infection is less sensitive and less specific compared to that of leukocytes scintigraphy, especially in the assessment of hip prostheses. Despite the proposed promising results in diagnosing PJI, clinical investigations concluded that this technique is not the preferred modality at the moment and therefore has not gained wide acceptance.

Fluorodeoxyglucose positron emission tomography (FDG-PET) had been successfully used in the assessment of multiple malignant disorders. Accumulation, however, was also observed in regions of nonmalignant inflammatory and infectious conditions, including in the musculoskeletal system. Therefore, this technique was introduced as potential useful tracer in the assessment of periprosthetic infections. Low dose CT is often added in order to obtain detailed anatomical information.

Table 3: Diagnostic accuracy of leukocyte scintigraphy in patients with PJI

Study	Remark	Prosthetic Joint	Year	No.	Sensitivity (%)	Specificity (%)
Gómez-Luzuriaga et al ¹		Hip	1988	40	95	90
Palestro et al ²		Hip	1990	92	87	94
Pelosi et al ³		Hip	2004	55	95	97
El Espera et al ⁴	combined with BMS	Hip	2004	45	67	97
Pill et al ⁵	combined with BMS	Hip	2006	51	50	95
Simonsen et al ⁶		Hip	2007	76	81	94
Fuster et al ⁷		Hip	2008	70	83	57
Fuster et al ⁷	combined with BMS	Hip	2008	70	92	98
Kim et al ⁸		Hip	2014	71	86	86
Basu et al ⁹	combined with BMS	Hip	2014	59	39	96
Palestro et al ¹⁰		Knee	1991	41	89	75
Larikka et al ¹¹	combined with BMS	Knee	2001	30	100	82
El Espera et al ⁴	combined with BMS	Knee	2004	28	71	95
Pelosi et al ³		Knee	2004	40	84	93
Basu et al ⁹	combined with BMS	Knee	2014	29	33	89
McKillop et al ¹²		Hip/Knee	1984	15	50	100
Pring et al ¹³		Hip/Knee	1986	50	100	89
Wukich et al ¹⁴		Hip/Knee	1987	50	100	45
Magnuson et al ¹⁵		Hip/Knee	1988	98	88	73
Johnson et al ¹⁶		Hip/Knee	1988	28	100	50
El Espera et al ⁴	combined with BMS	Hip/Knee	2004	73	69	97
Pelosi et al ³		Hip/Knee	2004	95	85	71
Love et al ¹⁷	combined with BMS	Hip/Knee	2004	59	100	91

3.5 Fluorodeoxyglucose positron emission tomography

¹⁸F-Fluorodeoxyglucose (FDG) is transported into cells via glucose transporters and phosphorylated to ¹⁸F-2-FDG-6 phosphate without being metabolized [78]. Normal distribution of FDG is observed in the brain, myocardium, and genitourinary tract. In areas of inflammatory and infectious processes, uptake of FDG depends on the detection of cells with increased glucose uptake and increased metabolic rate. The amount of expression of glucose transporters increases in activated leukocytes and subsequently results in increased affinity for FDG in the presence of cytokines and growth factor [79]. In order to minimize accumulation of FDG in normal tissue, patients must fast for several hours to reduce competition for glucose transporters and minimize physical activity. The procedure starts with administration of benzodiazepines, 30–60 min before injection of

FDG, decreasing muscle and brown adipose tissue activity and is completed within 2–3 h after injection of the tracer FDG.

Compared to conventional radionuclide imaging techniques, FDG-PET has a number of important advantages. (1) The PET technique provides high quality images with improved (high) spatial resolution. (2) Patient convenience; in contrast to LS and or BMS, the imaging procedures is completed within 2–3 h after one injection of FDG, without risk of contaminated blood products and laborious preparations. (3) Low conventional dose CT provides excellent anatomical correlation of areas with increased FDG uptake that improves the accuracy compared to PET alone. (4) In contrast to combined LS-BMS, treatment with antibiotics is assumed not to affect the sensitivity of FDG-PET in delineating sites of infections because FDG does not depend on leukocyte migration [80].

Unfortunately, leukocytes are present in both inflammation and infection and it is assumed that differentiation of accumulation resulting from the inflammatory reaction of mechanical loosening of prostheses and periprosthetic infections is subsequently difficult. However, clinical investigations proposed that site and pattern of FDG uptake is more important than intensity of uptake in the region on interest [81,82]. Standardized uptake values based analysis is assumed as not reliable in differentiating between aseptic loosening and PJI [21,83]. Uptake in bone-prosthesis interface of the middle portion of the hip prosthesis is considered specific, while only increased uptake at the tip is assumed nonspecific for periprosthetic hip infection (Fig. 7) [62,81,82]. Similar to conventional tracers, the postoperative remodeling conditions after implantation results in periprosthetic FDG uptake that remains for months to years. Several investigators concluded that this is a nonspecific uptake pattern around the head and neck of asymptomatic hip prosthesis [82,84,85]. Persistently increased nonspecific FDG uptake following knee arthroplasty has also been reported, however, not clinically validated.

Studies that investigated accuracy of FDG-PET in the assessment of PJI reported variable results (Table 12.4). Primary investigation on accuracy using FDG-PET for PJI reported sensitivity of 90%, 91% and specificity of 89%, 72% for hip and knee prostheses, respectively [82]. In subsequently published investigations, sensitivity ranged between 33% and 100% and specificity between 62% and 100%. Recent meta-analyses concluded pooled sensitivity of 86% and 83% and specificity of 93% and 90% for periprosthetic hip infection [39,92]. The most recent, largest, and prospective study reported 82%, 95% sensitivity and 93%, 88% specificity for hip and knee prostheses, respectively [62]. In the assessment of infected knee prostheses, Van Acker et al. reported 100% sensitivity and 73% specificity [90]. Metaanalysis concluded significantly higher specificity for hip prostheses (90%) compared to knee prostheses (75%) [92]. The lower specificity of FDG-PET in knee prostheses may be related to the relatively limited knowledge about the incidence and pattern of nonspecific FDG uptake. Most investigations reported that FDG-PET is a promising imaging tool in the assessment of PJI. In contrast, however, some authors

reported that FDG-PET is not reliable in differentiating between mechanical loosening and PJI [4,87,93]. The inconclusive published clinical results on accuracy in the assessment of periprosthetic infections is mainly due to the lack of uniform interpretation criteria used in the clinical investigations of diagnosing PJI. Different FDG uptake patterns and approaches (quantitative versus qualitative approach by means of standardized uptake values) were used as criterion for PJI in the published studies, with subsequent heterogeneity in the results of accuracy. However, in the most recent studies, accumulation of FDG extended along the bone-prosthesis-interface, not limited to only the femoral neck, headzone or periprosthetic soft tissue is the proposed most accurate criterion for periprosthetic hip infection [59,62,88,89]. Further clinical validation, however, is needed in order to confirm the diagnostic accuracy of FDG-PET in the assessment of PJI.

Table 4: Diagnostic accuracy of fluorodeoxyglucose positron emission tomography in patients with PJI

Study	Prosthetic Joint	Year	No.	Sensitivity (%)	Specificity (%)
Zhuang et al ¹	Hip	2001	38	90	89
Chacko et al ²	Hip	2003	41	92	97
Vanquickenborne et al ³	Hip	2003	17	88	78
Love et al ⁴	Hip	2004	40	43	96
Stumpe et al ⁵	Hip	2004	35	33	81
Mumme et al ⁶	Hip	2005	70	91	92
Reinartz et al ⁷	Hip	2005	92	94	95
Pill et al ⁸	Hip	2006	92	95	93
Garcia-Barrecheguren et al ⁹	Hip	2007	24	64	62
Chryssikos et al ¹⁰	Hip	2008	127	85	93
Mayer-Wagner et al ¹¹	Hip	2010	15	75	71
Basu et al ¹²	Hip	2014	134	82	93
Zhuang et al ¹	Knee	2001	36	91	72
Van Acker et al ¹³	Knee	2001	21	100	73
Manthey et al ¹⁴	Knee	2002	14	100	100
Basu et al ¹²	Knee	2014	87	95	88
Love et al ⁴	Hip/Knee	2004	59	36	97

Overall, FDG-PET is considered as potential, accurate imaging technique in the assessment of PJI. This technique enables visualization of hyperglycolytic inflammatory cells during PJI with excellent anatomical correlation and assumed as comparable or even higher diagnostic accuracy than LS. Moreover, this technique has important advantages compared to conventional radionuclide imaging. However, this modality will only gain full clinical

acceptance in the assessment of PJI when specific uptake pattern can be developed and its clinical added value is confirmed.

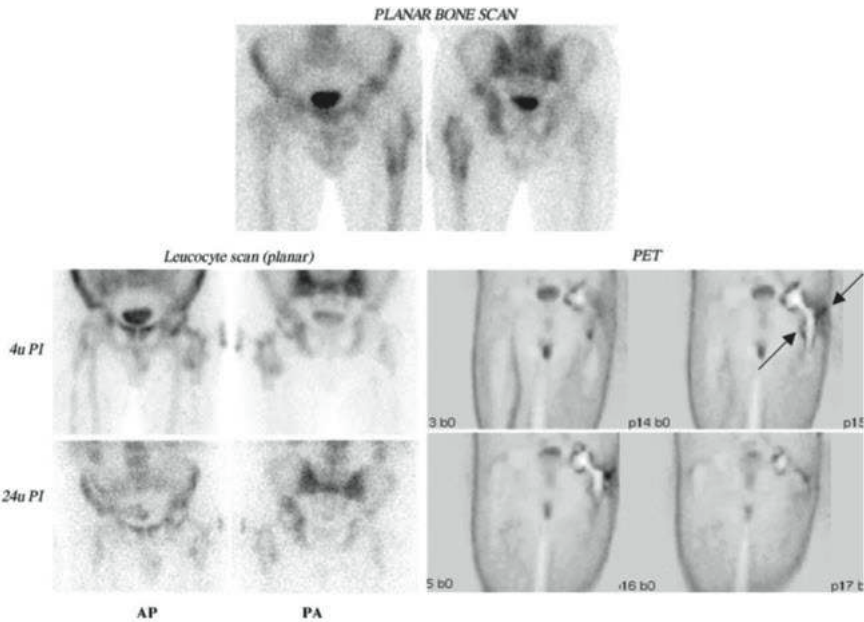


Fig. 7 Example of infection. A 77-year-old person who underwent a THP on the left side in 1992 with revision in 1998 and 1999. Pathological tracer accumulation is seen in the trochanteric region on both leucocyte scintigraphy and the the PET scan.

4 IMAGING IN THE ASSESSMENT OF PJI

4.1 Hybrid imaging and new infection-specific agents

In recent years, the use of nuclear medicine to characterize and diagnose infectious and inflammatory diseases is rapidly increasing. There are some important developments in experimental tracers and imaging techniques which could reflect improvement in current procedures of imaging of PJI. After the introduction of the hybrid imaging modality of PET/CT, preliminary data suggest that single-photon emission computed tomography (SPECT)/electronic computer X-ray tomography technique (CT) potentially contributes to the evaluation of failed joint arthroplasty. In SPECT/CT, which enables three-dimensional information, the CT component provides anatomical details necessary for accumulated radiopharmaceutical localization

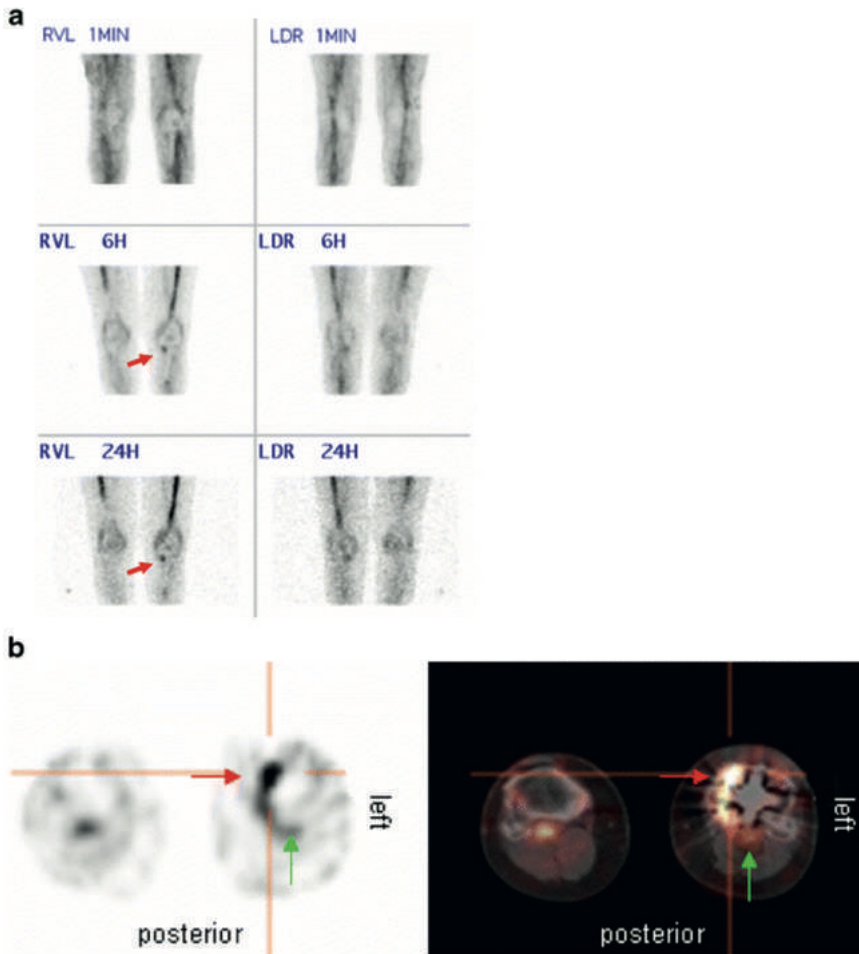


Fig. 8 Planar (A) and SPECT, SPECT/CT images (B) from a 61-year-old woman with total knee prosthesis on the left side, presented in ventral and dorsal orientation at 1 min, 6 h, and 24 h for planar imaging and at 6 h after tracer injection for SPECT/CT. Planar imaging revealed tracer accumulation at the tibial component of the prosthesis (red arrows). SPECT/CT images additionally demonstrated the extent of the infection in the cortical bone and lack of involvement of the bone marrow. The focal uptake of low intensity lying behind the prosthesis could be attributed to the arteria poplitea (green arrow). Hematology laboratory results were completely normal at the time of antigranulocyte scintigraphy (CRP 0.3 mg/dL, leukocytes $5.6 \times 10^9 \text{ L}^{-1}$). However, CRP had increased to 16.7 mg/dL 2 months later. The diagnosis of a low-grade infection was verified by needle aspiration of the left knee, from which *Lactobacillus gasseri* was isolated, such that the scintigraphic result was rated as true- positive. RVL, right ventral left; LDR, left dorsal right.

Initial clinical investigation of planar, antigranulocyte, scintigraphy compared to fused SPECT/CT images in low-grade PJI (mainly infected knee prostheses) reported improved sensitivity (66% vs. 89%) and specificity (60% vs. 73%) [94]. SPECT/CT made a contribution to the final diagnosis in 23% of the patients, compared to 13% for SPECT alone. Several authors concluded that additional SPECT/CT is capable of accurate anatomical as well as precise information of the extent of the infection, which improves interobserver reliability (Fig. 8) [95]. The results regarding hybrid imaging modalities, including PET/CT and SPECT/CT, whether or not combined with new infection agents, is a promising future perspective in diagnosing PJI.

Following the developments in hybrid imaging, there is an ongoing search for infection-specific tracers. Among the currently available radionuclide imaging techniques, none of the tracers is truly specific for infection and alternative agents have been explored and investigated [96]. The most important developments in potential tracers, with lack of clinical validation, for diagnosing PJI: (1) Radiolabeled antibiotics have been introduced as potential “infection-specific” tracers with encouraging results in initial reports of ^{99m}Tc -Ciprofloxacin in diagnosing PJI [74,97–99]. Theoretically, the tracers enter and accumulate in infection areas due to metabolic activity of bacteria. However, subsequent investigations did not confirm the clinical validations of previous studies [100,101]. (2) Radiolabeled synthetic fragments of the human antimicrobial peptide ubiquicidin, ^{99m}Tc -UBI 29–41, bind to the bacterial cell membrane. Expression may be constant or induced on contact with microbes and transported via leukocytes [102]. Recent primary data suggest that this agent is able to differentiate between infection and sterile inflammation, also in PJI [103–105]. (3) FDG is not exclusively used as tracer in PET imaging. The bone seeking tracer fluorine-18-fluoride-PET (fluoride-PET) has been investigated in PJI. Kobayashi et al. reported in a prospective study of 65 prosthetic hip joints, a sensitivity of 95% and specificity of 98% using a new uptake pattern classification system for differentiation of aseptic from septic loosening [106]. The authors concluded considerable potential in the assessment of periprosthetic hip infection with this relatively simple classification system. Other experimental alternatives for FDG is the use of ligand PK11195 coupled to a PET tracer, ^{11}C which binds to benzodiazepine receptors on macrophages, ^{11}C Choline, ^{68}Ga , ^{64}Cu , and ^{18}F -fluorothymidine which are currently been used as markers of cellular proliferation [36,107].

4.2 Multimodality diagnostic work-up of PJI

In the assessment of PJI, there is no universally accepted protocol and the algorithm is characterized by multimodality analysis: (1) The combination of elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) with traditional thresholds appeared a more accurate predictor than isolated elevations, however with poor specificity [108–110]. (2) Elevated synovial fluid white blood cell count and polymorphonuclear

neutrophils percentage are accurate predictors of PJI [111]. (3) Positive histological analysis of periprosthetic tissue is considered highly suggestive for PJI [112]. (4) Two positive periprosthetic cultures with phenotypically identical organism is definitive evidence for PJI, while one positive culture should be evaluated in the context of other available evidence [1,2]. (5) The presence of a sinus tract that communicates with the prosthesis is definitive PJI, while the presence of periprosthetic purulence is a subject of debate [1,2]. The multimodality evaluation of PJI reflects the diagnostic challenge and is subject of developments and consensus. The lack of golden standard is a potential source of bias in the reported diagnostic accuracy of imaging in PJI. Although several authors attempted to investigate and report pooled estimated of diagnostic accuracy of imaging PJI in meta-analyses, important variables including the time after surgery, use of antibiotics, sort of implants, and inter- and intraobserver reliability are often insufficiently investigated or reported. Furthermore, mainly due to inconclusive published diagnostic accuracy and high costs, prominent guidelines concluded that nuclear imaging should not be routinely used to diagnose PJI, although there was substantial evidence regarding the effectiveness in diagnosing PJI [1,2].

In recent published investigations with regard to the role of the promising modality of FDG-PET in evaluation of PJI, important developments are reported. In the clinical evaluation of patients suffering from PJI, FDG-PET is the preferred imaging modality in the detection of metastatic infectious foci in complicated gram-positive bacteremia [113]. The diagnosis of complicating infectious foci, including PJI as primarily or metastatic focus, is often difficult due to asymptomatic clinical presentation in up to 32% of the patients [114]. FDG PET/CT detected clinically relevant new complicating infectious foci in 30% of patients, including 30% in joint prostheses. The addition of FDG-PET/CT to the diagnostic work-up led to a decrease of relapse rates overall and infection-related mortality of gram-positive bacteremia by early detection and treatment of metastatic infectious foci [115,116]. CT, MRI, and ultrasonography are less suitable as screening methods when clues for specific sites of infection are absent [117,118]. Furthermore, FDG-PET/CT incorporated in the diagnostic algorithm appeared cost-effective and investigation concluded that it should be standardized in the work-up of complicated gram-positive bacteremia [119]. This sensitive imaging technique appears suitable for effective screening of complicated infectious foci and might identify patients in need of prolonged antibiotic treatment. No analog investigation regarding cost-effectiveness of FDG-PET in primary assessment of PJI has been published. With the introduction of these additional published data and optimal experience in the interpretation of FDG-PET within the setting of complicated arthroplasty, the role of this modality could potentially be firmly established in the literature and clinical evaluation of PJI.

In the context of other diagnostic tests, including clinical information, infectious parameters, and microbiological and histological analysis; nuclear imaging in diagnosing

PJI is confirmed valuable. However, each modality has its drawbacks and limitations in each phase of the diagnostic algorithm. Understanding the background, drawbacks, and added value of each technique, improves the effectiveness of imaging in differentiating PJI of other causes of loosening. Of the conventional imaging options, radiographs should be standardized in the diagnostic work-up and follow-up of prosthetic joints. Ultrasound is mostly useful in PJI in which effusion cannot be clinically diagnosed. CT and MRI are of limited value in diagnosing PJI, but could be useful in depicting periprosthetic soft tissue. Nuclear imaging is most valuable in determining whether or not a painful prosthetic joint is infected. BS is a sensitive technique in order to exclude any cause of failure. However, the use of this technique is limited in 12–24 months after implantation. In clinical practice, investigation with more specificity is often needed which could be provided by LS or FDG-PET. Although several authors reported LS-BMS as golden standard in diagnosing PJI, this technique has important drawbacks including laborious preparations and limited availability. FDG-PET is proposed as promising and accurate tool with several advantages in diagnosing PJI, including advanced anatomical images and time-efficient procedures. In conclusion, there is substantial evidence that nuclear imaging is valuable for determining PJI, although further investigation in order to determine the exact role of imaging in the diagnostic algorithm is needed. The future prospects of nuclear imaging of PJI is promising with the ongoing search of “infection-specific” tracers, whether or not combined with improved hybrid imaging modalities.

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The Accuracy of Imaging Techniques in the Assessment of Periprosthetic Hip Infection: a Systematic Review and Meta-Analysis

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ABSTRACT

Background: Various imaging techniques are used for excluding or confirming periprosthetic hip infection, but there is no consensus regarding the most accurate technique. The objective of this study was to determine the accuracy of current imaging modalities in diagnosing periprosthetic hip infection.

Methods: A systematic review and meta-analysis of the literature was conducted with a comprehensive search of MEDLINE and Embase to identify clinical studies in which periprosthetic hip infection was investigated with different imaging modalities. The sensitivity and specificity of each imaging technique were determined and compared with the results of microbiological and histological analysis, intraoperative findings, and clinical follow-up of >6 months.

Results: A total of 31 studies, published between 1988 and 2014, were included for meta-analysis, representing 1,753 hip prostheses. Quality assessment of the included studies identified low concerns with regard to external validity but more concerns with regard to internal validity including risk of bias (>50% of studies had insufficient information). No meta-analysis was performed for radiography, ultrasonography, computed tomography, and magnetic resonance imaging because of insufficient available clinical data. The pooled sensitivity and specificity were 88% (95% confidence interval [CI], 81% to 94%) and 92% (95% CI, 88% to 96%), respectively, for leukocyte scintigraphy; 86% (95% CI, 80% to 90%) and 93% (95% CI, 90% to 95%) for fluorodeoxyglucose positron emission tomography (FDG PET); 69% (95% CI, 58% to 79%) and 96% (95% CI, 93% to 98%) for combined leukocyte and bone marrow scintigraphy; 84% (95% CI, 70% to 93%) and 75% (95% CI, 66% to 82%) for antigranulocyte scintigraphy; and 80% (95% CI, 72% to 86%) and 69% (95% CI, 64% to 73%) for bone scintigraphy.

Conclusions: Of the currently used imaging techniques, leukocyte scintigraphy has satisfactory accuracy in confirming or excluding periprosthetic hip infection. Although not significantly different, combined leukocyte and bone marrow scintigraphy was the most specific imaging technique. FDG PET has an appropriate accuracy in confirming or excluding periprosthetic hip infection, but may not yet be the preferred imaging modality because of limited availability and relatively higher cost.

Level of Evidence: Diagnostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

INTRODUCTION

Total hip arthroplasty is one of the most reliable and cost-effective surgical procedures for the treatment of patients with a painful and diseased hip¹. A severe complication is infection, which may lead to revision surgery². Periprosthetic infection is considered one of the most devastating of prosthesis related complications and can result in substantial morbidity and a decline in functional outcome.³⁻⁴

The timely identification and precise localization of a periprosthetic hip infection, including a differentiation from mechanical loosening, is essential to allow the initiation of appropriate medical and surgical therapy⁵. Unfortunately, assessment of suspected periprosthetic hip infection has thus far not been standardized in a universally accepted diagnostic protocol⁶. Despite clinical suspicion, physical examination, multiple diagnostic tests, and complex algorithms, an accurate diagnosis remains challenging⁷⁻¹⁰. A delay in the diagnosis and treatment of a periprosthetic hip infection can have a critical impact on maintaining the prosthesis and joint function.

A variety of imaging techniques such as radiography, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, leukocyte scintigraphy, or fluorodeoxyglucose positron emission tomography (FDG PET) are used for the evaluation of a patient with a suspected periprosthetic hip infection^{6,11-15}. However, the choice of the most accurate imaging technique and optimal radiopharmaceutical remains controversial^{12,16}. Several authors have reported different diagnostic accuracies using the same imaging technique^{11,15-21}. A literature search revealed no previous systematic review or meta-analysis that provides a total overview of the imaging accuracy for diagnosing periprosthetic hip infection exclusively. The aim of this systematic review and meta-analysis was to obtain an estimate of the diagnostic accuracy of different imaging modalities used for diagnosing periprosthetic hip infection.

MATERIALS AND METHODS

Search Criteria

The imaging modalities that were reviewed for the assessment of periprosthetic hip infection were radiography, ultrasonography, CT, MRI, scintigraphy, and PET.

Search Strategy

A computer-aided search of the PubMed and Embase databases was conducted in June 2014 and was updated in April 2015. The search was restricted to primary studies that were written in English. For each database, a specific search strategy was developed (Fig. 1) with an information specialist. Reference lists of the identified studies and relevant reviews were hand-searched for supplementary eligible studies. The search was performed

according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement²².

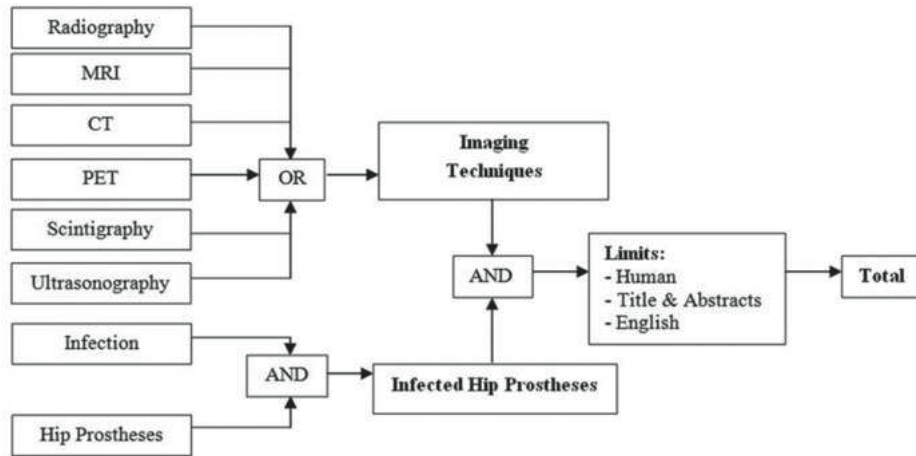


Fig. 1 Flowchart of the conducted search strategy.

MRI = magnetic resonance imaging, CT = computed tomography, and PET = positron emission tomography.

Study Selection

The following inclusion criteria were used to identify eligible studies: (1) Radiography, ultrasonography, CT, MRI, scintigraphy, or PET had been used to identify suspected periprosthetic hip infections. (2) The study had a valid reference standard of at least 1 positive intraoperative culture, regardless of whether it had been combined with histopathological evidence of acute inflammation of the periprosthetic tissue obtained from surgical debridement or prosthesis removal (highly suggestive evidence) and/or a sinus tract that communicated with the prosthesis (definitive evidence)^{13,23,24} and/or a clinical follow-up interval of at least 6 months. (3) Adequate details to reconstruct a 2 x 2 contingency table in order to determine that the results of the index tests were provided. Exclusion criteria were (1) nonhuman studies and (2) non-English language studies. Potential overlap of patient populations when >1 study was by the same author and/or institution was assessed by comparing the patient demographics. The study with the largest number of patients was selected when an overlap of patient populations between studies was observed.

The titles were screened for eligibility by 1 reviewer (S.J.V.) and then were processed for abstract assessment. The titles and abstracts were independently screened and assessed for eligibility in an unblinded standardized manner by 2 reviewers (S.J.V. and O.P.P.T.). Studies

considered to be of dubious eligibility were rejected. The final decision on inclusion was made on the basis of the full text of the article.

Methodological Quality Assessment

The criteria list of QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) for evaluating the internal and external validity of diagnostic studies recommended by the Cochrane Screening and Diagnostic Tests Methods Group (srdata.cochrane.org/handbook-dta-reviews) was used for grading the methodological quality of the selected studies²⁵. Evaluation was performed by the 2 reviewers (S.J.V. and O.P.P.T) independently. Internal and external criteria were used for the determination of the methodological limitations and for descriptive purposes.

Data Extraction

The 2 reviewers (S.J.V. and O.P.P.T) independently extracted relevant data that included demographic, implant, and index test characteristics. Imaging procedures, image interpretation, and the effects of time after surgery as determined by the publication data (to form subgroups when possible), such as data regarding diagnostic performance indexes (e.g., sensitivity and specificity), were analyzed in detail.

Statistical Methods

Qualitative Analysis

The quality of diagnostic accuracy studies, defined with both the internal and external validity, was assessed with use of the framework provided by QUADAS-2. Studies, however, were not excluded from the systematic review on the basis of quality.

Quantitative Analysis (Meta-Analysis)

For the diagnostic modalities, true-positive, false-positive, true-negative, and false-negative results were derived from a 2 x 2 contingency table. The interpretation criteria with the highest diagnostic accuracy were selected when multiple interpretation sets for the same index test were used. When studies noted results of >1 observer, the first reader's findings were included. The statistical heterogeneity of the diagnostic odds ratio (DOR) of each imaging index test across studies was tested by the chi-square test (Q^{DOR}) for independence with $k - 1$ degree of freedom (with k indicating the number of studies)²⁶. The Spearman rank correlation coefficient r value of the DOR was used in case of heterogeneity in order to measure the correlation between sensitivity and specificity. A r value of less than -0.40 suggests that the variation between studies may be explained by different cutoff points, or diagnostic thresholds, on a summary receiver-operating characteristic curve^{26,27}.

Sensitivity and specificity were pooled independently and were weighted by the inverse of the variance, with use of Meta-DiSc software²⁸. The logit-transformed sensitivity, specificity, and corresponding 95% confidence interval (CI) of the index tests were compared with use of z-test statistics. A p value of <0.05 was considered significant.

RESULTS

Studies Included

The search strategy identified 3,451 studies from MEDLINE and 3,344 studies from Embase. The source population was formed by the total of 6,795 studies (including duplicates). In 1,523 studies, overlap was found between the retrieved studies from Embase and MEDLINE. Of the initial 6,795 studies, 6,537 were excluded after analyzing the information provided in the title and abstract.

The full-text articles of the remaining 258 studies were reviewed for eligibility. No other studies were extracted from the reference lists of these studies. There was no disagreement between the reviewers regarding the definitive inclusion of the studies. The reasons for exclusion were that the study was not a clinical diagnostic study (25%), did not describe periprosthetic hip infection (19%), was not written in English (17%), or contained no specified definition of positivity regarding the index test for periprosthetic hip infection (13%); diagnostic imaging was not the main topic (10%); no differentiation was made regarding different prosthetic joint replacements (8%); a 2 x 2 contingency table could not be generated (7%); and there was potential overlap of the patient population (1%). Eventually, 36 studies were included in this review. In general, no differentiation a priori was made for the type of hip implant, the interpretation criteria used for the index test, or the time period between surgery and imaging.

Description of Study Characteristics

A total of 31 of the 36 studies, published between 1988 and 2014, were included for meta-analysis. Of those studies, 12 used FDG PET^{17,21,29-38}, 8 used bone scintigraphy^{33,35,36,39-43}, 6 used leukocyte scintigraphy^{19,44-48}, and 5 used antigranulocyte scintigraphy^{20,39,49-51}. Of these, 7 used combined leukocyte and bone-marrow scintigraphy^{17,29,34,44,46,52,53}, 3 used combined bone-gallium scintigraphy^{43,45,54}, and 3 used combined bone and leukocyte scintigraphy^{37,42,55}. Altogether, a total of 2,434 diagnostic images, 680 (28%) with and 1,754 (72%) without periprosthetic hip infection, were evaluated for 1,753 hip prostheses, 475 (27%) of which were associated with infection. The characteristics of the studies are detailed in the Appendix. Of the 5 studies not included for meta-analysis, 3 studies used radiography, 1 study used ultrasonography, and 1 study used CT (Table I).

Critical Appraisal and Methodological Quality

The Appendix contains data on the internal and external validity and the reproducibility of the included studies.

Analysis

Qualitative Analysis

The external validity showed low concerns with regard to applicability to clinical practice in >85% of the included studies. The internal validity of the included studies showed more concerns with regard to the risk of bias. More than 50% of the included studies did not provide sufficient information on patient selection, reference standard, and flow and timing. The details of the internal and external validity are shown in the Appendix.

Table I: Diagnostic Accuracy of Imaging Techniques Not Included in the Meta-Analysis

Study	No. of Patients with Disease	No. of Patients without Disease	Sensitivity* (95% CI)	Specificity* (95% CI)	Diagnostic Accuracy
<i>Radiography</i>					
Aryana et al. ⁷² (2012)	19	24	0.67 (0.36-0.97)	0.63 (0.43-0.82)	0.64
Stumpe et al. ³⁶ (2004)	9	26	0.89 (0.52-1.00)	0.50 (0.30-0.70)	0.60
Tehranzadeh et al. ⁷³ (1981)	19	60	0.53 (NR)	0.93 (NR)	0.84
<i>Ultrasonography</i>					
Földes et al. ⁷⁴ (1992)	14	6	0.93 (NR)	0.83 (NR)	0.90
<i>Computed tomography</i>					
Cyteval et al. ⁷⁵ (2002)	12	53	0.83 (NR)	0.96 (NR)	0.94

*NR = not reported.

Quantitative Analysis (Meta-Analysis)

Pooled estimated results with regard to diagnostic accuracy could not be calculated for radiography, ultrasonography, CT, and MRI because of insufficient available clinical data.

Meta-analysis was performed for bone scintigraphy, leukocyte scintigraphy, and FDG PET. The sensitivity and specificity of the included studies according to the index test and the pooled estimates by random effects analysis are described in the Appendix.

Bone scintigraphy: For the 8 studies (492 hip prostheses) that evaluated bone scintigraphy, the test of homogeneity for the DOR indicated no statistical heterogeneity

($Q^{\text{DOR}} = 6.66$, 7 degrees of freedom). The pooled sensitivity and specificity were 80% (95% CI, 72% to 86%) and 69% (95% CI, 64% to 73%), respectively, and the accuracy was 0.71.

Combined bone and gallium scintigraphy: The DOR of the 3 studies (121 hip prostheses) that evaluated bone-gallium scintigraphy was homogeneous ($Q^{\text{DOR}} = 1.23$, 2 degrees of freedom). The pooled sensitivity was 59% (95% CI, 42% to 74%), the specificity was 97% (95% CI, 91% to 99%), and the accuracy was 0.86.

Combined bone and leukocyte scintigraphy: For the 3 studies (172 hip prostheses) that evaluated bone-leukocyte scintigraphy, the DOR was homogeneous ($Q^{\text{DOR}} = 3.62$, 2 degrees of freedom). The pooled sensitivity and specificity were 77% (95% CI, 55% to 91%) and 95% (95% CI, 90% to 98%), respectively, with diagnostic accuracy of 0.93.

Leukocyte scintigraphy: The DOR of the included 6 studies (404 hip prostheses) that evaluated leukocyte scintigraphy was significantly heterogeneous ($Q^{\text{DOR}} = 11.57$, 5 degrees of freedom; $p = 0.041$). The pooled sensitivity and specificity were 88% and 85%, respectively, with an accuracy of 0.86. Evaluation of potential sources of heterogeneity showed a significant effect of the image review procedure (see Appendix), more specifically, the use of different cutoff points (regression coefficient $p = -0.543$, $p = 0.266$). One study used a sensitive criterion for a positive leukocyte scan, where any periprosthetic uptake was considered a positive index test⁴⁴. The exclusion of this study (leaving 5 studies in the analysis) resulted in a homogeneous DOR ($Q^{\text{DOR}} = 3.68$, 4 degrees of freedom), and the pooled sensitivity and specificity (334 hip prostheses) were 88% (95% CI, 81% to 94%) and 92% (95% CI, 88% to 96%), with an accuracy of 0.91.

Combined leukocyte and bone marrow scintigraphy: The test of homogeneity for the DOR of the included 7 studies (351 hip prostheses) that evaluated leukocyte-bone marrow scintigraphy indicated no statistical heterogeneity ($Q^{\text{DOR}} = 9.54$, 6 degrees of freedom). The pooled sensitivity was 69% (95% CI, 58% to 79%), the specificity was 96% (95% CI, 93% to 98%), and the accuracy was 0.91.

Antigranulocyte scintigraphy: Five studies (169 hip prostheses) evaluated periprosthetic hip infection with antigranulocyte scintigraphy, the Q^{DOR} of 5.24 (4 degrees of freedom) was homogeneous. The pooled sensitivity was 84% (95% CI, 70% to 93%) and the specificity was 75% (95% CI, 66% to 82%), with an accuracy of 0.81.

FDG PET: Twelve studies (725 hip prostheses) evaluating FDG PET were included, with a heterogeneous Q^{DOR} of 36.28 (11 degrees of freedom, $p < 0.0001$). The pooled sensitivity and specificity were 83% and 91%, with an accuracy of 0.88. Evaluation of potential sources of heterogeneity showed a significant effect of the image review procedure, more specifically, the use of various diagnostic thresholds (regression coefficient $p = -0.406$, $p = 0.191$). Most authors used increased uptake in the bone-prosthesis interface, with or without limitation of localization in the neck, head, fistulous tract, or synovial tissue, as the criterion for infection of the index test. Different criteria for positivity were used by 2 studies: 1 study compared uptake in the bone-prosthesis interface with bladder

activity³⁶, and 1 study used the stringent criterion that uptake in the bone-prosthesis interface should be more than uptake in the periprosthetic soft tissue, fistulous tract, or synovial tract³². Excluding these 2 studies with exceptional criteria compared with other studies (10 studies), the DOR was homogeneous ($Q^{\text{DOR}} = 10.64$, 9 degrees of freedom; $p = 0.301$). The pooled sensitivity and specificity ($n = 666$ hip prostheses) were 86% (95% CI, 80% to 90%) and 93% (95% CI, 90% to 95%), respectively, with diagnostic accuracy of 0.90.

Comparison of Techniques

The pooled estimates of the sensitivity and specificity are shown in Figure 2, and a detailed comparison is available in the Appendix.

Bone scintigraphy: Bone scintigraphy combined with gallium or leukocyte scintigraphy significantly improves specificity ($p < 0.0001$ for both), while bone-gallium scintigraphy significantly decreases sensitivity ($p = 0.013$).

Leukocyte scintigraphy: Leukocyte scintigraphy, whether combined with bone marrow scintigraphy or not, improves specificity compared with bone scintigraphy alone ($p < 0.0001$ for both). When leukocyte scintigraphy is combined with bone marrow scintigraphy, no significantly increased specificity was found, but sensitivity decreases significantly ($p < 0.0001$) compared with leukocyte scintigraphy alone. Leukocyte scintigraphy showed no significant difference compared with bone-leukocyte scintigraphy. Antigranulocyte scintigraphy was significantly less specific compared with leukocyte scintigraphy and leukocyte-bone marrow scintigraphy ($p < 0.0001$ for both).

FDG PET: Compared with leukocyte scintigraphy alone, FDG PET was not significantly different with regard to sensitivity ($p = 0.650$) and specificity ($p = 0.640$). Leukocyte scintigraphy combined with bone-marrow scintigraphy was significantly less sensitive compared with FDG PET ($p = 0.002$). FDG PET was significantly more specific compared with bone scintigraphy and with antigranulocyte scintigraphy ($p < 0.0001$ for both).

DISCUSSION

Imaging techniques have become important modalities for diagnosing periprosthetic joint infection. The results of this meta-analysis revealed that the most accurate, currently used imaging modalities with high specificity in diagnosing periprosthetic hip infection are leukocyte scintigraphy and FDG PET.

Leukocyte scintigraphy has a long history of use for the detection of infections, and the present analysis showed a relatively high accuracy for diagnosing periprosthetic hip infection. However, significant heterogeneity was found among the results of the included studies. The heterogeneity was related to interstudy differences of interpretation criteria. Excluding 1 study that used a sensitive reading procedure resulted in a homogeneous study set. The results of this meta-analysis showed that, when appropriate interpretation

criteria are used, leukocyte scintigraphy may be a specific and accurate imaging technique for diagnosing periprosthetic hip infection. Our results suggest that standardized interpretation criteria may be useful for improving the diagnostic performance of leukocyte scintigraphy. Therefore, the results of individual studies should be interpreted with caution.

Interpretation of leukocyte scintigraphy is potentially hampered by the fact that labeled leukocytes not only accumulate in infections but also accumulate physiologically in the bone marrow⁵⁶. In order to reduce the number of false-positive results, leukocyte scintigraphy is often combined with bone marrow scintigraphy, which has been proposed as an imaging modality of choice for diagnosing periprosthetic joint infection^{11,12,16,57}. The current results for periprosthetic hip infection showed increased specificity for combined leukocyte and bone marrow scintigraphy, as previously proposed¹⁸. Another potential drawback is the relatively time-consuming procedure of *in vitro* labeling of the leukocytes. More recently, antigranulocyte scintigraphy was introduced as an alternative for leukocyte scintigraphy, with the advantage of *in vivo* labeling of leukocytes, and was proposed as a promising diagnostic tool for the detection of infection. However, regarding the detection of periprosthetic hip infection, we found a relatively modest pooled specificity of 75%, which is significantly lower than that for FDG PET and for leukocyte scintigraphy. Our results suggest that antigranulocyte scintigraphy may not be the preferred imaging^{58,59}.

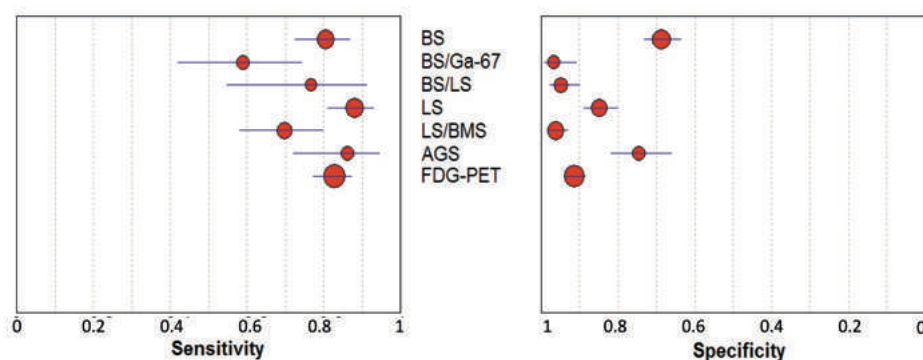


Fig. 2 Graphs showing the pooled estimates and corresponding confidence intervals of sensitivity and specificity for all index tests.

BS = bone scintigraphy, BS/Ga-67 = bone and gallium scintigraphy, BS/LS = bone and leukocyte scintigraphy, LS = leukocyte scintigraphy, LS/BMS = leukocyte and bone marrow scintigraphy, AGS = antigranulocyte scintigraphy, and FDG-PET = fluorodeoxyglucose positron emission tomography.

FDG PET is increasingly used and investigated in suspected periprosthetic joint infection^{11,60,61}, and current results showed that this modality has considerable potential for diagnosing periprosthetic hip infection^{17,32-34,36,37}. Compared with leukocyte scintigraphy, FDG PET offers advantages such as time efficiency, increased resolution, and the use of

low-dose CT. However, the exact role in diagnosing periprosthetic hip infection remains uncertain because of the limited availability, relatively high costs, and heterogeneity of the results in several studies^{16,30,36-38,62,63}. The present study showed that varying diagnostic thresholds influenced the homogeneity of study results¹⁸. Although more investigation is needed, uptake along the bone-prosthesis interface of the femoral component is considered the most reliable indicator for periprosthetic hip infection, while accumulation around the head, neck, and distal tip of the prosthesis can remain for up to 2 years after implantation^{32,34,63}. Altogether the results suggest that more studies on clinical accuracy using reliable and consistent diagnostic criteria are needed.

The results of this meta-analysis confirmed a high sensitivity and low specificity for the use of bone scintigraphy in the diagnosis of periprosthetic hip infection^{48,64-66}. Unfortunately, especially in the first years after implantation, bone scintigraphy lacks the specificity needed to differentiate between infection and mechanical loosening. Nevertheless, bone scintigraphy is widely available and can exclude any form of loosening in patients with a low suspicion for periprosthetic hip infection. However, a positive bone scintigraphy result frequently leads to a second, more specific investigation and can therefore be used in combination with gallium or leukocyte scintigraphy. Although it is a more specific diagnostic modality, the combination of bone and gallium scintigraphy is infrequently used in daily practice because of important drawbacks^{11,67-70}, including a relatively high radiation dose and uptake related to inflammation rather than infection^{43,45,54,57}. As for the combination of bone and leukocyte scintigraphy, our results showed that this technique is highly specific, in contrast to the conclusions of several authors that no added value was achieved with this technique^{68,71}. However, the limited number of available studies regarding both combined bone scintigraphy techniques means that these conclusions should be interpreted with caution.

Throughout the literature, evidence of heterogeneity in data concerning diagnostic accuracy in studies assessing periprosthetic joint infections was found. A possible explanation may lie in the lack of a gold standard, although a valid reference test (at least 1 positive culture) was an inclusion criterion in this meta-analysis. In addition, the diversity of interpretation criteria used for the index tests and the insufficient details regarding implants and imaging procedures reduced the statistical power. Furthermore, only a few of the primary studies described the reproducibility (interobserver and intraobserver variability) of the investigated imaging technique, which is a major limitation because diagnostic results may be hampered by large interobserver variability.

This meta-analysis demonstrated that leukocyte scintigraphy and FDG PET have appropriate accuracy in confirming or excluding the diagnosis of periprosthetic hip infection. Although not significantly different, combined leukocyte and bone marrow scintigraphy was the most specific imaging technique. Hence, on the basis of the current evidence, these 3 imaging modalities could be used with satisfactory accuracy in a

patient with suspected periprosthetic hip infection. However, FDG PET may not yet be the preferred imaging technique because of relatively high costs and limited availability. Furthermore, FDG PET will only receive full acceptance in the assessment of periprosthetic hip infection when consistent diagnostic criteria can be successfully developed.

APPENDIX

Tables listing the characteristics of the included studies; characteristics of the reference tests and implants; data on the diagnostic accuracy of bone scintigraphy, combined bone and gallium scintigraphy, combined bone and leukocyte scintigraphy, leukocyte scintigraphy, combined leukocyte and bone marrow scintigraphy, antigranulocyte scintigraphy, and FDG PET for the detection of periprosthetic hip infection; the search string used for identifying studies on diagnostic imaging of periprosthetic hip infection; the results of the search for studies on diagnostic imaging of periprosthetic hip infection; analysis of the interpretation criteria used in the included studies of FDG-PET for diagnosing periprosthetic hip infection using the z-test; comparison of imaging techniques in diagnosing periprosthetic hip infection with the z-test; and data on the QUADAS-2 evaluation; as well as figures showing the methodological quality of the included studies with QUADAS-2; charts showing the diagnostic accuracy of bone scintigraphy, combined bone and gallium scintigraphy, combined bone and leukocyte scintigraphy, leukocyte scintigraphy, combined leukocyte and bone marrow scintigraphy, antigranulocyte scintigraphy, and FDG-PET for the detection of periprosthetic hip infection; and the PRISMA 2009 flow diagram are available with the online version of this article at jbsj.org.

NOTE: The authors thank information specialist Chantal den Haan at Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, for her contribution in constructing a search strategy for this systematic review and meta-analysis.

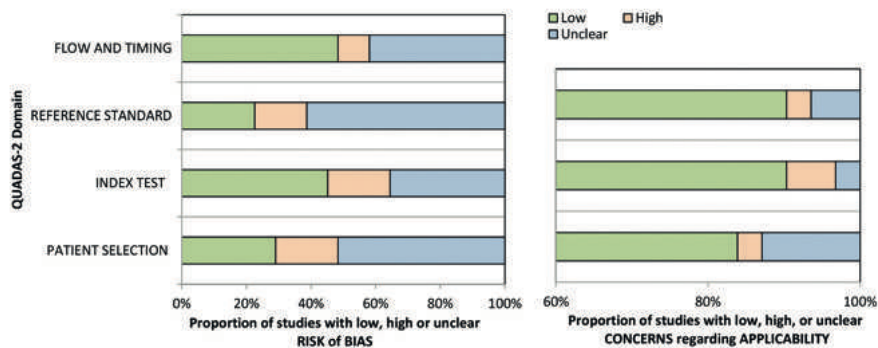


Fig. E-1 Methodological quality of the included studies with QUADAS-2.

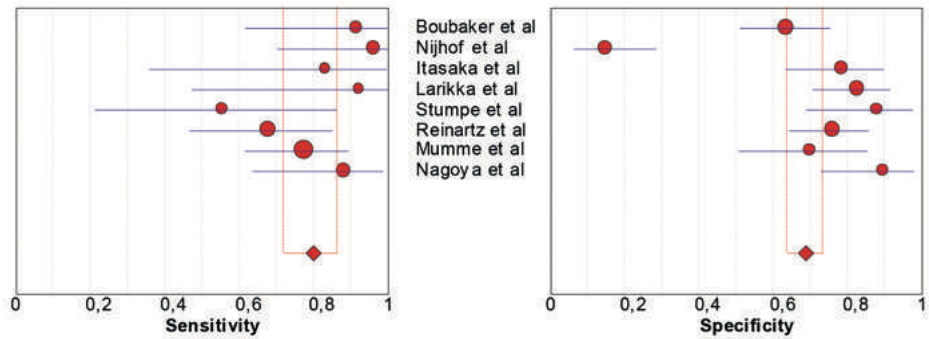


Fig. E-2 Diagnostic accuracy of bone scintigraphy for the detection of periprosthetic hip infection. The values are given as the mean with the 95% confidence interval. The diamond and vertical lines indicate the pooled estimate and the 95% confidence interval.

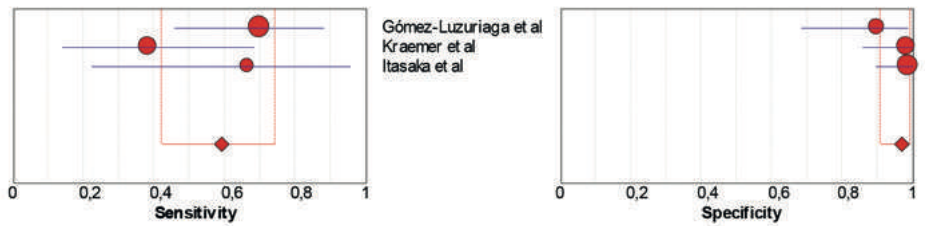


Fig. E-3 Diagnostic accuracy of combined bone and gallium scintigraphy for the detection of periprosthetic hip infection. The values are given as the mean with the 95% confidence interval. The diamond and vertical lines indicate the pooled estimate and the 95% confidence interval.

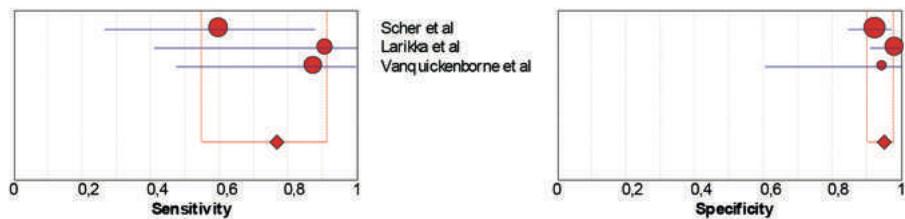


Fig. E-4 Diagnostic accuracy of combined bone and leukocyte scintigraphy for the detection of periprosthetic hip infection. The values are given as the mean with the 95% confidence interval. The diamond and vertical lines indicate the pooled estimate and the 95% confidence interval.

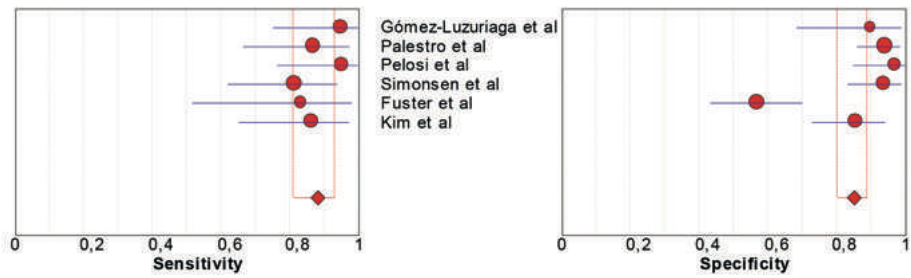


Fig. E-5 Diagnostic accuracy of leukocyte scintigraphy for the detection of periprosthetic hip infection. The values are given as the mean with the 95% confidence interval. The diamond and vertical lines indicate the pooled estimate and the 95% confidence interval.

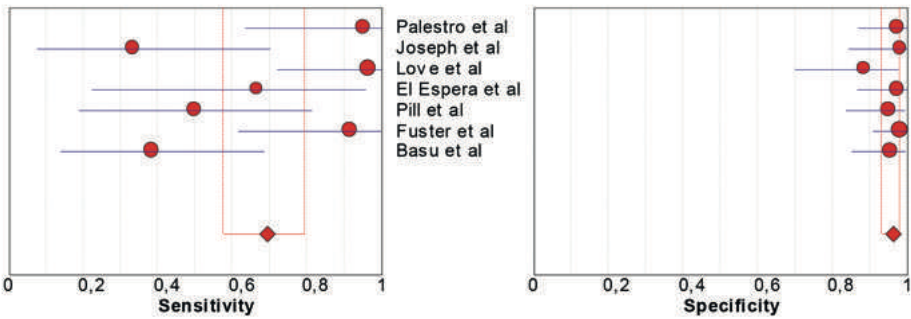


Fig. E-6 Diagnostic accuracy of combined leukocyte and bone marrow scintigraphy for the detection of periprosthetic hip infection. The values are given as the mean with the 95% confidence interval. The diamond and vertical lines indicate the pooled estimate and the 95% confidence interval.

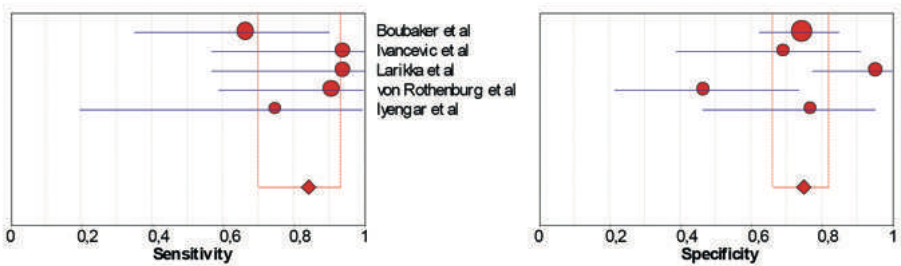


Fig. E-7 Diagnostic accuracy of antigranulocyte scintigraphy for the detection of periprosthetic hip infection. The values are given as the mean with the 95% confidence interval. The diamond and vertical lines indicate the pooled estimate and the 95% confidence interval.

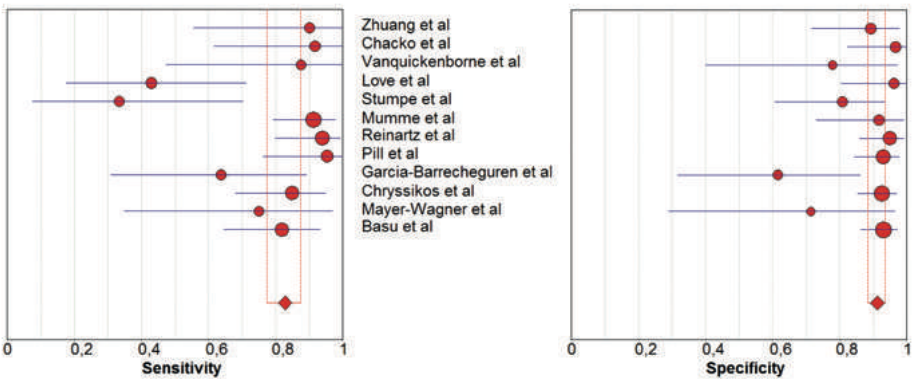


Fig. E-8 Diagnostic accuracy of FDG PET for the detection of periprosthetic hip infection. The values are given as the mean with the 95% confidence interval. The diamond and vertical lines indicate the pooled estimate and the 95% confidence interval.

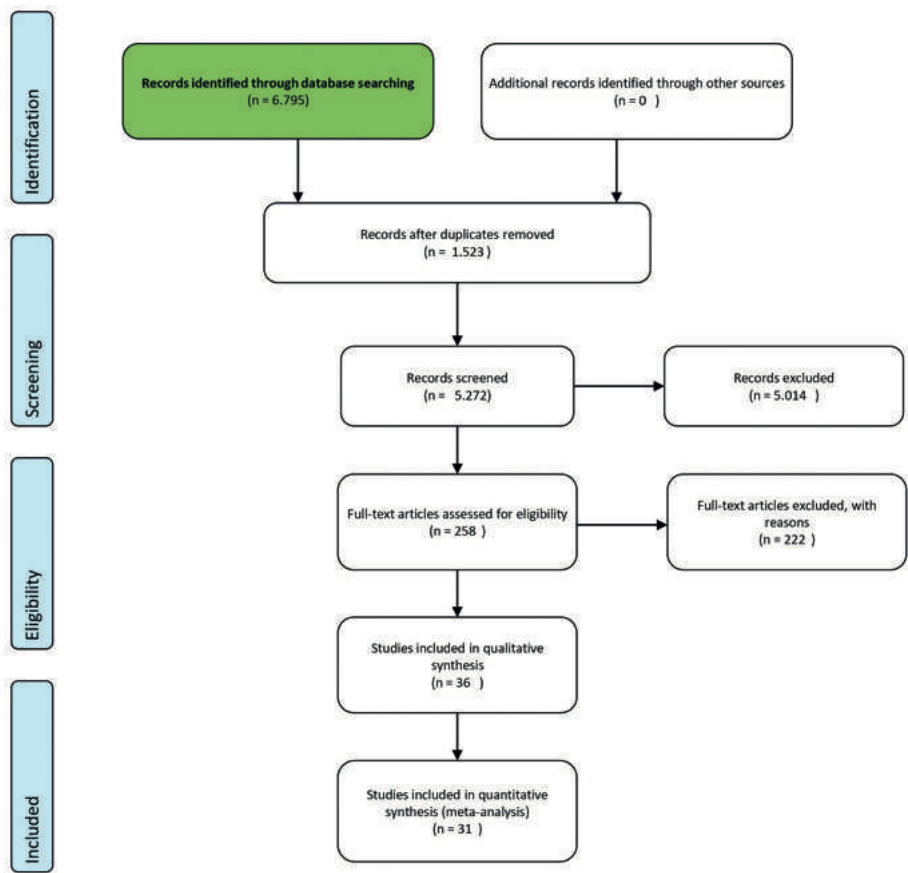


Fig. E-9 PRISMA 2009 flow diagram.

TABLE E-1 Characteristics of the Studies Included in the Meta-Analysis*

Study	Design	No. of patients	Sex M/F	Mean Age (Range) (yr)	No. of Prostheses	Reference Standard	Hip Prostheses/ No. Infected
Gómez-Luzuriaga et al ⁴⁵ (1988)	NR	40	NR	NR	40Hip	M	40/20
Palestro et al ⁴⁶ (1990)	Retro.	72	26/46	62.0 (20-87)	92Hip	M, IOF	92/23
Kraemer et al ⁵⁴ (1993)	Retro.	72	42/30	60.0 (21-82)	43Hip	M	43/13
Boubaker et al ³⁹ (1995)	Pro.	57	34/23	72.7 (29-92)	78Hip	M, IOF, CFU	78/12
Nijhof et al ⁴⁰ (1997)	NR	226	108/118	54.3 (5-90)	87Hip, 17Knee	M, IOF, A, CFU	87/21
Scher et al ⁵⁵ (2000)	NR	143	NR	61.0 (26-87)	91Hip, 40Knee	M, H, IOF	91/10
Itasaka et al ⁴³ (2001)	Retro.	46	8/38	67.5 (49-78)	48Hip	M, H	48/6
Joseph et al ⁵² (2001)	Retro.	58	18/40	60.0 (27-82)	36Hip, 22Knee	M, H, IOF	36/9
Larikka et al ⁴² (2001)	Pro.	64	18/46	NR	64Hip	M, IOF	64/6
Zhuang et al ³⁸ (2001)	NR	62	NR	NR (27-81)	38Hip, 36Knee	M, IOF, A, CFU	38/10
Ivanecvic et al ⁴⁹ (2002)	Retro.	30	13/17	62.0 (30-85)	21Hip, 6Knee	M, H	21/8
Larikka et al ⁵¹ (2002)	NR	30	11/19	NR (25-89)	30Hip	M, IOF, A, CFU	30/8
Chacko et al ³⁰ (2002)	Retro.	32	20/12	NR (27-89)	41Hip	M, H, IOF, CFU	41/12
Vanquickenborne et al ³⁷ (2003)	Pro.	17	8/9	NR (42-77)	17Hip	M, IOF, A, CFU	17/8
El Espera et al ⁵³ (2004)	NR	60	NR	NR	45Hip, 28Knee	M, IOF, A	45/6
Love et al ¹⁷ (2004)	NR	59	22/37	NR (35-89)	40Hip, 19Knee	M, H, IOF	40/14
Pelosi et al ⁴⁷ (2004)	Retro.	78	36/42	69.5 (30-87)	47Hip, 35Knee	M, IOF, CFU	47/21
Rothenburg, von, et al ⁵⁰ (2004)	Retro.	38	9/29	71.0 (45-81)	26Hip, 12Knee	M, IOF, A, L	26/11
Stumpe et al ³⁶ (2004)	Pro.	35	12/23	NR (46-81)	35Hip	M, H, IOF, A, CFU	35/9

TABLE E-1 Continued

Study	Design	No. of patients	Sex M/F	Mean Age (Range) (yr)	No. of Prostheses	Reference Standard	Hip Prostheses/ No. Infected
Iyengar et al ²⁰ (2005)	Retro.	38	18/20	NR (54-89)	17Hip, 13Knee, 8Other	M, H, IOF, A, I, CFU	17/4
Mumme et al ³³ (2005)	NR	50	19/31	68.7 (42-89)	70Hip	M, H, CFU	70/48
Reinartz et al ³⁵ (2005)	NR	63	32/31	68.0 (43-88)	92Hip	M, H, IOF, CFU	92/8
Pill et al ³⁴ (2006)	Pro.	89	NR	NR (29-85)	92Hip	M, H, S, IOF, A, L	92/21
García-Barrecheuren et al ³² (2007)	Pro.	24	12/12	67.8 (37-81)	24Hip	M, H, S, IOF	24/11
Simonsen et al ⁴⁸ (2007)	Retro.	66	25/41	NR (47-95)	76Hip	M, H, IOF, CFU	76/27
Chrysikos et al ³¹ (2008)	Pro.	113	54/59	NR (31-87)	127Hip	M, H, S, IOF, A, L	127/33
Fuster et al ⁴⁴ (2008)	Pro.	70	28/42	68.0 (NR)	70Hip	M, CFU	70/12
Nagoya et al ⁴¹ (2008)	NR	46	18/28	NR (28-81)	46Hip	M, H, IOF	46/17
Mayer-Wagner et al ²¹ (2010)	NR	32	13/19	NR (45-90)	15Hip, 22Knee	M	15/8
Basu et al ²⁹ (2014)	Pro.	221	112/109	57.0 (18-84)	134Hip, 87Knee	M, H, IOF	134/33
Kim et al ¹⁹ (2014)	Retro.	164	53/111	65.0 (17-82)	71Hip, 93Knee	M, H, IOF, CFU, A	71/26
Total		2,195					1753/475

*Retro. = retrospective, pro. = prospective, M = microbiology, H = histology, IOF = intraoperative findings, A = aspiration, L = laboratory (erythrocyte sedimentation rate and C-reactive protein), S = sinus tract, I = imaging, CFU = clinical follow-up of at least 6 months, and NR = not recorded. †Explicit notation in study.

TABLE E-2 Characteristics of the Reference Test(s) and Implants*

Study	Hip Prostheses	Fixation (C,U,H)	THP / HHP	Mean age of Hip Prostheses (Range)	Imaging: Min. time Postop.	Minimal Duration of FU _(mo)
Gómez-Luzuriaga et al ⁴⁵	NR	NR	40/0	M 4.3y (1-11y)	> 12 m	NR
Palestro et al ⁴⁶	P68, R24	C92, U0, H0	92/0	M 4.6y (1w - 17y)	> 1w	> 6 m
Kraemer et al ⁵⁴	NR	NR	NR	M 4.5y (8m-13y)	> 8 m	NR
Boubaker et al ³⁹	NR	C59, U19, H0	NR	M 6.3y (7-17y)	> 7 m	> 8 m
Nijhof et al ⁴⁰	NR	NR	87/0	NR	NR	> 12 m
Scher et al ⁵⁵	NR	NR	94/0	M 47m	NR	NR
Itasaka et al ⁴³	NR	C48, U0, H0	48/0	M 10.9y (2-18y)	> 2y	> 24 m
Joseph et al ⁵²	NR	NR	36/0	NR	NR	NR
Larikka et al ⁴²	NR	NR	64/0	Median 6.6 y(2 m - 22y)	> 2 m	> 12 m
Zhuang et al ³⁸	NR	NR	NR	(3m - 8y)	> 3 m	> 12 m
Ivancevic et al ⁴⁹	NR	NR	21/0	NR	NR	> 6m
Larikka et al ⁴²	NR	NR	30/0	M 12 m(1 w - 12y)	> 1 week	> 12 m
Chacko et al ³⁰	NR	NR	NR	NR	> 12 m	> 9 m
Vanquickenborne et al ³⁷	P10, R7	NR	17/0	(0-14y)	> 0 m	> 6 m
El Espera et al ⁵³	NR	NR	NR	M 5.4 y, (-)	NR	NR
Love et al ¹⁷	P30, R10	C14, U10, H16	37/3	M -, (1 m- 20 y)	> 1m	NR
Pelosi et al ⁴⁷	NR	NR	47/0	NR	NR	> 12 m
Rothenburg, von, et al ⁵⁰	NR	C3, U23, H0	NR	(2m - 10y)	> 2 m	NR
Stumpe et al ³⁶	P26, R17	C18, U17, H0	NR	M 71m, (12-260m)	> 1 y	> 6 m

TABLE E-2 Continued

Study	Hip Prostheses	Fixation (C,U,H)	THP / HHP	Mean age of Hip Prostheses (Range)	Imaging: Min. time Postop.	Minimal Duration of FU _(mo)
Iyengar et al ²⁰	NR	NR	NR	NR	NR	> 12 m
Mumme et al ³³	NR	C51, U17, H2	NR	M 9.2y, SD 5.7	> 12 m	> 9 m
Reinartz et al ³⁵	NR	C60, U32, H0	NR	M -, (1-31 m)	> 6 m (FDG-PET)	> 9 m
Pill et al ³⁴	NR	NR	NR	NR	NR	NR
García-Barrech. et al ³²	NR	NR	NR	NR	> 6 m	NR
Simonsen et al ⁴⁸	P68, R8	C35, U19, H22	62/14	NR	1.5-2 y (0.07-14)	> 12 m
Chrysikos et al ³¹	NR	NR	NR	NR	> 12 m	NR
Fuster et al ⁴⁴	NR	NR	70/0	M 46 m	> 3 m	> 12 m
Nagoya et al ⁴¹	NR	NR	30/16	8.5y (1m-28y)	> 1 m	NR
Mayer-Wagner et al ²¹	NR	NR	NR	NR	NR	NR
Basu et al ²⁹	NR	NR	NR	M 5.8y (FDG), M 6.4y (LS)	NR	> 6 m
Kim et al ¹⁹	NR	NR	NR	Median 3.0 (2w - 32y)	> 2 w	> 12 m
Totaal						

*P = primary implant, R = revision, NR = not recorded, C = cemented hip prostheses, U = uncemented hip prostheses, H = hybrid hip prostheses, SD = standard deviation, FDG PET = fluorodeoxyglucose positron emission tomography, and LS = leukocyte scintigraphy. †The value is given as the median.

TABLE E-3 Diagnostic Accuracy of Bone Scintigraphy for Detection of Periprosthetic Hip Infection*

Study	Pos.	Neg.	Sensitivity (95% CI)	Specificity (95% CI)	Tracer	Dose (MBq)	Criteria for infection
Boubaker et al ³⁹ (1995)	12	66	0.92 (0.62 - 1.00)	0.64 (0.51 - 0.75.0)	99mTc-DPD	740	Uptake in both the early and delayed phases
Nijhof et al ⁴⁰ (1997)	13	47	0.96 (0.70 - 1.00)	0.15 (0.06 - 0.28)	99mTc- MDP	600	Uptake in both the blood pool and late phases
Itasaka et al ⁴³ (2001)	6	42	0.83 (0.36 - 1.00)	0.79 (0.63 - 0.90)	99mTc- MDP	NR	Diffuse increased uptake femoral and/or acetabular (no early phase)
Larikka et al ⁴³ (2001)	6	58	0.92 (0.47 - 1.00)	0.83 (0.71 - 0.91)	99mTc- HDP	550	Uptake in arterial and soft phases
Stumpe et al ³⁶ (2004)	9	25	0.56 (0.21 - 0.86)	0.88 (0.69 - 0.97)	99mTc- DDP	700	Increased uptake in all three phases
Reinartz et al ³⁵ (2005)	25	67	0.68 (0.46 - 0.85)	0.76 (0.64 - 0.86)	99mTc- HDP	733	Wilson Criteria: uptake in both the blood pool and late phases
Mumme et al ³³ (2005)	40	30	0.78 (0.62 - 0.89)	0.70 (0.51 - 0.85)	99mTc- HDP	750	Wilson Criteria: uptake in both the blood pool and late phases
Nagoya et al ⁴¹ (2008)	17	29	0.88 (0.64 - 0.99)	0.90 (0.73 - 0.98)	99mTc- MDP	740	Increased uptake in all three phases
Total	128	364					
Pooled Estimate			0.80 (0.72 - 0.86)	0.69 (0.64 - 0.73)			

*Diagnostic odds ratio = 11,006; heterogeneity chi-squared = 6.66 (degrees of freedom = 7); $p = 0.465$. Inconsistency (I²) = 0.0%. Pos. = positive, neg. = negative, 95% CI = 95% confidence interval, 99mTc = 99m-technetium, MDP = methylene diphosphonate, HDP = hydroxymethylene diphosphonate, and DPD = dicalboxy diphosphonate.

TABLE E-4 Diagnostic Accuracy of Combined Bone and Gallium Scintigraphy for Detection of Periprosthetic Hip Infection*

Study	Pos.	Neg.	Sensitivity (95% CI)	Specificity (95% CI)	Tracer	Dose	Criteria for infection
Gómez-Luzuriaga et al ⁴⁵ (1988)	20	20	0.70 (0.46 - 0.88)	0.90 (0.68 - 0.99)	Tc99m/Ga67	NR	When Ga67 image was spatially incongruent with that of Tc99, or, if spatially congruent, of greater intensity
Kraemer et al ⁵⁴ (1993)	13	30	0.38 (0.14 - 0.68)	0.98 (0.86 - 1.00)	Tc99m/Ga67	NR	When the gallium uptake was spatially incongruent or spatially congruent but greater than the technetium uptake
Itasaka et al ⁴³ (2001)	6	42	0.67 (0.22 - 0.96)	0.99 (0.90 - 1.00)	Tc99m/Ga67	NR	When Ga67 image showed increased activity of a different distribution (incongruency) or of a relatively greater activity than the focus of the Tc99m scans
Total	49	72					
Pooled Estimate			0.59 (0.42 - 0.74)	0.97 (0.91 - 0.99)			

*Diagnostic odds ratio = 34.173; heterogeneity chi-squared = 1.23 (degrees of freedom = 2); p = 0.542. Inconsistency (I2) = 0.0%. Pos. = positive, neg. = negative, Tc99m = 99m-technetium, Ga67 = gallium-67, and NR = not recorded.

TABLE E-5 Diagnostic Accuracy of Combined Bone and Leukocyte Scintigraphy for Detection of Periprosthetic Hip Infection*

Study	Pos.	Neg.	Sensitivity (95% CI)	Specificity (95% CI)	Tracer	Dose (MBq)	Criteria for infection
Scher et al ³⁵ (2000)	10	81	0.60 (0.26 - 0.88)	0.93 (0.85 - 0.97)	99mTc-HDP/ 111In-Oxine	925 (25mCi)/14.8-18.5 (400-500)	When indium scan showed hyperactivity in a different distribution (incongruency) or a relatively greater intensity than the activity on the Tc99 scan
Larikka et al ⁴² (2001)	5	59	0.91 (0.41 - 1.00)	0.98 (0.91 - 1.00)	99mTc-HDP/ 99mTc- HMPAO	550 /370	When periprosthetic leukocyte uptake intensity was higher than that of the bone metabolic image in at least one zone, or if uptake was incongruent
Vanquickenborne et al ³⁷ (2003)	8	9	0.88 (0.47 - 1.00)	0.95 (0.60 - 1.00)	99mTc-MDP/ 99mTc-HMPAO	740 /185	Moderately or significant uptake around the hip prosthesis that was higher uptake than that of the contralateral hip region, but only when the lesions were congruous on both scans
Total	23	149					
Pooled Estimate			0.77 (0.55 - 0.91)	0.95 (0.90 - 0.98)			

*Diagnostic odds ratio = 67.336; heterogeneity chi-squared = 3.62 (degrees of freedom = 2); p = 0.164. Inconsistency (I2) = 44.7%. Tc99m = 99m-technetium, HDP = hydroxymethylene diphosphonate, and 99Tc-HMPAO = hexamethylpropyleneamine oxime.

TABLE E-6 Diagnostic Accuracy of Leukocyte Scintigraphy for Detection of Periprosthetic Hip Infection*

Study	Pos.	Neg.	Sensitivity (95% CI)	Specificity (95% CI)	Tracer	Dose (MBq)	Criteria for infection
Gómez-Luzuriaga et al ⁴⁵ (1988)	20	20	0.95 (0.75 - 1.00)	0.90 (0.68 - 0.99)	111In-Oxine	NR	More intense uptake than that of the contiguous bone and negative otherwise
Palestro et al ⁴⁶ (1990)	23	69	0.87 (0.66 - 0.97)	0.94 (0.86 - 0.98)	111In-Oxine	18.5 (500 uCi)	Activity in the headzone, regardless of activity in any other zone [†]
Pelosi et al ⁴⁷ (2004)	21	34	0.95 (0.76 - 1.00)	0.97 (0.85 - 1.00)	99Tc-HMPAO	430 - 600	SQ: $K_{late} > K_{early}$ by at least 10% ²
Simonsen et al ⁴⁸ (2007)	27	49	0.81 (0.62 - 0.94)	0.94 (0.83 - 0.99)	111In-Oxine or 99Tc-HMPAO	36 / 628*	When periprosthetic uptake was greater than the activity in surrounding bone tissue and in the contralateral site
Fuster et al ⁴⁴ (2008)	12	58	0.83 (0.52 - 0.98)	0.57 (0.43 - 0.70)	99Tc-HMPAO	185	Any extramedullary periprosthetic focal uptake
Kim et al ¹⁹ (2014)	22	49	0.86 (0.65 - 0.97)	0.86 (0.73 - 0.94)	99Tc-HMPAO	740 - 1100	Increased uptake in the periprosthetic area or if the foci in nearby soft tissue had greater activity than the background soft tissue activity.
Total	125	279					
Pooled Estimate			0.88 (0.81 - 0.93)	0.85 (0.80 - 0.89)			

*Diagnostic odds ratio = 60.329; heterogeneity chi-squared = 11.57 (degrees of freedom = 5); p = 0.041. Inconsistency (I2) = 56.8%. Pos. = positive, neg. = negative, NR = not recorded, SQ = semiquantitative, K = suspected region of infection/reference region (bone marrow), and HMPAO = hexamethylpropyleneamine oxime. †Mean dose.

TABLE E-7 Diagnostic Accuracy of Combined Leukocyte and Bone Marrow Scintigraphy for Detection of Periprosthetic Hip Infection*

Study	Pos.	Neg.	Sensitivity (95% CI)	Specificity (95% CI)	Tracer	Dose	Criteria for infection
Palestro et al ⁴⁶ (1990)	10	40	0.95 (0.63 - 1.00)	0.98 (0.87 - 1.00)	111In-Oxine/ 99mTc-SC	18.5MBq (500 uCi)/370MBq(10mCi)	Incongruent labeled leukocyte/sulfur colloid images
Joseph et al ⁵² (2001)	9	27	0.33 (0.07 - 0.70)	0.98 (0.84 - 1.00)	111In-Oxine/ 99mTc-SC	500 uCi /10 uCi	Pattern of activity on the indium image that was not matched on the colloid images
Love et al ¹⁷ (2004)	14	26	0.97 (0.72 - 1.00)	0.88 (0.70 - 0.98)	111In-Oxine/ 99mTc-SC	18.5 MBq (500uCi)/370 MBq(10mCi)	Periprosthetic activity on the indium image without corresponding activity on the marrow scan, regardless of intensity or location
El Espera et al ⁵³ (2004)	6	39	0.67 (0.22 - 0.96)	0.97 (0.87 - 1.00)	111In-Oxine/ 99mTc-SC	30 MBq/185 MBq	When increased activity was observed on the leukocyte image, without corresponding uptake on the bone marrow images (incongruent patterns)
Pill et al ³⁴ (2006)	10	41	0.50 (0.19 - 0.81)	0.95 (0.83 - 0.99)	111In-Oxine/ 99mTc-SC	500 uCi/15 mCi	When activity on the leukocyte image was observed, without corresponding activity on the bone marrow scans
Fuster et al ⁴⁴ (2008)	12	58	0.92 (0.62 - 1.00)	0.98 (0.91 - 1.00)	99Tc-HMPAO/ 99mTc-SC	185 MBq / 370 MBq	All uptake of leukocytes inconsistent with the bone marrow images
Basu et al ²⁹ (2014)	13	46	0.38 (0.14 - 0.68)	0.96 (0.85 - 0.99)	111In-Oxine/ 99mTc-SC	500 uCi/555 MBq	When activity in the periprosthetic region on the leukocyte image was observed, without corresponding activity on the bone marrow images
Total	74	277					
Pooled Estimate			0.69 (0.58 - 0.79)	0.96 (0.93 - 0.98)			

*Diagnostic odds ratio = 65,303; heterogeneity chi-squared = 9.54 (degrees of freedom = 6); p = 0.145. Inconsistency (I2) = 37.1%. Pos. = positive, neg. = negative, 99mTc-SC = 99mTc-sulfur colloid, and HMPAO = hexamethylpropyleneamine oxime.

TABLE E-8 Diagnostic Accuracy of Antigranulocyte Scintigraphy for Detection of Periprosthetic Hip Infection*

Study	Pos.	Neg.	Sensitivity (95% CI)	Specificity (95% CI)	Anti-body type	99mTc Dose	Criteria for infection
Boubaker et al ³⁹ (1995)	12	63	0.67 (0.35 - 0.90)	0.75 (0.62 - 0.85)	Besilesomab ¹	750 MBq	When there was accumulation of the antibody in the ROI that increased with time (SQ)
Ivancevic et al ⁴⁹ (2002)	8	13	0.94 (0.57 - 1.00)	0.69 (0.39 - 0.91)	Sulesomab ²	<1.1 GBq	Uptake higher than that in the bone marrow of the contralateral iliac crest (SQ)
Larikka et al ⁵¹ (2002)	8	22	0.94 (0.57 - 1.00)	0.95 (0.77 - 1.00)	Sulesomab ²	370 MBq	When there was distinct and constant uptake (Q)
von Rothenburg et al ⁵⁰ (2004)	11	15	0.91 (0.59 - 1.00)	0.47 (0.21 - 0.73)	Sulesomab ²	15 - 25 mCi	When there was abnormal uptake greater than could be expected from a blood pool effect (Q)
Iyengar et al ²⁰ (2005)	4	13	0.75 (0.19 - 0.99)	0.77 (0.46 - 0.95)	Sulesomab ²	650 MBq	Abnormal image that showed increased uptake in the region of the pathological process (Q)
Total	43	126					
Pooled Estimate			0.84 (0.70 - 0.93)	0.75 (0.66 - 0.82)			

*Diagnostic odds ratio = 13,147; heterogeneity chi-squared = 5.24 (degrees of freedom = 4); p = 0.263. Inconsistency (I²) = 23.7%. Pos. = positive, neg. = negative, SQ = semiquantitative, Q = qualitative, and ROI = region of interest. ¹A mouse monoclonal antibody labeled with 99mTc-anti-NCA 95. ²A mouse monoclonal antibody labeled with 99mTc-anti-NCA90.

TABLE E-9 Diagnostic Accuracy of FDG PET for Detection of Periprosthetic Hip Infection

Study	Pos.	Neg.	Sensitivity (95% CI)	Specificity (95% CI)	Tracer	Dose	Criteria for infection
Zhuang et al ³⁸ (2001)	10	28	0.90 (0.55 - 1.00)	0.89 (0.72 - 0.98)	18F-FDG	4.22 - 4.56 MBq/kg	Increased uptake in the BPI compared with PST, not if uptake was limited to only femoral head or neck
Chacko et al ³⁰ (2002)	12	29	0.92 (0.62 - 1.00)	0.97 (0.82 - 1.00)	18F-FDG	2.52 MBq/kg	Uptake in the BPI
Vanquickenborne et al ³⁷ (2003)	8	9	0.88 (0.47 - 1.00)	0.78 (0.40 - 0.97)	18F-FDG	370 MBq	Moderately or significantly higher uptake than contralateral distal femur ¹
Love et al ¹⁷ (2004)	14	26	0.43 (0.18 - 0.71)	0.96 (0.80 - 1.00)	18F-FDG	150 - 220 MBq	Semi-Quantitative analysis of BPI activity in femoral with T/B ratio
Stumpe et al ³⁶ (2004)	9	26	0.33 (0.07 - 0.70)	0.81 (0.61 - 0.93)	18F-FDG	300 - 400 MBq	Diffusely increased uptake in BPI, less or comparable with bladder uptake
Mumme et al ³³ (2005)	46	24	0.91 (0.79 - 0.98)	0.92 (0.73 - 0.99)	18F-FDG	200 - 250 MBq	Increased uptake in the BPI and PST
Reinartz et al ³⁵ (2005)	33	59	0.94 (0.80 - 0.99)	0.95 (0.86 - 0.99)	18F-FDG	283 ± 38 MBq	Uptake in the PST
Pill et al ³⁴ (2006)	21	71	0.95 (0.76 - 1.00)	0.93 (0.84 - 0.98)	18F-FDG	140 µCi/kg	Uptake in BPI, not if uptake was limited to only PST or neck of prosthesis
García-Barrecheuren et al ³² (2007)	11	13	0.64 (0.31 - 0.89)	0.62 (0.32 - 0.86)	18F-FDG	10 - 15 mCi	Uptake in BPI, more than PST, fistulous or synovial uptake
Chrysikos et al ³¹ (2008)	33	94	0.85 (0.68 - 0.95)	0.93 (0.85 - 0.97)	18F-FDG	140 µCi/kg	Uptake in BPI, not if uptake was limited to only PST or neck of prosthesis

TABLE E-9 Continued

Study	Pos.	Neg.	Sensitivity (95% CI)	Specificity (95% CI)	Tracer	Dose	Criteria for infection
Mayer-Wagner et al ²¹ (2010)	8	7	0.75 (0.35 - 0.97)	0.71 (0.29 - 0.96)	18F-FDG	180 MBq	Uptake in BPI, not if uptake was limited to tip of stem or neck
Basu et al ²⁹ (2014)	33	101	0.82 (0.65 - 0.93)	0.93 (0.86 - 0.97)	18F-FDG	0.14 mCi/kg	Uptake in BPI in middle portion of stem, not if uptake was limited to only PST, neck or synovial uptake
Total	238	487					
Pooled Estimate			0.83 (0.77 - 0.87)	0.91 (0.89 - 0.94)			

*Diagnostic odds ratio = 38,189; heterogeneity chi-squared = 36.28 (degrees of freedom = 11); p < 0.0001. Inconsistency (I2) = 69.7%. 18F-FDG = fluorodeoxyglucose, BPI = bone-prosthesis interface, T/B = target-to-background, and PST = periprosthetic soft tissue.

TABLE E-10 Search String Used for Identifying Studies on Diagnostic Imaging in Diagnosing Periprosthetic Hip Infection**MEDLINE:**

(((((((("Hip"[Mesh] OR "Hip Joint"[Mesh]) OR "Femur"[Mesh]) OR "Acetabulum"[Mesh])
 OR (hip[tiab] OR (hips[tiab] OR (femur*[tiab] OR (femoral[tiab] OR (coxa*[tiab] OR
 (Trochanter*[tiab] OR (acetabul*[tiab] OR (Cotyloid Cavit*[tiab] OR (cups[tiab] OR
 (cup[tiab] OR (stem[tiab] OR (stems[tiab] OR (socket*[tiab])))) AND (((((((("Prostheses
 and Implants"[Mesh:noexp] OR "Joint Prosthesis"[Mesh:noexp] OR "Hip
 Prosthesis"[Mesh] OR "Metal-on-Metal Joint Prostheses"[Mesh] OR "Prosthesis
 Implantation"[Mesh:noexp] OR "Arthroplasty, Replacement"[Mesh:noexp])) OR
 prosth*[tiab] OR implant*[tiab] OR arthroplast*[tiab] OR replac*[tiab])) OR
 metal-on-metal[tiab])) AND (((((((("Infection"[Mesh] OR "Biofilms"[Mesh])
 OR "Bacterial Adhesion"[Mesh] OR "Adhesins, Bacterial"[Mesh] OR "Bacterial
 Infections"[Mesh])) OR infect*[tiab] OR sepsi*[tiab] OR septi*[tiab] OR bacterie*[tiab]
 OR bacteria*[tiab] OR biofilm*[tiab] OR (bacterem*[tiab] OR bacteraem*[tiab]))
 OR inflammat*[tiab])))) AND (((((((("Magnetic Resonance Imaging"[Mesh] OR
 ("magnetic resonance"[tiab] AND (image[tiab] OR images[tiab] OR imaging[tiab]))
 OR zeugmatograph*[tiab] OR MRI*[tiab] OR NMR*[tiab] OR Magnetization*[tiab]
 OR Magnetisation*[tiab] OR fMRI*[tiab] OR MR imag*[tiab])) OR (Magnetic
 Resonance Spectroscopy[Mesh] AND (chemical shift[tiab] AND imag*[tiab])))) OR
 (((((((("ultrasonography"[Subheading] OR "Ultrasonography"[Mesh]) OR ultraso*[tiab]
 OR echograph*[tiab] OR sonograph*[tiab] OR echotomograph*[tiab])) OR
 (((((((("Radionuclide Imaging"[Mesh] OR "radionuclide imaging"[Subheading])
 OR "Radiopharmaceuticals"[Pharmacological Action])) OR (scintigraph*[tiab] OR
 scintiphotograph*[tiab])) OR (radionuclid*[tiab] OR radioisotop*[tiab])) OR Gamma
 Camera Imag*[tiab] OR (indium[tiab] OR in-111[tiab] OR 111in*[tiab])) OR (99mtc[tiab]
 OR 99m[tiab] OR scintiscan*[tiab])) OR (((((((("Positron-Emission Tomography"[Mesh]
 OR "Tomography, Emission-Computed"[Mesh]) OR "Tomography"[Mesh:noexp])
 OR PET[tiab] OR tomograph*[tiab] OR (((("Fluorodeoxyglucose F18"[Mesh] OR
 "Deoxyglucose"[Mesh])) OR (deoxyglucose[tiab] OR deoxy-glucose[tiab] OR
 2deoxyglucose[tiab])) OR (fluorin*[tiab] OR fluoro[tiab] OR fluorodeoxyglucose[tiab]
 OR 18F[tiab] OR 18FDG[tiab] OR F-18DG[tiab])))) OR (((("Tomography, X-Ray
 Computed"[Mesh] OR (compute*[tiab] AND tomograph*[tiab])) OR (CT[tiab] OR
 CTs[tiab] OR CT's[tiab])) OR electron beam[tiab] OR Tomodensitometr*[tiab])) OR
 (((((((("Radiography"[Mesh] OR "radiography"[Subheading]) OR radiograph*[tiab]
 OR x-ray*[tiab] OR x-radiograph*[tiab] OR xray*[tiab] OR Zonograph*[tiab] OR
 fluoroscop*[tiab] OR arthrograph*[tiab] OR roentgen*[tiab] OR rontgen*[tiab])) OR
 image subtraction*[tiab]))

EMBASE:

((('radiography'/exp OR ('fluoroscopy'/exp OR 'xray'/exp OR 'image subtraction'/exp) OR (xradiograph*:ab,ti OR xray*:ab,ti OR zonograph*:ab,ti OR fluoroscop*:ab,ti OR arthrograph*:ab,ti OR roentgen*:ab,ti OR rontgen*:ab,ti) OR (image NEAR/1 (subtraction OR subtractions)):ab,ti) OR ('computer assisted tomography'/exp OR (compute*:ab,ti AND tomograph*:ab,ti) OR (ct*:ab,ti OR (electron AND beam:ab,ti) OR tomodensitometr*:ab,ti)) OR (('emission tomography'/exp OR 'tomography'/de OR 'fluorodeoxyglucose f 18'/exp OR 'deoxyglucose'/exp) OR (pet:ab,ti OR tomograph*:ab,ti OR deoxyglucose:ab,ti OR 2deoxyglucose:ab,ti OR fluorin*:ab,ti OR fluoro:ab,ti OR fluorodeoxyglucose:ab,ti OR 18f:ab,ti OR 18fdg:ab,ti OR f18dg:ab,ti)) OR (('radioisotope diagnosis'/exp OR 'radiopharmaceutical agent'/exp OR 'radioisotope'/exp) OR (scintigraph*:ab,ti OR scintiphotograph*:ab,ti OR radionuclid*:ab,ti OR radioisotop*:ab,ti OR indium:ab,ti OR in111:ab,ti OR 111in*:ab,ti OR 99mtc:ab,ti OR 99m:ab,ti) OR ('gamma camera image':ab,ti OR 'gamma camera images':ab,ti OR 'gamma camera imaging':ab,ti)) OR ('echography'/exp OR (ultraso*:ab,ti OR echograph*:ab,ti OR sonograph*:ab,ti OR echotomograph*:ab,ti)) OR ('nuclear magnetic resonance imaging'/exp OR (magnetic AND resonance:ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti) OR zeugmatograph*:ab,ti OR mri*:ab,ti OR nmr*:ab,ti OR magnetization*:ab,ti OR magnetisation*:ab,ti OR fmri*:ab,ti OR mr AND imag*:ab,ti))) AND (('hip prosthesis'/exp OR 'joint prosthesis'/de OR 'metal on metal joint prosthesis'/exp OR 'prosthesis'/de OR 'implantation'/de OR 'metal implantation'/exp OR 'hip arthroplasty'/exp) OR (prosthe*:ab,ti OR implant*:ab,ti OR arthroplast*:ab,ti OR replac*:ab,ti OR 'metal on metal':ab,ti)) AND (('acetabulum'/exp OR 'hip'/exp OR 'femur'/exp) OR (hip:ab,ti OR hips:ab,ti OR femur*:ab,ti OR femoral:ab,ti OR coxa*:ab,ti OR trochanter*:ab,ti OR acetabul*:ab,ti OR cups:ab,ti OR cup:ab,ti OR stem:ab,ti OR stems:ab,ti OR socket*:ab,ti) OR (cotyloid:ab,ti AND cavit*:ab,ti)) AND (('infection'/exp OR 'biofilm'/exp OR 'bacterium adherence'/exp OR 'adhesin'/exp) OR (infect*:ab,ti OR sepsi*:ab,ti OR septi*:ab,ti OR bacterie*:ab,ti OR bacteria*:ab,ti OR biofilm*:ab,ti OR bacterem*:ab,ti AND orbacteraem*:ab,ti OR inflammat*:ab,ti))

TABLE E-11 Results of Search for Studies on Diagnostic Imaging in Diagnosing Periprosthetic Hip Infection

No.	Search string	MEDLINE* (no. of studies)	EMBASE* (no. of studies)
1	Hip prostheses	74.103	91.982
2	Infected hip prostheses	11.341	16.476
3	Radiography or MRI or CT or Scintigraphy or Ultrasonography	2.305.863	3.834.824
4	No. 1 and no.2 and no. 3	3.451	3.344

*Search conducted on April 1, 2015.

TABLE E-12 Analysis of the Interpretation Criteria Used in the Included Studies of FDG PET for Diagnosing Periprosthetic Hip Infection Using the Z-Test*

Criteria for Positivity for Index Test	Sensitivity (95% CI)	Comparison (p-value)	Specificity (95% CI)	Comparison (p-value)
1. BPI without limitation of location of uptake	0.87 (0.79 - 0.92)		0.91 (0.85 - 0.95)	
2. BPI with limitation of location of uptake	0.79 (0.71 - 0.86)		0.91 (0.88 - 0.94)	
1 versus 2		0.2973		1.0000
3. BPI uptake compared with uptake in bladder	0.33 (0.07 - 0.70)		0.81 (0.63 - 0.93)	
4. BPI uptake not compared with uptake in bladder	0.85 (0.79 - 0.89)		0.92 (0.89 - 0.94)	
3 versus 4		0.0064		0.0714
5. Only uptake in PST	0.94 (0.80 - 0.99)		0.95 (0.86 - 0.99)	
6. Uptake not only in PST	0.81 (0.75 - 0.86)		0.91 (0.88 - 0.93)	
7. BPI uptake > uptake PST	0.76 (0.53 - 0.92)		0.81 (0.65 - 0.91)	
8. BPI without comparison uptake PST	0.83 (0.78 - 0.88)		0.92 (0.89 - 0.95)	
5 versus 6		0.1207		0.3843
5 versus 7		0.1135		0.0588
5 versus 8		0.1648		0.4985
6 versus 7		0.6315		0.0594
7 versus 8		0.4855		0.0403

TABLE E-12 Continued

Criteria for Positivity for Index Test	Sensitivity (95% CI)	Comparison (<i>p</i> -value)	Specificity (95% CI)	Comparison (<i>p</i> -value)
9. BPI uptake only in femoral component	0.81 (0.65 - 0.91)		0.92 (0.85 - 0.96)	
10. BPI uptake not limited to uptake in femoral component	0.83 (0.77 - 0.88)		0.91 (0.88 - 0.94)	
9 versus 10		0.7759		0.7570

*FDG PET = fluorodeoxyglucose positron emission tomography, BPI = bone-prosthesis interface, and PST = periprosthetic soft tissue.

TABLE E-13 Comparison of Imaging Techniques in Diagnosing Periprosthetic Hip Infection with the Z-Test

Imaging Techniques Compared*		Sensitivity		Comparison		Specificity		Comparison	
Technique 1	Technique 2	Technique 1	Technique 2	(p-value)	Technique 1	Technique 1	Technique 2	(p-value)	Technique 1
BS	BS-GA	0.80	0.59	0.013	0.69	0.97	0.000		
BS	BS-LS	0.80	0.77	0.760	0.69	0.95	0.000		
BS-GA	BS-LS	0.59	0.77	0.189	0.97	0.95	0.463		
LS	BS	0.88	0.80	0.097	0.92	0.69	0.000		
LS	LS-BMS	0.88	0.96	0.000	0.92	0.96	0.102		
LS	BS-LS	0.88	0.77	0.200	0.92	0.95	0.341		
LS	BS-GA	0.88	0.59	0.000	0.92	0.97	0.115		
LS-BMS	BS	0.69	0.80	0.083	0.96	0.69	0.000		
LS-BMS	BS-GA	0.69	0.59	0.314	0.96	0.97	0.657		
LS-BMS	BS-LS	0.69	0.77	0.494	0.96	0.95	0.669		
AGS	BS	0.84	0.80	0.584	0.75	0.69	0.218		
AGS	BS-GA	0.84	0.59	0.022	0.75	0.97	0.000		
AGS	BS-LS	0.84	0.77	0.519	0.75	0.95	0.000		
AGS	LS	0.84	0.88	0.528	0.75	0.92	0.000		
AGS	LS-BMS	0.84	0.69	0.094	0.75	0.96	0.000		
FDG-PET	BS	0.86	0.80	0.157	0.93	0.69	0.000		
FDG-PET	BS-GA	0.86	0.59	0.000	0.93	0.97	0.146		
FDG-PET	BS-LS	0.86	0.77	0.293	0.93	0.95	0.449		
FDG-PET	LS	0.86	0.88	0.650	0.93	0.92	0.640		
FDG-PET	LS-BMS	0.86	0.69	0.002	0.93	0.96	0.123		
FDG-PET	AGS	0.86	0.84	0.748	0.93	0.75	0.000		

*BS = bone scintigraphy, BS-GA = combined bone and gallium scintigraphy, LS = leukocyte scintigraphy, LS-BMS = combined leukocyte and bone marrow scintigraphy, AGS = antigranulocyte scintigraphy, and FDG PET = fluorodeoxyglucose positron emission tomography.

TABLE E-14 QUADAS-2 Evaluation

Study	RISK OF BIAS			APPLICABILITY CONCERNS			
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Gómez et al ⁴⁵	☹	☹	?	☹	?	☹	☹
Palestro et al ⁴⁶	?	☹	☹	?	?	☹	☹
Kraemer et al ⁵⁴	?	?	?	?	☹	☹	☹
Boubaker et al ³⁹	?	☹	?	?	☹	☹	☹
Nijhof et al ⁴⁰	?	☹	?	☹	☹	☹	☹
Scher et al ⁵⁵	☹	?	?	☹	☹	☹	☹
Itasaka et al ⁴³	?	?	☹	?	☹	☹	☹
Joseph et al ⁵²	☹	☹	☹	☹	☹	☹	☹
Larikka et al ⁴²	☹	?	☹	☹	☹	☹	☹
Zhuang et al ³⁸ 2	☹	☹	☹	?	☹	☹	☹
Ivancevic et al ⁴⁹	☹	☹	☹	☹	☹	☹	☹
Larikka et al ⁵¹	?	☹	?	☹	☹	☹	☹
Chacko et al ³⁰	?	☹	?	?	☹	☹	☹
Vanquickenborne et al ³⁷	☹	☹	☹	☹	☹	☹	?
El Espera et al ⁵³	?	☹	☹	☹	☹	☹	☹
Love et al ¹⁷	☹	☹	?	?	?	☹	☹
Pelosi et al ⁴⁷	☹	☹	?	?	☹	☹	☹
Rothenburg, von, et al ⁵⁰	?	?	?	?	☹	☹	☹

	☺ Low Risk	☹ High Risk	? Unclear Risk
Stumpe et al ³⁶	☺	☺	?
Iyengar et al ²⁰	?	?	☹
Mumme et al ³⁵	?	☺	?
Reinartz et al ³⁵	☺	☺	?
Pill et al ³⁴	?	?	☹
Garcia-Barrecheuren et al ³²	☹	?	?
Simonsen et al ⁴⁸	?	?	?
Chryssikos et al ³¹	?	☹	?
Fuster et al ⁴⁴	?	?	☺
Nagoya et al ⁴¹	☺	?	?
Mayer-Wagner et al ²¹	☹	☺	?
Basu et al ²⁹	☺	☺	?
Kim et al ¹⁹	?	☺	?

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What is the Accuracy of Nuclear Imaging in the Assessment of Periprosthetic Knee Infection? A Meta-analysis

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ABSTRACT

Background In the assessment of possible periprosthetic knee infection, various imaging modalities are used without consensus regarding the most accurate technique.

Questions/Purposes To perform a meta-analysis to compare the accuracy of various applied imaging modalities in the assessment of periprosthetic knee infection.

Methods A systematic review and meta-analysis was conducted with a comprehensive search of MEDLINE and Embase1 in accordance with the PRISMA and Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) recommendations to identify clinical studies in which periprosthetic knee infection was investigated with different imaging modalities. The sensitivity and specificity of each imaging technique were determined and compared with the results of microbiologic and histologic analyses, intraoperative findings, and clinical follow-up of more than 6 months. A total of 23 studies, published between 1990 and 2015, were included for meta-analysis, representing 1027 diagnostic images of symptomatic knee prostheses. Quality of the included studies showed low concerns regarding external validity, whereas internal validity indicated more concerns regarding the risk of bias. The most important concerns were found in the lack of uniform criteria for the diagnosis of a periprosthetic infection and the flow and timing of the included studies. Differences among techniques were tested at a probability less than 0.05 level. Where there was slight overlap of confidence intervals for two means, it is possible for the point estimates to be statistically different from one another at a probability less than 0.05. The z-test was used to statistically analyze differences in these situations.

Results Bone scintigraphy was less specific than all other modalities tested (56%; 95% CI, 0.47–0.64; $p \leq 0.001$), and leukocyte scintigraphy (77%; 95% CI, 0.69–0.85) was less specific than antigranulocyte scintigraphy (95%; 95% CI, 0.88–0.98; $p \leq 0.001$) or combined leukocyte and bone marrow scintigraphy (93%; 95% CI, 0.86–0.97; $p \leq 0.001$). Fluorodeoxyglucose positron emission tomography (FDG-PET) (84%; 95% CI, 0.76–0.90) was more specific than bone scintigraphy (56%; 95% CI, 0.47–0.64; $p \leq 0.001$), and less specific than antigranulocyte scintigraphy (95%; 95% CI, 0.88–0.98; $p = 0.02$) and combined leukocyte and bone marrow scintigraphy (93%; 95% CI, 0.86–0.97; $p \leq 0.001$). Leukocyte scintigraphy (88%; 95% CI, 0.81–0.93; $p = 0.01$) and antigranulocyte scintigraphy (90%; 95% CI, 0.78–0.96; $p = 0.02$) were more sensitive than FDG-PET (70%; 95% CI, 0.56–0.81). However, because of broad overlapping of confidence intervals, no differences in sensitivity were observed among the other modalities, including combined bone scintigraphy (93%; 95% CI, 0.85–0.98) or combined leukocyte and bone marrow scintigraphy (80%; 95% CI, 0.66–0.91; $p \geq 0.05$ for all paired comparisons).

Conclusions Based on current evidence, antigranulocyte scintigraphy and combined leukocyte and bone marrow scintigraphy appear to be highly specific imaging modalities in confirming periprosthetic knee infection. Bone scintigraphy was a highly sensitive imaging technique but lacks the specificity needed to differentiate among various conditions that cause painful knee prostheses. FDG-PET may not be the preferred imaging modality because it is more expensive and not more effective in confirming periprosthetic knee infection.

Level of Evidence Level III, diagnostic study.

INTRODUCTION

After primary TKA, as many as 2% of patients have prosthetic joint infection (PJI) develop; this risk is as great as 5% after revision surgery [3, 26]. Accurate diagnosis of periprosthetic infection remains a clinical challenge, particularly in subacute or chronic infections. The evaluation of suspected PJI is characterized by a multimodality workup including microbiologic, laboratory (elevated erythrocyte sedimentation rate, C-reactive protein [CRP]), synovial marker, and histologic tests [35, 57]. Recently, promising results have been reported regarding synovial biomarkers tests, including the alpha defensin immunoassay and synovial fluid CRP tests [5, 54]. However, these tests are not yet widely available and their utility has been confirmed in only a few studies [54]. In addition to these diagnostic tests, various imaging techniques including radiographs, ultrasound, CT, MRI, bone, leukocyte, bone marrow, or antigranulocyte scintigraphy, and positron emission tomography (PET) can be used in the assessment of suspected periprosthetic knee infection [10, 11, 29, 31, 57], especially in the case of a challenging diagnosis of a chronic or low-grade infection [45–48].

A delay in diagnosing and treating a periprosthetic knee infection can have a critical effect on loosening or maintaining the prosthesis and joint function. Timely identification of a periprosthetic infection is essential to allow initiation of appropriate medical and surgical therapies [49] in which various imaging modalities can contribute when other tests are inconclusive. However, inconsistent diagnostic accuracies across studies investigating periprosthetic knee infection have been published [10, 11, 22]. Consequently, the choice of the most accurate imaging technique remains controversial [11, 31]. To our knowledge, there has been no meta-analysis comparing the most commonly used imaging modalities to evaluate TKA PJI.

The aim of this systematic review and meta-analysis was to compare the diagnostic accuracy of different imaging modalities used for diagnosing periprosthetic knee infection.

MATERIALS AND METHODS

Search Criteria and Strategy

The imaging modalities that were reviewed for the assessment of periprosthetic knee infection were radiography, ultrasound, CT, MRI, scintigraphy (including bone, antigranulocyte, leukocyte, and bone marrow scintigraphy), and PET.

In June 2015 a computer-aided search of the PubMed and Embase1 databases was conducted and updated in January 2016 (Appendix 1. Supplemental material is available with the online version of CORR1). The search was restricted regarding primary studies that were written in English. For each database, a specific search strategy was developed (Fig. 1) with a medical informatics specialist. Reference lists of the identified studies and relevant reviews were hand-searched for supplementary eligible studies. The search was

performed according to the PRISMA Statement (Appendix 2. Supplemental material is available with the online version of CORR) [24].

Study Selection

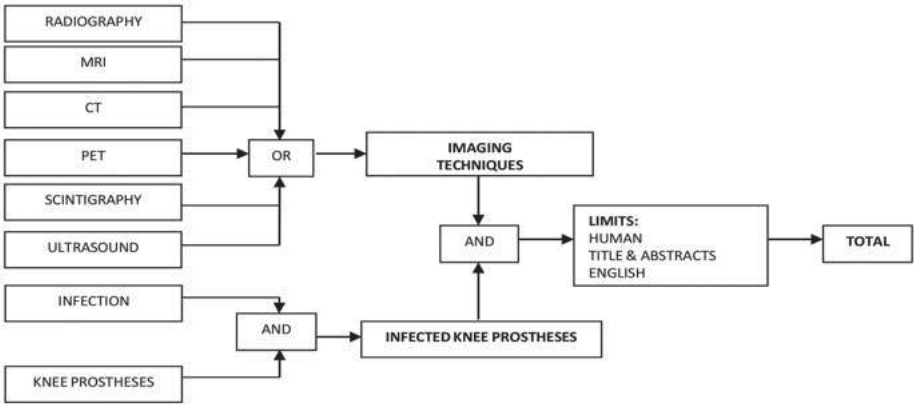


Fig. 1 The flowcart shows the search strategy we used for this study.

The following inclusion criteria were used for eligible studies: (1) radiography, ultrasound, CT, MRI, scintigraphy, and PET were used to identify suspected periprosthetic knee infections; (2) a valid reference standard of positive intraoperative culture whether combined with histopathologic evidence regarding acute inflammation of the periprosthetic tissue of surgical debridement or prosthesis removal and/or the presence of a sinus tract that communicates with the prosthesis [8, 13, 29] and/or a clinical follow-up of at least 6 months; and (3) adequate details to reconstruct a two-by-two contingency table to determine the results of the index tests. Exclusion criteria were (1) animal studies; (2) non-English studies; (3) studies that did not differentiate between various joint replacements; and (4) case reports. Potential overlap of patient populations was assessed when more than one study was selected by the same author or institution by comparing the patient demographics. The study with the largest number of patients was selected when an overlap of patient populations between studies was observed.

The titles were screened for eligibility by one reviewer (SJV) and then processed for abstract assessment. The titles and abstracts were independently screened and assessed in an unblinded standardized manner for eligibility by two reviewers (SJV, RJAS). The final decision regarding inclusion was based on the full article. Disagreement in the evaluation of three studies was resolved with consensus by a third reviewer (OPPT). A priori, no differentiation was made for the type of knee implant, the interpretation criteria used for the index test, or the time between surgery and imaging.

Studies Included

The search strategy identified 3708 studies from MEDLINE and 2864 studies from Embase¹. The source population was formed by the total of 6572 studies (including duplicates). In 1933 studies, overlap was found between the retrieved studies from Embase¹ and MEDLINE. Of the initial 6572 studies, 6433 were excluded after analyzing the information provided in the title and abstract. The full articles of the remaining 139 studies were reviewed for eligibility (Appendix 2. Supplemental material is available with the online version of CORR). No other studies were extracted from the reference list of these studies. A total of 116 studies were excluded because the study was not a clinical diagnostic study (32%), did not describe periprosthetic knee infection (12%), was not written in English (17%), did not specify the definition of positivity regarding the index test or applied an insufficient reference standard for periprosthetic knee infection (7%), did not differentiate regarding different prosthetic joint replacements (15%), did not provide data to reproduce two-by-two contingency tables (16%), or the study revealed a potential overlap of the patient population (1%). Eventually, 23 studies were included in this review.

Description of Study Characteristics

Of the 23 studies included for meta-analysis, six used bone scintigraphy [12, 20, 27, 34, 40, 50], four used bone leukocyte scintigraphy [20, 34, 41, 50], six used leukocyte scintigraphy [18, 28, 34, 37, 38, 50], seven used leukocyte bone marrow scintigraphy [2, 7, 9, 16, 17, 21, 34], five used antigranulocyte scintigraphy [14, 15, 40, 44, 52], and five used fluorodeoxyglucose (FDG)-PET [2, 21, 23, 50, 56]. Altogether, a total of 1027 diagnostic images, 404 (39%) with and 623 (61%) without periprosthetic knee infection, were evaluated in 1502 patients with 763 knee prostheses, of which 288 (38%) were infected (Table 1). Of the studies not included for meta-analysis, two studies used ciprofloxacin scintigraphy and one used IgG scintigraphy. No studies were included that used radiographs, ultrasound, CT, MRI, or combined bone and gallium scintigraphy. The two reviewers (SJV, RJAS) independently extracted relevant data of the included studies, which included demographic, implant, and index test characteristics (Table 2). Imaging procedures, image interpretation, and the effects of time after surgery as determined by the publication data (to form subgroups when possible) were analyzed in detail, such as data regarding diagnostic performance indices (eg, sensitivity and specificity).

Methodologic Quality Assessment

The criteria list of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) for evaluating internal and external validity of diagnostic studies recommended by the Cochrane Screening and Diagnostic Tests Methods Group (<http://methods.cochrane.org/sdt/handbook-dta-reviews>) was used for grading the methodologic quality of the selected studies [53]. Evaluation was performed by two reviewers (SJV, RJAS) independently. Internal and external criteria were used for determination of the methodologic limitations, respectively, for descriptive purposes. Studies, however, were not excluded from the systematic review on the basis of quality.

Table 1. Characteristics of the included studies

Study	Year	Design*	Number of patients	Patients demographics (male/female)	Range	Mean	Number of prostheses	Reference standard	Number of knee prostheses (total/infected)
Rand et al. ³⁷	1990	Retrospective	38	16/22	26-86	65.0	38 knee	M, H, IOF	38/18
Palestro et al. ³³	1991	Retrospective	28	7/21	23-85	65.0	32 knee	M, IOF, CFU	32/9
Ooi et al. ²⁷	1993	NR	19	11/8	25-84	NR	6 knee	M, H, IOF, CFU	6/3
Nijhof et al. ²⁶	1997	NR	226	108/118	5-90	54.0	87 hip, 17 knee	M, IOF, CFU	17/3
Scher et al. ⁴⁰	2000	NR	143	NR	26-87	61.0	91 hip, 40 knee	M, H, IOF	40/14
van Acker et al. ⁴⁹	2001	Prospective	21	8/13	33-78	66.0	22 knee	M, CFU	22/6
Joseph et al. ¹⁵	2001	Retrospective	58	18/40	27-82	60.0	36 hip, 22 knee	M, H, IOF	22/6
Larikka et al. ¹⁹	2001	Prospective	28	4/24	47-82	75.0	30 knee	M, IOF	30/8
Zhuang et al. ⁵⁵	2001	NR	62	NR	27-81	NR	38 hip, 36 knee	M, IOF, A, CFU	36/11
Ivancevic et al. ¹³	2002	Retrospective	30	13/17	30-85	Median 62.0	21 hip, 6 knee	M, H	6/2
El Esper et al. ⁶	2004	NR	60	NR	NR	NR	45 hip, 28 knee	M, IOF, A	28/7
Love et al. ²⁰	2004	NR	59	22/37	35-89	NR	40 hip, 19 knee	M, H, IOF	19/11
Pelosi et al. ³⁶	2004	Retrospective	78	36/42	30-87	70.0	47 hip, 40 knee	M, IOF, CFU	40/25
von Rothenburg et al. ⁵¹	2004	Retrospective	38	9/29	45-81	71.0	26 hip, 12 knee	M, IOF, A, L	12/4
Iyengar et al. ¹⁴	2005	Retrospective	38	18/20	54-89	NR	17 hip, 13 knee, 8 other	M, IOF, A, I, CFU	13/2
Stumpe et al. ⁴³	2006	Prospective	28	13/15	50-86	67.0/59.0	28 knee	M, CFU	28/3
Rubello et al. ³⁹	2008	Prospective	78	27/51	49-81	50	78 knee	M, CFU	78/41

Table 1. Continued

Study	Year	Design*	Number of patients	Patients demographics (male/female)	Range	Mean	Number of prostheses	Reference standard	Number of knee prostheses (total/infected)
Mayer-Wagner et al. ²²	2010	NR	32	13/19	45-90	NR	30 hip, 44 knee	M	16/7
Fuster et al. ⁸	2011	Prospective	40	14/26	NR	66.0	21 hip, 16 knee, 3 shoulder	M, IOF, CFU	16/6
Jung et al. ¹⁶	2012	Prospective	11	2/9	NR	72.0	11 knee	M, H, IOF, CFU	11/5
Basu et al. ²	2014	Prospective	87	35/52	32-83	57.0	134 hip, 87 knee	M, H, IOF	87/19
Kim et al. ¹⁷	2014	Retrospective	164	53/111	17-82	65.0	71 hip, 93 knee	M, H, IOF, CFU, A	93/63
Granados et al. ¹¹	2015	Prospective	120	50/70	NR	71.0	63 hip, 57 knee	M, CFU	57/8
Total	24								

* Explicit notation in study; M = microbiology; H = histology; IOF = intraoperative findings; A = aspiration; L = laboratory (erythrocyte sedimentation rate, C-reactive protein); I = imaging; CFU = clinical follow-up at least 6 months; NR = not recorded.

Table 2. Characteristics of the reference test(s) and implants

Study	Knee prostheses (P/R)	C/U	Age of knee prostheses	Imaging: minimal time AS	Minimal follow-up (months)
Rand et al. ³⁷	P30, R8	C34, U2, H2	Mean 27 months	> 1 month	NR
Palestro et al. ³³	NR	NR	Mean 6 years (3 weeks to 13 years)	> 3 weeks	> 6
Ooi et al. ²⁷	NR	NR	3-18 months	> 3 months	NR
Nijhof et al. ²⁶	NR	C16, U1	4.5 years (6 weeks to 21 years)	> 6 weeks	> 12
Scher et al. ⁴⁰	P40	NR	NR	Mean 71 months (median 47 months)	NR
van Acker et al. ⁴⁹	P16, R5	C12, U9	Mean 35.0 months (7 months to 9 years)	> 7 months	> 6
Joseph et al. ¹⁵	NR	NR	NR	NR	NR
Larikka et al. ¹⁹	NR	NR	Median 4 years 8 months (1 month to 16 years)	NR	> 12
Zhuang et al. ⁵⁵	NR	NR	3 months to 8 years	> 3 months	> 12
Ivancevic et al. ¹³	NR	NR	NR	Median 13 months (2-80 months)	> 6
El Esper et al. ⁶	NR	NR	Mean 5.4 years	NR	> 3
Love et al. ²⁰	P17, R2	C18, U1	1 week to 19 years	> 1 week	NR
Pelosi et al. ³⁶	NR	NR	NR	NR	> 12
von Rothenburg et al. ⁵¹	NR	C6, U6	2 months to 10 years	> 2 months	NR
Iyengar et al. ¹⁴	NR	NR	NR	NR	> 12

Table 2. Continued

Study	Knee prostheses (P/R)	C/U	Age of knee prostheses	Imaging: minimal time AS	Minimal follow-up (months)
Stumpe et al. ⁴³	P24, R4	C15, U13	NR	> 6 months (mean 28 [6-108 months])	> 6
Rubello et al. ³⁹	NR	NR	4 months to 9.5 years	> 4 months	> 12
Mayer-Wagner et al. ²²	NR	NR	NR	NR	NR
Fuster et al. ⁸	NR	NR	Median 1.5 years	NR	> 12
Jung et al. ¹⁶	P24, R4	NR	3.4 years (> 3 months	> 3m	> 12
Basu et al. ²	NR	NR	NR	Mean 3.7 years (FDG), 6.4 (LS-BMS)	> 6
Kim et al. ¹⁷	NR	NR	Median 3 years (2 weeks to 32 years)	NR	> 12
Granados et al. ¹¹	NR	NR	Average 78 months	NR	> 12
Total					

P = primary implant; R = revision; C = cemented knee prostheses; U = uncemented knee prostheses; NR = not recorded; AS = after surgery; H = hinged; Un = unilateral; Bi = bilateral.

The external validity showed low concerns regarding applicability in more than 85% of the included studies (Fig. 2). The internal validity of the included studies showed more concerns regarding the risk of bias. Approximately 50% of the included studies did not provide sufficient information regarding patient selection, reference standard, and flow and timing.

Quantitative Analysis (Meta-analysis)

For the diagnostic modalities, true-positive, false-positive, true-negative, and false-negative results were derived from a two-by-two contingency table. The interpretation criteria with the highest diagnostic accuracy were selected in case multiple interpretation sets for the same index test were used. When studies reported results for more than one observer, the first readers' findings were included. The statistical heterogeneity of the diagnostic odds ratio (DOR) of each imaging index test across studies was tested using the chi-square test (Q^{DOR}) for independence with $k-1$ degrees of freedom (k = number of studies) [6]. The Spearman rank correlation coefficient p value of the DOR was used in case of heterogeneity to measure the correlation between sensitivity and specificity. A p of 0.40 or less suggests that the variation between studies may be explained by different cutoff points, or diagnostic thresholds, on a summary receiver operating characteristic curve [6, 25]. The symmetry of funnel plots was visually interpreted to evaluate possible publication bias.

For all included studies, the test of homogeneity for the DOR indicated no statistical heterogeneity. The studies that evaluated bone scintigraphy (six studies, n = 216 knee prostheses), combined bone and leukocyte scintigraphy (four studies, n = 114 knee prostheses), leukocyte scintigraphy (six studies, n = 238 knee prostheses), combined leukocyte and bone marrow scintigraphy (seven studies, 144 knee prostheses), antigranulocyte scintigraphy (five studies, n = 136 knee prostheses), and FDG-PET (five studies, 179 knee prostheses), the Q DOR was 8.09 (5 DOF), 2.90 (3 DOF), 3.52 (5 DOF), 4.69 (6 DOF), 4.70 (4 DOF), and 6.92 (4 DOF), respectively. The funnel plots did not suggest the presence of positive-outcome bias (data not shown).

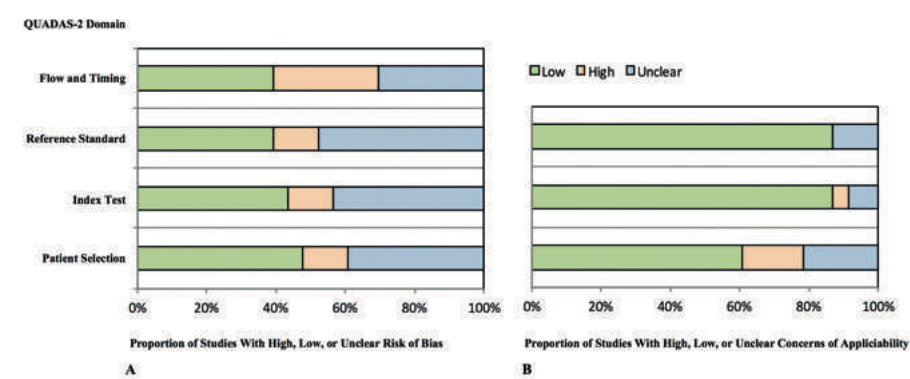


Fig. 2 A-B The methodologic quality of the included studies using QUADAS-2 shows the proportions of studies with high, low, or unclear risk of bias (A) and concerns regarding applicability (B).

The sensitivity and specificity were pooled independently and were weighted by the inverse of the variance with use of Meta-DiSc software (Available at: http://www.hrc.es/investigacion/metadisc_en.htm) [55]. The logit-transformed sensitivity, specificity, and corresponding 95% CI of the index tests were compared with use of z-test statistics. A probability less than 0.05 was considered significant (Table 3). In the comparison of two imaging modalities, confidence intervals for two means can overlap and yet the two means can be statistically different from one another at a probability less than 0.05 [1, 19, 36]. The z-test was used to statistically analyze these differences. A secondary analysis was performed to evaluate possible influence of the methodologic quality on the sensitivity and specificity.

Table 3. Comparison of imaging techniques in diagnosing periprosthetic knee infection using the z-test

Imaging techniques compared		Sensitivity		Specificity		Comparison (p value)	Technique 2	Technique 1	Comparison (p value)	Technique 2	Technique 1	Comparison (p value)
Technique 1	Technique 2	Technique 2	Technique 1	Technique 2	Technique 1							
BS	BS-LS	0.93	0.87	0.87	0.56	0.39	0.82	0.56	0.39	0.82	0.56	< 0.001
LS	BS-LS	0.88	0.87	0.87	0.77	0.89	0.82	0.77	0.89	0.82	0.77	0.44
LS	BS	0.88	0.93	0.93	0.77	0.34	0.56	0.77	0.34	0.56	0.77	< 0.001
LS	LS-BMS	0.88	0.80	0.80	0.77	0.24	0.93	0.77	0.24	0.93	0.77	< 0.001
LS-BMS	BS	0.80	0.93	0.93	0.93	0.08	0.56	0.93	0.08	0.56	0.93	< 0.001
LS-BMS	BS-LS	0.80	0.87	0.87	0.93	0.47	0.82	0.93	0.47	0.82	0.93	< 0.001
AGS	BS	0.90	0.93	0.93	0.95	0.60	0.56	0.95	0.60	0.56	0.95	< 0.001
AGS	BS-LS	0.90	0.87	0.87	0.95	0.70	0.82	0.95	0.70	0.82	0.95	0.01
AGS	LS	0.90	0.88	0.88	0.95	0.72	0.77	0.95	0.72	0.77	0.95	< 0.001
AGS	LS-BMS	0.90	0.80	0.80	0.95	0.21	0.93	0.95	0.21	0.93	0.95	0.47
FDG-PET	BS	0.70	0.93	0.93	0.84	0.06	0.56	0.84	0.06	0.56	0.84	< 0.001
FDG-PET	BS-LS	0.70	0.87	0.87	0.84	0.11	0.82	0.84	0.11	0.82	0.84	0.73
FDG-PET	LS	0.70	0.88	0.88	0.84	0.01	0.77	0.84	0.01	0.77	0.84	0.21
FDG-PET	LS-BMS	0.70	0.80	0.80	0.84	0.30	0.93	0.84	0.30	0.93	0.84	< 0.001
FDG-PET	AGS	0.70	0.90	0.90	0.84	0.02	0.95	0.84	0.02	0.95	0.84	0.02

BS = bone scintigraphy; LS = leukocyte scintigraphy; BMS = bone marrow scintigraphy; AGS = antigranulocyte scintigraphy; FDG-PET = fluorodeoxyglucose positron emission tomography.

RESULTS

Bone scintigraphy was less specific (Table 3) than all other modalities tested (56%; 95% CI, 0.47–0.64; $p \leq 0.001$), and leukocyte scintigraphy (77%; 95% CI, 0.69–0.85) was less specific than antigranulocyte scintigraphy (95%; 95% CI, 0.88–0.98; $p \leq 0.001$) or combined leukocyte and bone marrow scintigraphy (93%; 95% CI, 0.86–0.97; $p \leq 0.001$). FDG-PET (84%; 95% CI, 0.76–0.90) was more specific than bone scintigraphy (56%; 95% CI, 0.47–0.64; $p < 0.001$), and less specific than antigranulocyte scintigraphy (95%; 95% CI, 0.88–0.98; $p = 0.02$) and combined leukocyte and bone marrow scintigraphy (93%; 95% CI, 0.86–0.97; $p < 0.001$).

Leukocyte scintigraphy (88%; 95% CI, 0.81–0.93; $p = 0.01$) and antigranulocyte scintigraphy (90%; 95% CI, 0.78–0.96; $p = 0.02$) were more sensitive than FDG-PET (70%; 95% CI, 0.56–0.81). However, because of broad overlapping of confidence intervals, no differences in sensitivity were observed among the other modalities, including combined bone scintigraphy (93%; 95% CI, 0.85–0.98) or combined leukocyte and bone marrow scintigraphy (80%; 95% CI, 0.66–0.91; $p > 0.05$ for all paired comparisons (Table 3).

The secondary analysis, when high risk of bias studies were excluded, showed a higher sensitivity for FDG-PET (93%; 95% CI, 0.80–0.98) that was not different than leukocyte scintigraphy (86%; 95% CI, 0.76–0.93; $p = 0.39$) and anti-granulocyte scintigraphy (91%; 95% CI, 0.78–0.98; 0.18). Combined leukocyte and bone marrow scintigraphy was highly specific (92%; 95% CI, 0.84–0.97) and more specific than bone scintigraphy (55%; 95% CI, 0.45–0.64; $p \leq 0.001$) and leukocyte scintigraphy (71%; 95% CI, 0.56–0.84; $p = 0.01$). However, antigranulocyte scintigraphy (98%; 95% CI, 0.92–0.99) was more specific than all other compared imaging modalities; $p < 0.05$ for all paired comparisons.

DISCUSSION

In the assessment of suspected periprosthetic knee infection, various diagnostic tests including blood tests, synovial fluid microbiologic analyses, and synovial fluid marker tests (such as alpha defensin and synovial fluid CRP), can be used. However, accurate diagnosis of periprosthetic knee infection remains challenging, especially in chronic or low-grade infections, and inconsistent diagnostic accuracies with various tests across studies have been published [10, 11, 22]. Because of that, imaging tests remain important, but studies do not agree on which imaging technique is the most accurate [11, 31]. Our meta-analysis revealed that in diagnosing periprosthetic knee infection, antigranulocyte scintigraphy and combined leukocyte and bone marrow scintigraphy were highly specific imaging techniques (Fig. 3).

Although the included studies showed statistical homogeneity of data, the reliability of the pooled estimates depends on the methodologic quality of the included studies. There are several limitations of this meta-analysis to consider. Collecting large sample

sizes of patients with suspected periprosthetic knee infection is difficult; the total number of infected TKAs included in this meta-analysis was only 288. Subsequently, several studies showed wide confidence intervals, because of small numbers of patients who were evaluated using each diagnostic modality. This means that there may have been differences in sensitivity or specificity between certain modalities that we did not detect. Future comparative studies might help resolve this issue. Studies were not excluded on the basis of methodologic quality. Our secondary analysis, with exclusion of studies that showed a high risk of bias, suggested that FDG-PET might be more sensitive than the primary analysis showed; indeed, it may be comparably sensitive to leukocyte scintigraphy and antigranulocyte scintigraphy. The methodologic quality of the included studies did not substantially influence the sensitivity and specificity of other imaging modalities (data not shown). However, there were important concerns regarding the flow and timing of the included studies. Most of the studies often insufficiently described important variables, including types of implants, use of antibiotics, imaging time after surgery, improvement of imaging techniques, and inter- and intraobserver reliability variance. Consequently, analyses of the effect of these variables on the accuracy of imaging was not possible, but could influence the diagnostic performance of the imaging modalities we studied. In addition, the long period evaluated here (1990 to 2015) saw the introduction of numerous new diagnostic tests (such as alpha defensin and synovial fluid CRP) and new diagnostic standards [4], which might have changed the apparent performance of the imaging modalities we studied and how they might be used in practice. The differentiation between acute or chronic infection influences the decision to evaluate a suspected infection with additional imaging, and should be investigated in additional studies.

Another important limitation of the included studies is the lack of uniform criteria for diagnosis of a periprosthetic infection. We could not restrict inclusion to studies using the Musculoskeletal Infection Society criteria [35] because many of the included studies were performed before the development of these criteria. Although a valid reference standard with microbiologic confirmation was a stringent inclusion criterion in this meta-analysis, there is a risk of false-positive diagnosis of infection, which potentially could decrease specificity. When a diagnosis of no infection was considered, clinical follow-up sometimes was used to monitor the final diagnosis. Only studies with a clinical follow-up of at least 6 months were included. For obvious reasons, surgery with microbiologic evaluation could not be performed in all patients (patients believed to be without infection did not always undergo surgery). However, this could result in more false-negative results and potentially decrease the reported specificity when an infection is found after the final diagnosis, especially in the case of a low-grade infection.

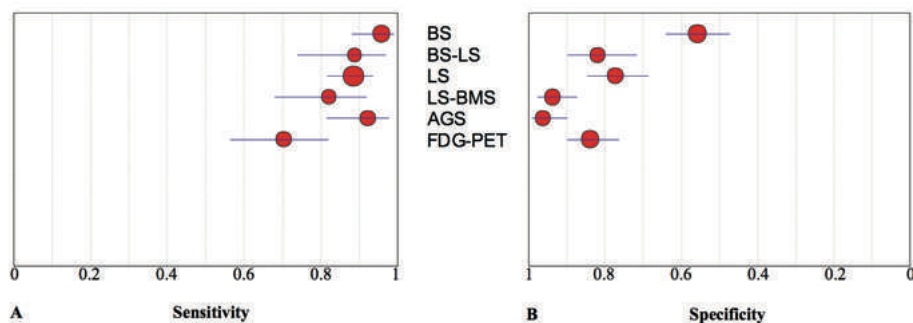


Fig. 3A–B The graphs show the pooled estimates and corresponding 95% CIs for (A) sensitivity and (B) specificity for all index tests. The size of the circles is proportionate to the number of patients investigated by each technique. BS = bone scintigraphy; BS/LS = bone and leukocyte scintigraphy; LS = leukocyte scintigraphy; LS/BMS = leukocyte and bone marrow scintigraphy; AGS = antigranulocyte scintigraphy; FDG-PET = fluorodeoxyglucose positron emission tomography.

Our meta-analysis defined test performance for the various imaging modalities when used in isolation. However, multiple diagnostic tests including aspiration results and laboratory tests can contribute in diagnosing periprosthetic infection, which could influence the diagnostic performance of the evaluated imaging techniques, and generally should improve their performance. During the years, important developments have been described in the diagnosis of periprosthetic infection, including the introduction of alpha defensin and synovial fluid tests [5, 54]. When the diagnostic evaluation using synovial fluid markers clearly indicates infection, there is little or no need for additional nuclear imaging tests. However, if those tests cannot be obtained or are inconclusive, nuclear imaging can be used in concert with other elements of diagnostic evaluation, including microbiologic analysis and blood testing, to arrive at a more-precise diagnosis than is possible with imaging or laboratory testing alone. Nuclear imaging seldom is used in isolation, and probably should not be used that way [57].

Using bone scintigraphy during the first years after implantation, postoperative tracer (Table 4) uptake can be caused by various factors and therefore lacks the specificity needed to differentiate between aseptic and septic loosening [10, 32]. Our results (Table 5) confirmed the reputation of high sensitivity and low specificity of this technique [30, 31, 42, 43]. Unfortunately, subgroup analysis of imaging time after implantation could not be performed owing to insufficient data. In clinical practice, imaging often is used to rule out an infection. Bone scintigraphy is widely available and a sensitive tool for evaluation of painful knee prostheses (Fig. 4). However, when confirmation of infection is needed, a positive bone scintigraphy outcome usually leads to a second, more-specific, investigation.

Leukocyte scintigraphy is assumed to be a more specific-imaging modality and has a long history of use in detection of infections [11, 51]. However, our meta-analysis showed that this technique alone may not be the preferred modality for confirming periprosthetic knee infection, given that it has only moderate specificity (77%) (Table 6). We found that leukocyte scans are very sensitive (88%) (Fig. 5). However, in contrast to bone scintigraphy, leukocyte scintigraphy is a time-consuming procedure with higher costs and therefore may not be the preferred imaging technique to rule out periprosthetic knee infection. The explanation for the moderate specificity may be that labeled leukocytes (Table 7) not only accumulate in infections, but also physiologically in the bone marrow [33]. To reduce the consequent number of false-positive results, leukocyte scintigraphy can be combined with bone marrow scintigraphy (Table 8), which has been proposed as the preferred imaging modality for diagnosing prosthetic joint infections [10, 11, 22, 32]. The current results for knee prostheses confirmed an increased specificity of 93% versus 77% when combining leukocyte with bone marrow scintigraphy (Table 9). Another assessed option to improve specificity (Table 10) was combining leukocyte with bone scintigraphy (Table 11). As expected, specificity did not improve (Fig. 6) [10]. More recently, antigranulocyte scintigraphy was introduced as a less time-consuming alternative for leukocyte scintigraphy with the advantage of in vivo labeling of leukocytes with considerable potential in the detection of infection (Table 12) [10, 11]. We found antigranulocyte scintigraphy (Table 13) to be more specific than leukocyte scintigraphy and FGD-PET (Table 14). However, its role in the assessment of periprosthetic infection is not yet fully established [10]. An important drawback in clinical practice is that neither antigranulocyte scintigraphy nor leukocyte scintigraphy are widely available and used in clinical practice [10].

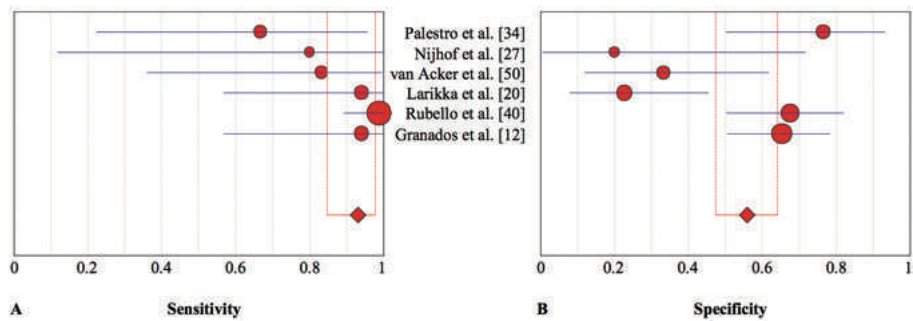


Fig. 4A–B The pooled (A) sensitivity and (B) specificity of bone scintigraphy in the assessment of periprosthetic knee infection with 95% CIs are presented.

Table 4. Study characteristics of bone scintigraphy for detection of periprosthetic knee infection

Study	Tracer	Doses	Criteria for infection
Palestro et al. ³⁴	99mTc-MDP	740 MBq	When hyperperfusion and hyperemia around at least one component of the prosthesis were present on dynamic and blood pool images and periprosthetic activity of at least grade 2 around the same component was present on delayed images
Nijhof et al. ²⁷	99mTc-MDP	600 MBq	When there was increased activity in at least two phases (blood pool and late phase) in the area of interest
van Acker et al. ⁵⁰	99mTc-MDP	740 MBq	Any periprosthetic focal uptake in the delayed phase
Larikka et al. ²⁰	99mTc-HDP	550 MBq	Uptake in the arterial/flow phase
Rubello et al. ⁴⁰	99mTc-MDP	NR	Uptake in the arterial/flow phase
Granados et al. ¹²	99mTc-HDP	925 MBq	Uptake in the arterial/flow phase

Diagnostic odds ratio 8.956; heterogeneity chi-square = 8,09 (df = 5) p = 0.151; Inconsistency (I²) = 38,2%; 99mTc = 99m-technetium; MDP = methylenediphosphonate; HDP = hydroxymethylenediphosphonate.

Table 5. Diagnostic accuracy of bone scintigraphy for detection of periprosthetic knee infection

Study	Year	Disease +	-	Sensitivity	95% CI	Specificity	95% CI
Palestro et al. ³⁴	1991	6	17	0.67	0.22-0.96	0.76	0.50-0.93
Nijhof et al. ²⁷	1997	2	5	1.00	0.12-1.00	0.20	0.00-0.72
van Acker et al. ⁵⁰	2001	6	15	0.83	0.36-1.00	0.33	0.12-0.62
Larikka et al. ²⁰	2001	8	22	1.00	0.57-1.00	0.23	0.08-0.54
Rubello et al. ⁴⁰	2008	41	37	1.00	0.89-1.00	0.68	0.50-0.82
Granados et al. ¹²	2015	8	49	1.00	0.94-1.00	0.65	0.50-0.78
Total		71	145				
Pooled estimate				0.93	0.85-0.98	0.56	0.47-0.64

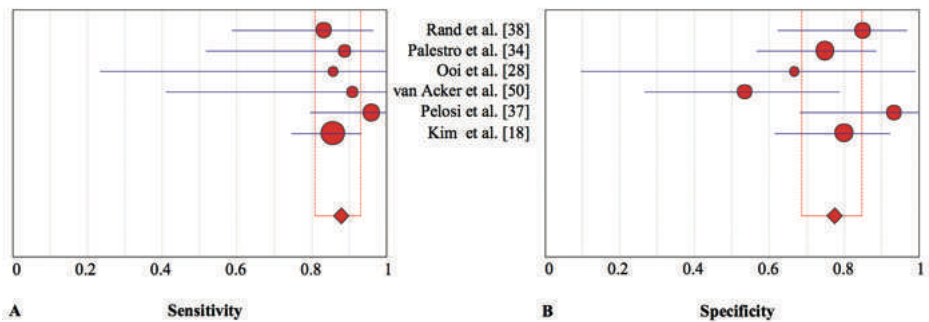


Fig. 5A–B The pooled (A) sensitivity and (B) specificity of leukocyte scintigraphy in the assessment of periprosthetic knee infection with 95% CIs are shown.

Table 6. Diagnostic accuracy of leukocyte scintigraphy for detection of periprosthetic knee infection

Study	Year	Disease	-	Sensitivity	95% CI	Specificity	95% CI
		+					
Rand et al. ³⁸	1990	18	20	0.83	0.59-0.96	0.85	0.62-0.97
Palestro et al. ³⁴	1991	9	32	0.89	0.52-1.00	0.75	0.57-0.89
Ooi et al. ²⁸	1993	3	3	1.00	0.23-1.00	0.67	0.09-0.99
van Acker et al. ⁵⁰	2001	5	15	1.00	0.41-1.00	0.53	0.27-0.79
Pelosi et al. ³⁷	2004	25	15	0.96	0.80-1.00	0.93	0.68-1.00
Kim et al. ¹⁸	2014	63	30	0.86	0.75-0.93	0.80	0.61-0.92
Total		123	115				
Pooled estimate				0.88	0.81-0.93	0.77	0.69 - 0.85

Table 7. Study characteristics of leukocyte scintigraphy for detection of periprosthetic knee infection

Study	Tracer	Doses*	Criteria for infection
Rand et al. ³⁸	111In-Oxine	NR	A focus of moderate to marked increased activity
Palestro et al. ³⁴	111In-Oxine	18.5 MBq	Periprosthetic activity more intense than that in corresponding contralateral region
Ooi et al. ²⁸	111In-Oxine	7.5-15 MBq	When there was a focal accumulation at the area of interest
van Acker et al. ⁵⁰	99Tc-HMPAO	185 MBq	Any periprosthetic focal uptake
Pelosi et al. ³⁷	99Tc-HMPAO	430-600 MBq	SQ: $K_{late} > K_{early}$ by at least 10%
Kim et al. ¹⁸	99Tc-HMPAO	740-1100 MBq	Increased uptake in the periprosthetic area or if the foci in nearby soft tissue had greater activity than the background soft tissue activity

* Mean doses; SQ = semiquantitative; diagnostic odds ratio 28,143; heterogeneity chi-square = 3.52 (df = 5); p = 0.620; inconsistency (I²) = 0.0%; K = suspected region of infection/reference region (bone marrow); HMPAO = hexamethylpropyleneamine oxime; NR = not reported.

Table 8. Study characteristics of combined leukocyte and bone marrow scintigraphy

Study	Tracer	Doses	Criteria for infection
Palestro et al. ³⁴	111In-Oxine/99mTc-SC	18.5 MBq/370 MBq	If activity was observed on labeled leukocyte images without corresponding activity on the sulfur colloid images (incongruent)
Joseph et al. ¹⁶	111In-Oxine/99mTc-SC	500 uCi /10 uCi	Pattern of activity on the indium image that was not matched on the colloid images
El Esper et al. ⁷	111In-Oxine/99mTc-SC	30 MBq/185 MBq	When increased activity was observed on the leukocyte image at the ROI, without corresponding uptake on the bone marrow images (incongruent patterns)

Table 8. Continued

Study	Tracer	Doses	Criteria for infection
Love et al. ²¹	111In-Oxine/99mTc-SC	18.5 MBq/370 MBq	Periprosthetic activity on the indium image without corresponding activity on the marrow scan, regardless of intensity or location
Fuster et al. ⁹	99Tc-HMPAO/99mTc-SC	NR	Global imaging analysis; BMS scan inconsistent with LS
Jung et al. ¹⁷	99mTc-HMPAO /99mTc-phytate	555-740 MBq/185 MBq	Concordant if the distribution of the two radiotracers was spatially identical, and as discordant if activity was observed in the LS without corresponding activity in the BMS (discordant was positive for infection)
Basu et al. ²	111In-Oxine/99mTc-SC	500 uCi/555 MBq	When activity in the periprosthetic region on the leukocyte image was observed, without corresponding activity on the bone marrow images

Diagnostic odds ratio 41,063; heterogeneity chi-square = 4.69 (df = 6), p = 0.584, inconsistency (I²) = 0.0%; 99mTc-SC = 99mTc-sulfur colloid; HMPAO = hexamethylpropyleneamine oxime; ROI = region of interest; LS = leukocyte scintigraphy; BMS = bone marrow scintigraphy; NR = not reported.

Table 9. Diagnostic accuracy of combined leukocyte and bone marrow scintigraphy for detection of periprosthetic knee infection

Study	Year	Disease +	-	Sensitivity	95% CI	Specificity	95% CI
Palestro et al. ³⁴	1991	7	12	0.86	0.42-0.97	1.00	0.68-1.00
Joseph et al. ¹⁶	2001	6	16	0.67	0.22-0.96	1.00	0.75-1.00
El Esper et al. ⁷	2004	7	21	0.71	0.29-0.96	0.95	0.76-1.00
Love et al. ²¹	2004	11	8	1.00	0.66-1.00	1.00	0.57-1.00
Fuster et al. ⁹	2011	6	10	0.83	0.36-1.00	0.90	0.56-1.00
Jung et al. ¹⁷	2012	5	6	1.00	0.41-1.00	0.83	0.36-1.00
Basu et al. ²	2014	26	3	0.33	0.01-0.91	0.88	0.70-0.98
Total		68	76				
Pooled estimate				0.80	0.66-0.91	0.93	0.86-0.97

Table 10. Diagnostic accuracy of combined bone and leukocyte scintigraphy for detection of periprosthetic knee infection

Study	Year	Disease +	-	Sensitivity	95% CI	Specificity	95% CI
Palestro et al. ³⁴	1991	6	18	0.67	0.23-0.96	0.78	0.53-0.94
Scher et al. ⁴¹	2000	17	23	0.88	0.64-0.99	0.78	0.56-0.93
van Acker et al. ⁵⁰	2000	5	15	1.00	0.41-1.00	0.93	0.68-1.00
Larikka et al. ²⁰	2001	8	22	1.00	0.56-1.00	0.82	0.60-0.95
Total		36	78				
Pooled estimate				0.87	0.71-0.96	0.82	0.72-0.90

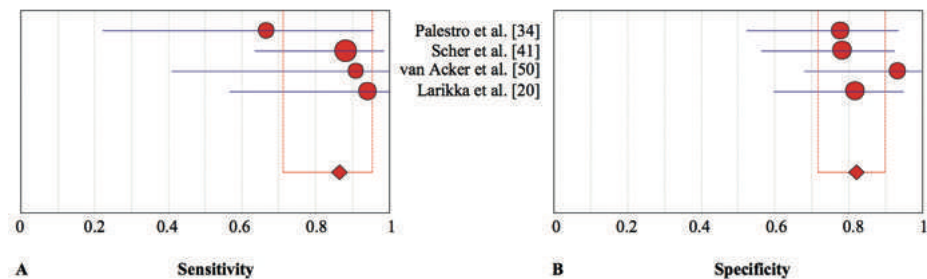
**Fig.6A–B** The pooled (A) sensitivity and (B) specificity of combined bone and leukocyte scintigraphy in the assessment of periprosthetic knee infection with 95% CIs are presented.

Table 11. Study characteristics of combined bone and leukocyte scintigraphy for detection of periprosthetic knee infection

Study	Tracer	Doses	Criteria for infection
Palestro et al. ³⁴	99mTc-MDP/111In-Oxine	740 MBq/18.5 MBq	If the distribution of periprosthetic activity on leukocyte images was spatially similar to the distribution of activity on bone images but relatively more intense or if the spatial distribution of the two traces was different (incongruent)
Scher et al. ⁴¹	99mTc-HDP/111In-Oxine	925 MBq/14.8-18.5 MBq	When indium scan showed hyperactivity in a different distribution (incongruency) or a relatively greater intensity than the activity on the Tc99 scan
van Acker et al. ⁵⁰	99mTc-MDP/ 9mTc-HMPAO	740 MBq/185 MBq	Lesions on WBC scan that were also found on the third phase of the bone scan
Larikka et al. ²⁰	99mTc-HDP/99mTc-HMPAO	550 MBq/370 MBq	When periprosthetic leukocyte uptake intensity was higher than that of the bone metabolic image in at least one zone, or if uptake was incongruent

Diagnostic odds ratio 23,869; heterogeneity chi-square = 2.90 (df = 3); p = 0.408; inconsistency (I²) = 0.0%; Tc99 m = 99 m-technetium; MDP = methylenediphosphonate; HDP = hydroxymethylenediphosphonate; 99Tc-HMPAO = hexamethylpropyleneamine oxime.

Table 12. Study characteristics of antigranulocyte scintigraphy for detection of periprosthetic knee infection

Study	Antibody type	99mTc doses	Criteria for infection
Ivancevic et al. ¹⁴	Sulesomab ²	< 1.1 GBq	Uptake higher than that in the bone marrow of the contralateral iliac crest
von Rothenburg et al. ⁵²	Sulesomab ²	15-25 mCi	When there was abnormal uptake greater than could be expected from a blood pool effect (Q)
Iyengar et al. ¹⁵	Sulesomab ²	650 MBq	Uptake in the ROI was greater than the uptake in the surrounding normal tissue or the contralateral side
Stumpe et al. ⁴⁴	Besilesomab ¹	NR	If the intensity of accumulation around the BPI exceeded physiological bone marrow uptake or if the intensity of radionuclide uptake increased from 4-24 hours
Rubello et al. ⁴⁰	Sulesomab ²	740 MBq	Dual interpretation (early and delayed): if the delayed Leukoscan imaging, the uptake increased by one step or more in comparison to the baseline (early Leukoscan)

Diagnostic odds ratio 84,598, heterogeneity chi-square = 4.70 (df = 4), p = 0.320, inconsistency (I²) = 14.9%; SQ = semiquantitative; Q = qualitative; ROI = region of interest; BPI = bone-prosthesis interface; 199mTc-anti-NCA 95; 299mTc-anti-NCA90.

Table 13. Diagnostic accuracy of antigranulocyte scintigraphy for detection of periprosthetic knee infection

Study	Year	Disease +	-	Sensitivity	95% CI	Specificity	95% CI
Ivancevic et al. ¹⁴	2002	2	3	1.00	0.12-1.00	0.67	0.10-0.99
von Rothenburg et al. ⁵²	2004	4	8	1.00	0.33-1.00	1.00	0.57-1.00
Iyengar et al. ¹⁵	2005	2	11	1.00	0.12-1.00	0.82	0.48-0.98
Stumpe et al. ⁴⁴	2006	3	25	0.67	0.10-0.99	1.00	0.83-1.00
Rubello et al. ⁴⁰	2008	41	37	0.93	0.80-0.99	1.00	0.88-1.00
Total		52	84				
Pooled estimate				0.90	0.78-0.96	0.95	0.88-0.98

Table 14. Diagnostic accuracy of fluorodeoxyglucose-positron emission tomography for detection of periprosthetic knee infection

Study	Year	Disease	-	Sensitivity	95% CI	Specificity	95% CI
		+					
van Acker et al. ⁵⁰	2001	6	15	1.00	0.47-1.00	0.73	0.45-0.92
Zhuang et al. ⁵⁶	2001	11	25	0.91	0.59-1.00	0.72	0.51-0.88
Love et al. ²¹	2004	11	8	0.27	0.06-0.61	1.00	0.57-1.00
Mayer-Wagner et al. ²³	2010	7	9	0.14	0.00-0.58	0.89	0.52-1.00
Basu et al. ²	2014	19	68	0.95	0.74-1.00	0.88	0.78-0.95
Total		54	125				
Pooled estimate				0.70	0.56-0.81	0.84	0.76-0.90

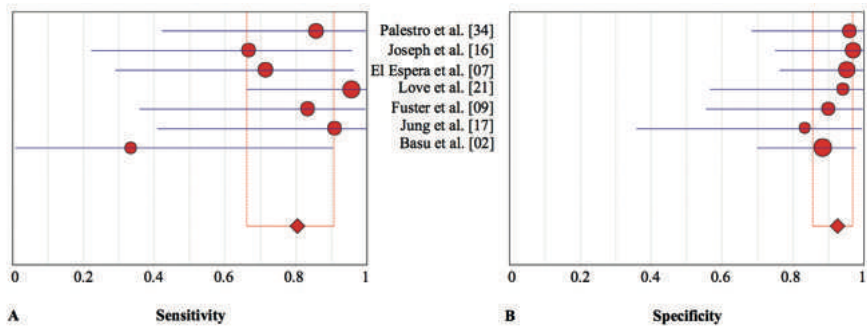


Fig. 7A–B The pooled (A) sensitivity and (B) specificity of combined leukocyte and bone marrow scintigraphy in the assessment of periprosthetic knee infection with 95% CIs are presented.

Table 15. Study characteristics of fluorodeoxyglucose positron emission tomography for detection of periprosthetic knee infection

Study	Tracer	Doses	Criteria for infection
van Acker et al. ⁵⁰	18F-FDG	3.7*Kg/8 MBq	Focal FDG uptake at the BPI
Zhuang et al. ⁵⁶	18F-FDG	4.22-4.56 MBq/kg	When an area of increased uptake was detected in the BPI, compared with adjacent soft tissue
Love et al. ²¹	18F-FDG	150-220MBq	Semiquantitative analysis of bone-prosthesis-interface (target-background ratio)
Mayer-Wagner et al. ²³	18F-FDG	180 MBq	Increased uptake at the distal BPI of the femoral shield and/or of the stem of the tibial prosthesis
Basu et al. ²	18F-FDG	0.14 mCi/kg	Only uptake in the BPI

Diagnostic odds ratio 19,083; heterogeneity chi-square = 6.92 (df = 4), p = 0.140, inconsistency (I²) = 42.2%; 18F-FDG = fluorodeoxyglucose (18F-FDG); BPI = bone-prosthesis interface.

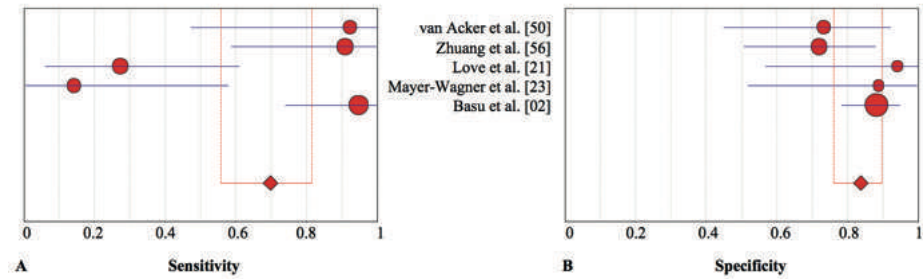


Fig. 8A–B The pooled (A) sensitivity and (B) specificity of FDG-PET in the assessment of periprosthetic knee infection with 95% CIs are shown. FDG-PET = fluorodeoxyglucose-positron emission tomography.

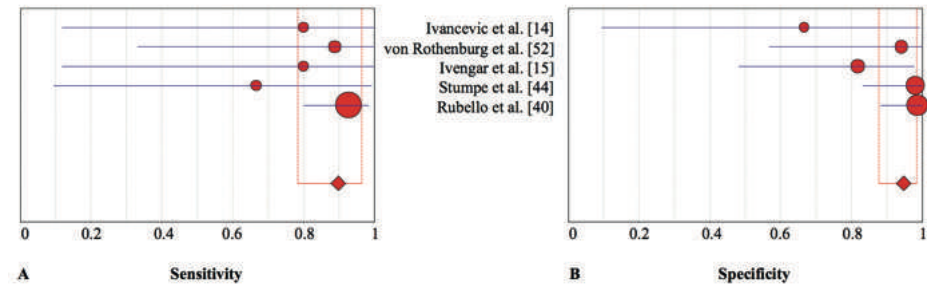


Fig. 9A–B The pooled (A) sensitivity and (B) specificity of antigranulocyte scintigraphy in the assessment of periprosthetic knee infection with 95% CIs are shown.

FDG-PET is increasingly used and has proposed potential in the diagnosis of PJI, especially regarding hip arthroplasty [10, 39, 51, 58]. Although this technique offers advantages such as time efficiency, increased resolution, and the use of low-dose CT, our results revealed that this technique was less specific in diagnosing periprosthetic knee infection than combined leukocyte and bone marrow scintigraphy and antigranulocyte scintigraphy (Fig. 7). Some investigations concluded that uptake patterns rather than intensity in the bone-prosthesis interface are specific in diagnosing periprosthetic infection (Table 15) [2, 56]. In particular, the sensitivity of 70% is only moderate (Fig. 8) and was lower than the sensitivity of leukocyte or anti-granulocyte scintigraphy (Fig. 9). However, our secondary analysis revealed that FDG-PET was highly sensitive (93%) when low-quality studies were excluded [21, 23], which is not less sensitive than the other imaging techniques evaluated. This should be considered further in well-designed studies. The specificity was not higher than that of combined leukocyte and bone marrow scintigraphy and antigranulocyte scintigraphy. An important drawback of FDG-PET is the high cost

compared with other imaging modalities. Therefore, FDG-PET may not be the preferred imaging modality in the evaluation of a suspected infected knee prosthesis.

This meta-analysis revealed that, based on current evidence, antigranulocyte scintigraphy and combined leukocyte and bone marrow scintigraphy were highly specific in confirming periprosthetic knee infection. However, the time-consuming procedures and limited availability are important drawbacks of these techniques. Bone scintigraphy was highly sensitive but lacks the specificity in differentiating between various conditions of painful knee prostheses. FDG-PET may not be the preferred imaging modality because it is more expensive and not more effective in confirming infected knee prostheses. In practice, other tests should be used in concert with the evaluated imaging modalities to arrive at more sensitive and specific diagnostic decisions than are possible with imaging or laboratory testing alone. Future, larger prospective studies should assess the utility of imaging in the diagnostic algorithm of a suspected periprosthetic knee infection, providing more data to evaluate important variables, including the differentiation between acute and chronic infections.

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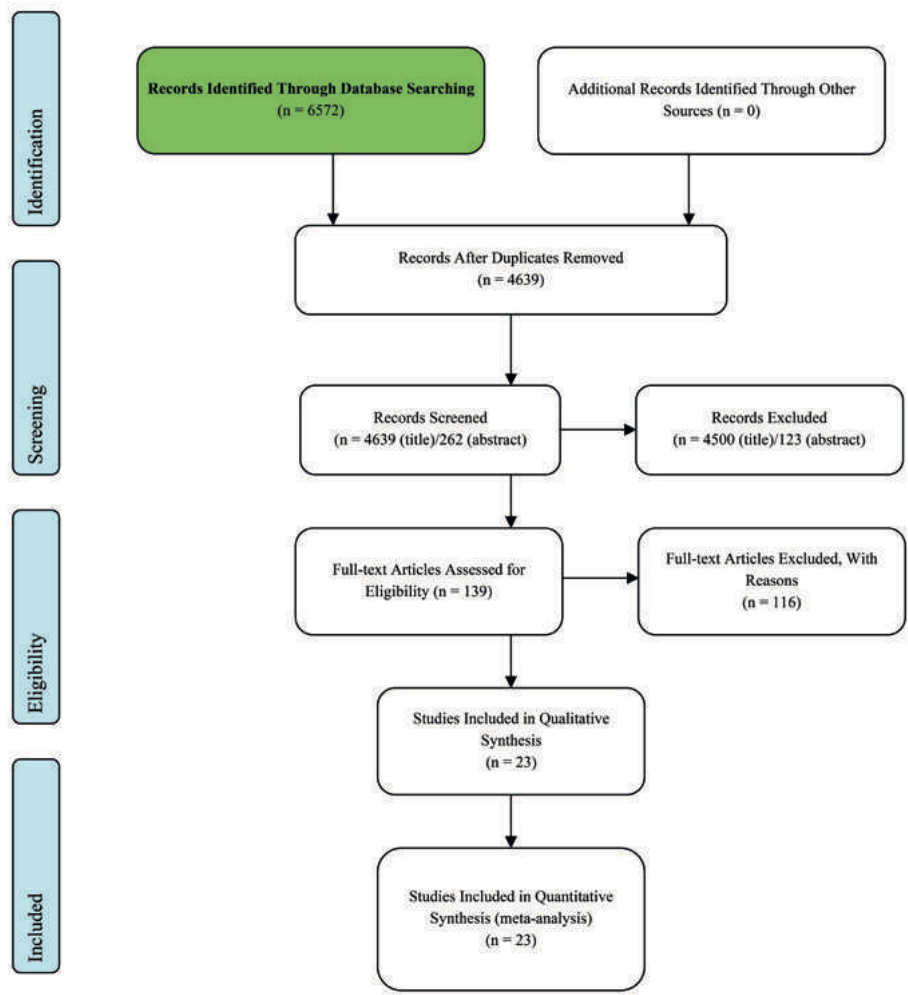
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Appendix 1 Search string used for identifying studies on diagnostic imaging in diagnosing periprosthetic knee infection.

MEDLINE (((((((((((("Infection"[Mesh]) OR "Biofilms"[Mesh]) OR "Bacterial Adhesion"[Mesh]) OR "Adhesins, Bacterial"[Mesh]) OR "Bacterial Infections"[Mesh])) OR infect*[tiab]) OR sepsi*[tiab]) OR septi*[tiab]) OR bacterie*[tiab]) OR bacteria*[tiab]) OR biofilm*[tiab]) OR (bacterem*[tiab] OR bacteraem*[tiab])) OR inflammat*[tiab])) AND ((((((("Knee"[Mesh] OR "Knee Joint"[Mesh]) OR "Femur"[Mesh]) OR "Tibia"[Mesh]) OR (knee[tiab]) OR (femur*[tiab]) OR (femoral[tiab]) OR (tibia*[tiab])))) AND (((((((((((("Prostheses and Implants"[Mesh:noexp]) OR "Joint Prosthesis"[Mesh:noexp]) OR "Knee Prosthesis"[Mesh]) OR "Metal-on-Metal Joint Prostheses"[Mesh]) OR "Prosthesis Implantation"[Mesh:noexp]) OR "Arthroplasty, Replacement"[Mesh:noexp])) OR prosth*[tiab]) OR implant*[tiab]) OR arthroplast*[tiab]) OR replac*[tiab])) OR metal-on-metal[tiab])) AND (((("Magnetic Resonance Imaging"[Mesh] OR ("magnetic resonance"[tiab] AND (image[tiab] OR images[tiab] OR imaging[tiab])) OR zeugmatograph*[tiab] OR MRI*[tiab] OR NMR*[tiab] OR Magnetization*[tiab] OR Magnetisation*[tiab] OR fMRI*[tiab] OR MR imag*[tiab])) OR (Magnetic Resonance Spectroscopy[Mesh] AND (chemical shift[tiab] AND imag*[tiab])))) OR (((("Tomography, X-Ray Computed"[Mesh]) OR (compute*[tiab] AND tomograph*[tiab])) OR (CT[tiab] OR CTs[tiab] OR CT's[tiab])) OR electron beam[tiab]) OR Tomodensitometr*[tiab])) OR (((((((((((("Radiography"[Mesh]) OR "radiography"[Subheading])) OR radiograph*[tiab]) OR x-ray*[tiab]) OR x-radiograph*[tiab]) OR xray*[tiab]) OR Zonograph*[tiab]) OR fluoroscop*[tiab]) OR arthrograph*[tiab]) OR roentgen*[tiab]) OR rontgen*[tiab])) OR image subtraction*[tiab]) OR (((((((("Radionuclide Imaging"[Mesh]) OR "radionuclide imaging"[Subheading]) OR "Radiopharmaceuticals"[Pharmacological Action])) OR (scintigraph*[tiab] OR scintiphotograph*[tiab])) OR (radionuclid*[tiab] OR radioisotop*[tiab])) OR Gamma Camera Imag*[tiab]) OR (indium[tiab] OR in-111[tiab] OR 111in*[tiab])) OR (99mtc[tiab] OR 99m[tiab]) OR scintiscan*[tiab])) OR (((((((("Positron-Emission Tomography"[Mesh]) OR "Tomography, Emission-Computed"[Mesh])) OR "Tomography"[Mesh:noexp])) OR PET[tiab]) OR tomograph*[tiab]) OR (((("Fluorodeoxyglucose F18"[Mesh]) OR "Deoxyglucose"[Mesh])) OR (deoxyglucose[tiab] OR deoxy-glucose[tiab] OR 2deoxyglucose[tiab])) OR (fluorin*[tiab] OR fluoro[tiab] OR fluorodeoxyglucose[tiab] OR 18F[tiab] OR 18FDG[tiab] OR F-18DG[tiab])))) OR (((("ultrasonography"[Subheading] OR "Ultrasonography"[Mesh])) OR ultraso*[tiab]) OR echograph*[tiab]) OR sonograph*[tiab]) OR echotomograph*[tiab] **EMBASE** 'radiography'/exp OR 'fluoroscopy'/exp OR 'xray'/exp OR 'image subtraction'/exp OR xradiograph*:ab,ti OR xray*:ab,ti OR zonograph*:ab,ti OR fluoroscop*:ab,ti OR arthrograph*:ab,ti OR roentgen*:ab,ti OR rontgen*:ab,ti OR (image NEAR/1 (subtraction OR subtractions)):ab,ti OR 'computer assisted tomography'/exp OR (compute*:ab,ti

AND tomograph*:ab,ti) OR 'emission tomography'/exp OR 'tomography'/de OR 'fluorodeoxyglucose f 18'/exp OR 'deoxyglucose'/exp OR pet:ab,ti OR tomograph*:ab,ti OR deoxyglucose:ab,ti OR 2deoxyglucose:ab,ti OR fluorin*:ab,ti OR fluoro:ab,ti OR fluorodeoxyglucose:ab,ti OR 18f:ab,ti OR 18fdg:ab,ti OR f18dg:ab,ti OR 'radioisotope diagnosis'/exp OR 'radiopharmaceutical agent'/exp OR 'radioisotope'/exp OR scintigraph*:ab,ti OR scintiphotograph*:ab,ti OR radionuclid*:ab,ti OR radioisotop*:ab,ti OR indium:ab,ti OR in111:ab,ti OR 111in*:ab,ti OR 99mtc:ab,ti OR 99m:ab,ti OR 'gamma camera image':ab,ti OR 'gamma camera images':ab,ti OR 'gamma camera imaging':ab,ti OR ultraso*:ab,ti OR echograph*:ab,ti OR sonograph*:ab,ti OR echotomograph*:ab,ti OR 'echography'/exp OR 'nuclear magnetic resonance imaging'/exp OR (magnetic AND resonance:ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti) OR zeugmatograph*:ab,ti OR mri*:ab,ti OR nmr*:ab,ti OR magnetization*:ab,ti OR magnetisation*:ab,ti OR fmri*:ab,ti OR mr AND imag*:ab,ti) AND ('knee prostheses' OR 'joint prostheses' OR 'prostheses' OR 'implantation' OR 'knee arthroplasties' OR prosth*:ab,ti OR implant*:ab,ti OR arthroplast*:ab,ti OR replac*:ab,ti OR 'metal on metal':ab,ti) AND (knee OR tibia OR 'femur'/exp OR knee:ab,ti OR femoral:ab,ti OR tibia*:ab,ti OR femur*:ab,ti) AND ('infection'/exp OR 'biofilm'/exp OR 'bacterium adherence'/exp OR 'adhesin'/exp OR (infect*:ab,ti OR sepsi*:ab,ti OR septi*:ab,ti OR bacterie*:ab,ti OR bacteria*:ab,ti OR biofilm*:ab,ti OR bacterem*:ab,ti AND orbacteraem*:ab,ti) OR inflammat*:ab,ti)

Appendix 2. PRISMA 2009 flow diagram



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Systematic review of the Literature on Reproducibility of Nuclear Imaging in the Assessment of Painful Hip- and Knee Replacements

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ABSTRACT

Background

Nuclear imaging is used in the evaluation of painful arthroplasties for diagnosing loosening or periprosthetic joint infection (PJI). The purpose of this systematic review is to depict the reproducibility of the various nuclear imaging modalities used in the assessment of painful hip- and knee arthroplasties.

Methods

A systematic review of the literature was conducted with a comprehensive search of MEDLINE to identify clinical studies investigating the intra- and interobserver agreement of nuclear imaging modalities in diagnosing PJI and mechanical loosening.

Results

A total of 3.000 studies, published between 2004 and 2020, were reviewed and 16 studies met the inclusion criteria. Quality assessment identified concerns with regard to the internal validity in approximately 40% of the included studies. A meta-analysis could not be performed because of insufficient available clinical data. The intra-observer agreement was poorly investigated. The included studies reported an interobserver agreement of “slight” to “excellent” for bone scintigraphy, “moderate” to “substantial” for leukocyte scintigraphy, “substantial” to “almost perfect” for combined leukocyte- and bone marrow scintigraphy and “fair” to “substantial” for antigranulocyte scintigraphy. Hybrid imaging with SPECT/CT and FDG-PET/CT demonstrated “substantial” and “almost perfect” interobserver agreement for symptomatic hip prostheses, respectively.

Conclusions

The reproducibility of nuclear imaging is underreported in clinical studies investigating painful knee- and hip arthroplasties. Moreover, the included studies demonstrated methodological concerns with a high risk of bias. The available evidence demonstrated a wide range of interobserver agreement using scintigraphy. Hybrid imaging with SPECT/CT and FDG-PET/CT may improve the accuracy of interpretation and reproducibility. However, literature provide limited data to support this assumption.

Keywords: Nuclear Imaging - Prosthetic Joint Infection - Reproducibility - Review - Painful Arthroplasties

INTRODUCTION

The incidence of complications after total hip- and knee replacements is low, but due to the increased frequency of implantations, complications are commonly encountered and require an appropriate diagnostic algorithm. Among the variety of complications (including heterotopic ossification, pseudotumor, inflammatory disorders, hardware failure, and foreign body granulomatosis causing osteolysis), the two major complications are mechanical (aseptic) loosening and periprosthetic joint infection (PJI). PJI is considered one of the most devastating prostheses-related complications. However, reliable differentiation between PJI and aseptic loosening is often difficult since both may be accompanied by similar symptoms.

Currently, there is no diagnostic algorithm and despite multiple diagnostic tests, diagnosing PJI and differentiation from mechanical loosening remains challenging. Although current guidelines do not recommend the routine use of nuclear imaging^{43, 101}, a variety of radionuclide imaging modalities can contribute to the evaluation of suspected PJI or loosening. These modalities include bone scintigraphy (BS), leukocyte scintigraphy (LS), antigranulocyte scintigraphy (AGS), fluorodeoxyglucose positron emission tomography (FDG-PET), single-photon emission computed tomography (SPECT) and combined techniques¹⁰²⁻¹⁰⁴. In the assessment of PJI of the hip, a meta-analysis reported pooled sensitivity and specificity of 80%-69%, respectively, for BS, 88%-92% for LS, 69%-96% for combined LS-Bone Marrow scintigraphy (LS-BMS), 84%-75% for AGS, and 86%-93% for FDG-PET/CT.¹⁰³ For PJI of the knee, the reported pooled sensitivity and specificity were 93%-56%, respectively, for BS, 88%-77% for LS, 80%-93% for LS-BMS, 90%-95% for AGS, and 70%-84% for FDG-PET/CT.¹⁰⁴ For aseptic loosening of hip arthroplasties, the reported pooled sensitivity and specificity were 85%-72%, respectively, for BS.¹⁰⁵ In one clinical study which investigated symptomatic hip arthroplasties with SPECT/CT, a sensitivity of 94% and a specificity of 100% was reported.¹⁰⁶ In the evaluation of aseptic loosening of knee arthroplasties, the reported range of sensitivity and specificity were 76%-100% and 33%-100%, respectively, for BS, 56%-100% and 56%-100% for FDG-PET/CT, 86%-100% and 63%-93% for SPECT/CT.¹⁰⁷

The reported diagnostic accuracies of the nuclear imaging modalities in the assessment of symptomatic arthroplasties reflects the agreement of the interpretation of the scan (index test) with the reference standard. However, understanding the variables which are of influence to the interpretation of a scan is important for the outcome of (false) positive or (false) negative results. These variables are related to several domains such as the index test, the reference standard and observer related factors. Important variables related to the subject (the painful arthroplasty) are the time interval between imaging and surgery, location and type of implant, and severity of the infection. For example, the interpretation of a low grade PJI could be more challenging for the observer and lead to more false

negative results compared to diagnosing an acute PJI. The type of imaging modality (index test), the performed imaging protocol, and the used diagnostic criteria could also affect the interpretation and outcome. For example, a variety of diagnostic criteria was reported for various nuclear imaging modalities which could lead to different diagnostic accuracy outcomes regarding the investigated imaging modality.^{103, 104} Finally, in the interpretation of the scans, the background of the observer such as the level of expertise and experience may also affect the diagnostic outcome. These factors could not only affect the reported diagnostic accuracy, but may also introduce variations in intra- and interobserver agreement. These variations are important and potential compromising factors for the reproducibility and therefore the clinical application of the imaging modalities in the assessment of symptomatic arthroplasties

The (statistical) reliability of an imaging modality is defined by the degree of agreement when different observers use the same imaging technique, classification and procedure to assess the same subject. Each of the nuclear imaging modalities is characterized by specific benefits and drawbacks in diagnosing PJI or aseptic loosening. For example, scintigraphy is potentially hampered by non-specific tracer uptake which could lead to unsatisfactory results of interobserver reliability. In literature, it has been suggested that the interpretation of nuclear imaging could be improved by more recently introduced hybrid techniques as SPECT/CT and PET/CT.^{76, 79} For other pathologies, including infectious bone diseases, the improved diagnostic accuracy and reproducibility of hybrid imaging has been well established.¹⁰⁸ However, in the assessment of symptomatic arthroplasties this improvement in terms of reproducibility has not been well defined in literature.

The level of reproducibility and variables that could influence the individual interpretation of images are not always clear and therefore a suitable subject for systematic literature investigation. To the best of our knowledge, no systematic review that investigated this topic has been published before. The objective of this study is to systematically review the reproducibility of currently used nuclear imaging modalities in the evaluation of symptomatic hip- and knee arthroplasties.

MATERIALS AND METHODS

Search Criteria

The imaging modalities that were reviewed for the assessment of painful arthroplasties were planar scintigraphy, PET, SPECT, and combined techniques.

Search Strategy

A computer-aided search of the PubMed databases was conducted in June 2019 and updated in April 2020. The search was restricted to primary studies that were written in English. For each database, a specific search strategy was developed (Fig. 1) with an

informatics specialist. Reference lists of the identified studies and relevant reviews were hand-searched for supplementary eligible studies. The search was performed according to the PRISMA guideline (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement ¹⁰⁹.

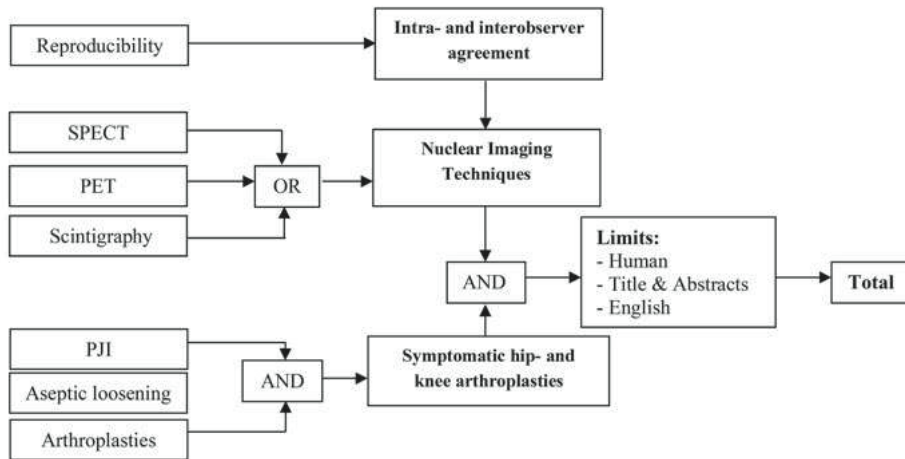


Fig. 1 Flowchart of the conducted search strategy.

CT = Computed Tomography, PET = Positron Emission Tomography, SPECT = Single-photon emission computed tomography, PJI = Prosthetic Joint Infection.

Study selection

The following inclusion criteria were used to identify eligible, clinical studies: (1) planar scintigraphy, SPECT or PET had been used to identify suspected PJI or loosening of hip- and/or knee arthroplasties. (2) The study used a valid reference standard for PJI (criteria by the Musculoskeletal Infection Society and/or the criteria of Infectious Diseases Society of America)^{24, 43} or aseptic loosening with preoperative findings (3) a clinical follow-up interval of at least 6 months when surgery was not performed. (3) The study reported the calculated intra- and interobserver agreement with multiple observers. Exclusion criteria were (1) nonhuman studies, (2) non-English language studies or (3) studies in which differentiation between osteomyelitis without arthroplasties and PJI was not possible. There was no restriction regarding the date of publication.

The titles were screened for eligibility by 1 reviewer (S.V.) and were then processed for abstract assessment. The titles and abstracts were independently screened and assessed for eligibility in an unblinded standardized manner by 2 reviewers (S.V. and J.K.) Studies considered to be of dubious eligibility were rejected. The final decision on inclusion was made on the basis of the full text of the article.

Methodological Quality Assessment

The criteria list of QUADAS2 for evaluating internal and external validity of diagnostic studies recommended by the Cochrane-Methods-Group-on-Systematic-Review-of Screening-and-Diagnostic-Tests was used for grading the methodological quality of the selected studies.¹¹⁰ Evaluation was performed by the two reviewers (S.V. and J.K.) independently. The internal and external validity were evaluated and the criteria of QUADAS2 were used for the determination of the methodological limitations for descriptive purposes. All studies that met the inclusion criteria were included and, a priori, no studies were excluded from the systematic review on the basis of quality. A quantitative analysis could not be performed due to insufficient available data.

RESULTS

Included Studies

The search strategy identified 2.994 studies from MEDLINE. There was no overlap found between the retrieved studies. No additional studies were identified through other sources. Of the initial 2.994 studies, 2.761 were excluded after analyzing the information provided in the title and abstract. The full articles of the remaining 233 studies were reviewed for eligibility. Six studies were extracted from the reference lists of these studies (n = 239). There was no disagreement between the reviewers regarding the definitive inclusion of the studies. The main reason for exclusion was the absence of intra- and interobserver agreement calculation in the use of imaging for diagnosing PJI or aseptic loosening (n = 179). Other reasons for exclusion were the absence of a valid reference standard (n = 5), no differentiation between osteomyelitis and periprosthetic complications (n = 3), or absence of symptomatic arthroplasties inclusion (n = 36). Meta-analysis was not performed due to insufficient available clinical data. In general, no differentiation a priori was made for the type of implant, the interpretation criteria used for the index test, or the time period between surgery and imaging.

Table 1: The measurement of observer agreement for categorical data

k < 0 reflects 'poor'
0 to 0.20 'slight'
0.21 to 0.4 'fair'
0.41 to 0.60 'moderate'
0.61 to 0.8 'substantial',
above 0.81 'almost perfect'

The measurement of observer agreement for categorical data(15) Icc correlation(16)

< 0.40	poor.
0.40 to 0.59	fair.
0.60 to 0.74	good.
0.75 to 1.00	excellent

Description of Study Characteristics

A total of 16 studies, published between 2004 and 2020, were included for systematic review. Two studies reported the interobserver agreement for nuclear imaging in the assessment of **aseptic** loosening of hip- and knee arthroplasties.^{111, 112} In 4 studies, the results of reproducibility were reported without differentiation between PJI and aseptic loosening using bone scintigraphy.^{106, 113-115} Of those studies, one reported the reproducibility of bone scintigraphy combined with SPECT/CT.¹⁰⁶ The intra- or interobserver agreement of nuclear imaging in the assessment of **PJI** was investigated by 10 studies. Of those studies, 2 studies used leukocyte scintigraphy^{66, 116}, 1 study used combined leukocyte- and bone scintigraphy⁵⁷, 3 studies used combined leukocyte- and bone marrow scintigraphy^{57, 58, 88}, 3 studies used anti-granulocyte scintigraphy^{64, 117, 118}, 1 study used combined anti-granulocyte- and bone marrow scintigraphy⁶⁴, and 3 studies used FDG-PET/CT.^{50, 119, 120} The characteristics of the studies are detailed in Table 2.

Qualitative Analysis

The external validity showed high concerns with regard to applicability to clinical practice in approximately 40% of the included studies for the domain “patient selection.” The internal validity of the included studies showed more concerns with regard to the risk of bias. Approximately 40% of the included studies did not provide sufficient information regarding the domains “index test” and “patient selection (Fig. 2).” More than 70% of the studies did not provide detailed data regarding the domain “flow and timing.” The details of the internal and external validity are shown in Figure 3.

Bone Scintigraphy and combined techniques

Of the 6 studies that investigated the use of bone scintigraphy, one study reported “excellent” (ICC = 0.89) intraobserver agreement of two observers in the assessment of the symptomatic hip.¹¹⁵ In the assessment of aseptic loosening of THA, a “fair”(ICC=0.43) and “good”(ICC=0.67) interobserver agreement was reported for the acetabular and femoral component, respectively.^{111, 112} No significant differences between the cemented and uncemented prostheses was found. In 4 studies, the reproducibility was reported without differentiation between PJI and aseptic loosening. For the symptomatic hip, two studies reported a kappa value for interobserver agreement of 0.11 (slight)⁵⁰ and an ICC of 0.81 (excellent).¹¹⁵ One study did not differentiate between hip- and knee replacements and

reported a kappa of 0.92, 0.81 and 0.80 for the blood flow, blood pool and bone phase, respectively (overall kappa was not reported).¹¹⁴ One study combined bone scintigraphy with SPECT and reported a “fair” ($\kappa = 0.27$) and “moderate” ($\kappa = 0.60$) interobserver agreement in the assessment of THA and TKA respectively.¹⁰⁶ The same study found a “moderate” ($\kappa = 0.58$) and “substantial” ($\kappa = 0.80$) interobserver agreement when bone scintigraphy was combined with SPECT/CT in the assessment of THA and TKA respectively.

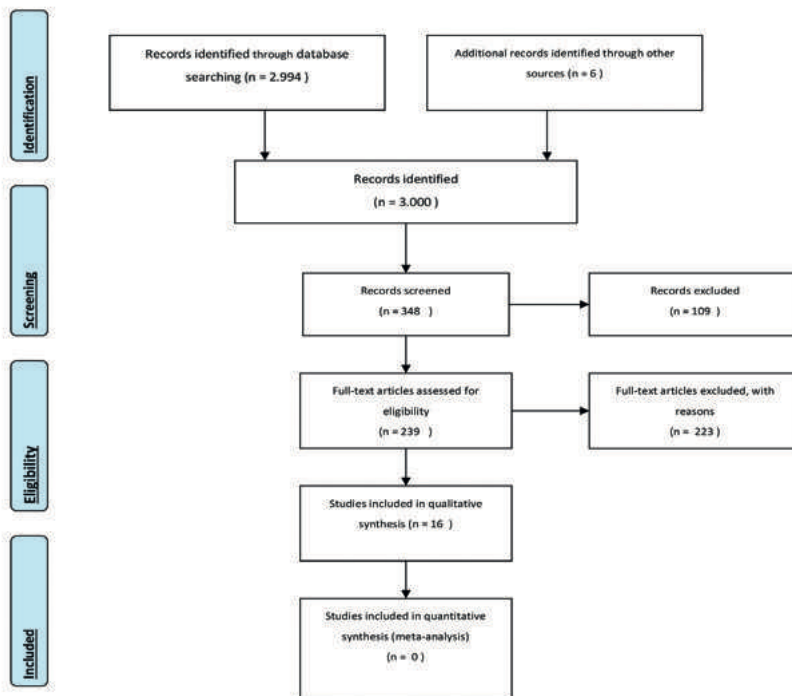


Fig 2. PRISMA 2009 flow diagram

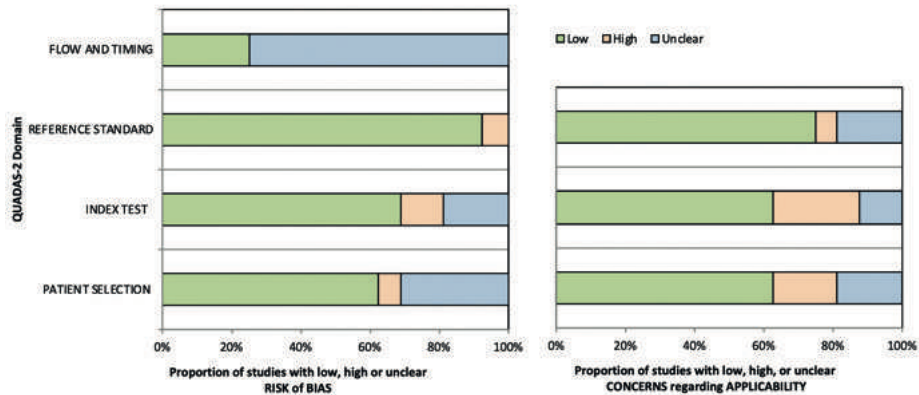


Fig. 3. QUADAS-2, risk bias and applicability

Leukocyte Scintigraphy and combined techniques

One study⁶⁶ reported the interobserver agreement of leukocyte scintigraphy in diagnosing PJI and reported "moderate" to "substantial" as a result of interpretation by three observers ($\kappa = 0.55, 0.60$ and 0.74). There was a no significant difference of concordance in 24% ($n=55$) and 33% ($n=40$) of the hip and knee group, respectively. Combined leukocyte- and bone marrow scintigraphy demonstrated in one study "almost perfect" interobserver agreement of three pairs of observers in the assessment of TKA and THA together.⁵⁷ For the assessment of hip arthroplasty, a kappa value of 0.74 (substantial) was reported by another study.⁵⁸ None of the 5 studies that investigated the use of leukocyte scintigraphy reported the intraobserver agreement.

Anti-granulocyte scintigraphy and combined techniques

The 3 studies^{64, 117, 118} that investigated the use of anti-granulocyte scintigraphy in the evaluation of PJI reported "excellent" interobserver agreement for TKA/UKA ($\kappa = > 0.75$), "fair to moderate" for THA/TKA together ($\kappa = 0.31 - 0.52$) and "fair to excellent" agreement depending on the grade of infection (mild to severe). One study⁶⁴ reported the anti-granulocyte scintigraphy combined with bone-marrow scintigraphy and reported kappa values of $0.55 - 0.72$ without differentiation between THA and TKA. None of the 3 studies reported the intraobserver agreement of anti-granulocyte scintigraphy in the assessment of PJI.

Table 2 Characteristics of the included studies

Study	Year	Design	No. of Patients	Patients Demographics (male/female)	Age (range)	Age (mean)	No. of Prostheses (resection arthroplasty/revision)	Prostheses	C/U	TAS	CFU
El Esper et al	2004	NR	60	NR	NR	NR	43 (30res)	26H, 17K	NR	mean 5.4y	NR
Pelosi et al	2004	RS	78	36 / 42	30y - 87y	70y	95	47H, 35K	NR	NR	> 1y
Stumpe et al	2004	PS	35	12 / 23	47y - 89y	71y	35(9rev)	35H	18C, 17U	71m (12-260mo)	> 6m
Temmerman et al*	2004	RS	73	19 / 54	34y - 54y	72y	83	73H	51C, 22U	NR	NR
Temmerman et al*	2006	RS	78	20 / 58	29y - 88y	70y	78	78H	55C, 23U	3m (1-10mo)	>1y
Fuster et al	2008	PS	70	28 / 42	55y - 81y	68y	70	70H	NR	46m	>1y
Gratz et al	2009	PS	26	9 / 17	49y - 85y	71y	26	26K	18C, 8U	>1y	> 6m
Fuster et al	2011	PS	40	14 / 26	56y - 76y	66y	40	21H, 16K, 3S	NR	mean 1.5y	>1y
Sousa et al	2011	PS	27	3 / 24	NR	65y (a)	27	2H, 25K	NR	mean 29.7y	>1y
Gratz et al	2012	PS	20	NR	60y - 76y	68y	20	6Uk, 14K	14C	31m (2-148mo)	>1y
Erba et al	2014	RS	235	104 / 131	16y - 93y	61y	132	H63, K66, S3	NR	NR	>6m
Arican et al*	2015	RS	50	15 / 35	41y-84y	63y	50	H20, 30K	NR	62m (3-120mo)	NR
Granados et al	2015	PS	120	50 / 70	60y - 82y	71y	120	H63, K57	NR	78m (2-154mo)	>1y
Yoldas et al	2016	RS	52	17 / 35	57y - 77y	66y/69y	52	52H	52U	>2y	NR
Kumar et al	2016	PS	42	25 / 17	23y - 76y	53y	42	42H	NR	1y - 7.6y	NR
Verberne et al	2018	RS	43	18 / 25	54y - 92y	76y	43(12rev)	43H	11C, 22U	47m(1m - 415m)	>1y
Total											

*Study investigated aseptic loosening, NR not reported, RS retrospective study design, PS prospective study design, (res) resection arthroplasty, (rev) revision, H hip arthroplasty, K knee arthroplasty, UKP unicompartment knee replacement, C cemented, U uncemented, S shoulder arthroplasty, CFU clinical follow-up

FDG-PET/CT

Of the 3 studies that investigated the use of PET/CT in the evaluation of PJI, two studies reported the interobserver agreement of the tracer ^{18}F -FDG. Stumpe et al reported "moderate" interobserver agreement with ($\kappa = 0.47$)¹¹³. Verberne et al reported for the interobserver agreement for 4 different criteria for PJI with kappa values ranging from 0.77 - 0.85.¹²⁰ One study reported "substantial" ($\kappa = 0.67$) interobserver agreement when ^{18}F -PET/CT was combined with ^{18}F Fluoride. None of the studies reported the intraobserver agreement for the use of PET/CT in the assessment of PJI.

DISCUSSION

Various nuclear imaging modalities can contribute in the challenging diagnosis and differentiation between PJI and mechanical loosening of hip- and knee replacements. The reproducibility of these imaging modalities is an important factor for the clinical usability and could concern a major limitation in the evaluation of symptomatic joint replacements and will be discussed in the section below.

Bone Scintigraphy and SPECT/CT

Bone scintigraphy is known as a highly sensitive imaging modality for diagnosing aseptic loosening. This modality is widely available and can exclude any form of loosening. $^{99\text{mTc}}$ -labeled bisphosphonates are the most commonly used radiopharmaceuticals to depict osteoblastic activity. In patients with mechanical loosening of the hip- or knee replacement, negative perfusion and blood pool but positive osseous phases are often interpreted as loosening. Throughout literature, one investigation group^{111, 112} reported the diagnostic accuracy of bone scintigraphy for the acetabulum and femoral component of THA and reported "fair" and "good" interobserver agreement, respectively. No substantial differences between cemented and uncemented prostheses were found. However, the results of these studies have not yet been confirmed by other studies. None of the included studies reported the reproducibility of bone scintigraphy for diagnosing mechanical loosening of TKA.

In the assessment of PJI, the increased osteoblastic activity on bone scintigraphy results in a highly sensitive modality. However, in the first years after implantation, specificity is dramatically lower and differentiation between infection and mechanical loosening (1-2 years for hip prostheses, 4-5 years after knee prostheses) is not accurate^{103, 104}. A bone scan is defined as positive for infection when there is uptake in all three phases (positive perfusion, blood pool and osseous phase), and this criterion was used by all four studies that investigated bone scintigraphy in the assessment of painful prostheses. However, a wide variety in the level of reproducibility was reported ("slight" to "almost perfect" interobserver agreement)^{50, 114, 115}. This wide range of observer agreement may be explained

by the low-resolution images of scintigraphy which could lead to unsatisfactorily results of interobserver reliability.

The introduction of hybrid imaging with SPECT/CT could improve diagnostic accuracy and reproducibility of the low-resolution scintigraphy. Adding only SPECT may not improve the reproducibility of bone scintigraphy alone¹⁰⁶. This may be the result of the missing CT portion, which results in less anatomical relation and therefore less accurate interpretation of the images. For other pathologies, it has been reported, that adding SPECT/CT to planar images results in higher diagnostic accuracy because of better resolution, direct (anatomic) correlation of functional and morphological abnormalities, and better distinguishing of bone infection from soft tissue infections through improved assessment of the extent of the infection.¹⁰⁸ A previous study showed that when SPECT/CT was added, interobserver agreement regarding the location of infectious foci increased from $\kappa = 0.68$ to $\kappa = 1.0$ in the assessment of osteomyelitis.¹⁰⁸ In agreement with the first clinical studies, 4 studies demonstrated "excellent" intra- and interobserver agreement when SPECT/CT was added in the interpretation of symptomatic hip- and knee arthroplasties.¹²¹⁻¹²⁴ However, these studies did not correlate the nuclear imaging results with surgical findings or clinical follow-up whether the prosthesis was loose or not. Because of this major methodological concern, no conclusions can be drawn regarding the clinical applicability and were therefore excluded from this review. In contrary to these studies, the one study that did correlate the SPECT/CT findings with a valid reference standard reported "moderate" to "substantial" agreement for the hip ($\kappa = 0.58$) and knee ($\kappa = 0.80$).¹⁰⁶ Unfortunately, these findings are not yet confirmed by other studies. Although it is plausible that adding SPECT/CT improves the reliability of the interpretation of scintigraphy in the assessment of symptomatic joint replacement, there is limited clinical data in literature to support this assumption. The clinical impact of SPECT/CT and its improvement in terms of reproducibility would be a suitable subject for further investigation in the field of symptomatic arthroplasties.

Leukocyte scintigraphy and combined techniques

Leukocyte scintigraphy has a long history in the evaluation of PJI as it can be used as a more specific imaging modality in order to differentiate between aseptic loosening and PJI. When the appropriate criteria are used, leukocyte scintigraphy may be an specific and accurate imaging modality for diagnosing PJI.^{103, 104} Only one study reported "moderate" to "substantial" interobserver agreement of three different pairs of readers ($\kappa = 0.55-0.74$). In 26 (27,4%) of the 95 investigated knee- and hip arthroplasties, there was no concordance between the three observers. There were differences in concordance between the hip (76%) and knee (67%) group; however, not significant. The diagnostic accuracy of leukocyte scintigraphy is potentially hampered by the fact that labeled leukocytes not only accumulate in infections but also accumulate physiologically in the bone marrow. In order to reduce the number of false-positive results, leukocyte scintigraphy is often combined

with bone marrow scintigraphy, which has been proposed as the imaging modality of choice for diagnosing PJI.¹²⁵ Besides the improved sensitivity and specificity compared to leukocyte scintigraphy alone, this combined technique demonstrated “substantial” to “almost perfect” interobserver agreement in two studies.^{57,58} An explanation for the good reproducibility of LS-BMS scans may lie in the fact that comparison of images improve interpretation, which was also found by Sousa et al.⁶⁴ It is important to note that different diagnostic accuracies were found between knee- and hip arthroplasties in previous studies.^{103, 104} The one study that investigated the reproducibility of THA alone reported “moderate” interobserver agreement,⁵⁸ while “almost perfect” concordance was found in another study with a combined hip- and knee group.⁵⁷ For further studies it is important to separately analyze the reproducibility of both arthroplasties.

Antigranulocyte scintigraphy and combined techniques

Antigranulocyte scintigraphy was introduced as an alternative for leukocyte scintigraphy with the advantage of in vivo-labeling of leukocytes and was proposed as a promising diagnostic tool for the detection of PJI. Image acquisition and interpretation are the same as for leukocyte scintigraphy. In recent meta-analyses, less satisfying diagnostic accuracies of antigranulocyte scintigraphy in the assessment of THA compared to TKA were found.^{103, 104} The included studies in this review did not report interobserver agreement in the assessment of THA alone. For TKA, a wide variety of kappa values between “fair” to “substantial” agreement ($\kappa = 0.31 - > 0.75$) was reported. Interestingly, for the combined knee- and hip group,⁶⁴ only “fair” to “moderate” interobserver agreement was found, while another study reported “excellent” reproducibility ($\kappa = > 0.75$) for TKA alone.¹¹⁸ Hence, one may suggest that variation in diagnostic accuracy outcomes between the knee- and hip arthroplasties also apply to the level of reproducibility since interpretation is less accurate for THA. However, there is no available evidence to support this assumption because symptomatic THA has not been separately analyzed. Another important result was found in a study that reported important differences between the interobserver agreement of mild PJI ($\kappa = 0.25$) versus severe PJI ($\kappa = > 0.75$).¹¹⁷ This could implicate that the degree of infection directly influences the interpretation and reproducibility of the antigranulocyte scintigraphy scan in the assessment of PJI of the knee. Unfortunately, none of the other included studies differentiated in the degree of infection. In accordance with combined leukocyte- and bone marrow scintigraphy, one study found higher levels of interobserver agreement for combined antigranulocyte scintigraphy and bone marrow scintigraphy compared to antigranulocyte scintigraphy alone.⁶⁴ This supports the conclusion that the combination of these imaging modalities may improve interpretation and reproducibility.

FDG-PET/CT

FDG-PET has assumed considerable potential in the assessment of periprosthetic infection. Important advantages of FDG-PET/CT, compared to planar scintigraphy, is its increased resolution, anatomic correlation with coregistered CT and availability of simple visual interpretation criteria of images. In the assessment of PJI of the hip, in contrary to PJI of the knee,¹⁰⁴ FDG-PET/CT is considered a promising imaging modality with assumed simple visual interpretation of uptake patterns. However, the visual interpretation of uptake patterns could potentially be hampered by interobserver variation in the interpretation of imaging. One of the first studies on clinical application of FDG-PET/CT stated that the simplicity of the diagnostic criteria should reduce potential interobserver variation and increase the accuracy of the scan.⁷⁶ Throughout literature, however, this has not been investigated in literature. Moreover, a variety of diagnostic criteria has been used. Based on the best available evidence it is assumed that extended uptake at the middle portion of the femoral bone-prosthesis-interface is the most accurate criterion for PJI.¹²⁰ This criterion demonstrated “almost perfect” interobserver agreement ($\kappa = 0.85$) in one study.¹²⁰ An alternative criterion, increased uptake along the bone-prosthesis interface compared to the physiological uptake in the bladder, demonstrated only “moderate” interobserver agreement.¹¹³ Unfortunately, the literature search revealed no additional clinical data to support these findings and more clinical investigation is needed in order to validate these results.

Limitations and concerns

This systematic review depicts an overview of the currently available literature on the reproducibility of the various nuclear imaging modalities in the assessment of painful arthroplasties. This review demonstrated that the level of evidence is hampered by serious limitations.

There are several concerns regarding the methodological quality of the included studies. Most studies investigated the diagnostic accuracy and intra- and interobserver agreement was not the main research question. Ideally, the degree of agreement is investigated between multiple and different observers using the same imaging technique, classification and procedure to assess the same subject. An important factor of influence to the reproducibility of the images is the level of experience of the observers. Interpretation of images by nuclear medicine physicians with or without experience in musculoskeletal imaging and the level of experience may directly influence the diagnostic accuracy. However, the level of experience and expertise was poorly or not described by 12 of the 16 included studies. Moreover, the number of observers is important to calculate the interobserver agreement properly and avoid the possibility of agreement occurring by chance. Only 5 of the 16 included studies reported the results of more than 2 readers (Table 3-10).

Table 3 Intra- and inter-observer agreement of bone scintigraphy in diagnosing symptomatic hip and knee replacements

Study	Year	Imaging	Tracer	Doses	Prostheses	Observers	Intra-OA	Inter-OA
Temmerman et al	2004	BS	^{99m} Tc-HDP	370 MBq	THA(a)	2*	-	ICC 0.43 (cemented 0.39, uncemented 0.53)
Stumpe et al	2004	BS	^{99m} Tc-DCP	700MBq	THA	2(1)	-	κ 0.11
Temmerman et al	2006	BS	^{99m} Tc-HDP	370 MBq	THA(f)	2*	-	ICC 0.67
Yoldas et al	2016	BS	^{99m} Tc-HMDP	NR	THA	2*	ICC 0.89	ICC 0.81
Granados et al	2015	BS	^{99m} Tc-HMDP	925MBq	THA/TKA	3*	-	κ 0.80 - 0.92
Arıcan et al	2015	BS-SPECT	^{99m} Tc-MDP	740 MBq	THA	2(2)	-	κ 0.27 (0.43 ¹⁾)
		BS-SPECT/CT	^{99m} Tc-MDP	740 MBq	THA	2(2)	-	κ 0.58 (0.72 ¹⁾)
		BS-SPECT	^{99m} Tc-MDP	740 MBq	TKA	2(2)	-	κ 0.60 (0.43 ¹⁾)
		BS-SPECT/CT	^{99m} Tc-MDP	740 MBq	TKA			κ 0.80 (0.72 ¹⁾)

BS bone scintigraphy, ^{99m} Tc-DCP, ^{99m} Tc dicarboxidiphosphonate. ^{99m} Tc-HDP, ^{99m} Tc hydroxydiphosphonate. ^{99m} Tc-HMDP, ^{99m} Tc hydroxymethylene diphosphonate. ^{99m} Tc-MDP, ^{99m} Tc methylene diphosphonate. THA total hip arthroplasty, TKA total knee arthroplasty. (a), acetabular component. (f), femoral component. ICC intra-class correlation coefficients (ICC). κ Kappa (1)(2)Two nuclear medicine physicians, > 5-year-experience. Two nuclear medicine physicians, level of experience not reported *Level of experience and expertise was not defined. OA observer agreement

Table 4 Bone scintigraphy in diagnosing symptomatic hip and knee replacements; index test, and reference standard

Study	Year	Imaging	Prostheses	Reference Standard	Criteria for PJI or aseptic loosening
Temmerman et al ¹	2004	BS	THA(a)	S	Acetabulum: a moderate increased uptake in > two zones or intense uptake in at least one zone (scale 0-5)
Stumpe et al ¹	2004	BS	THA	M, S	PJI: Focally or diffusely increased periprosthetic uptake in all three phases Loosening: Increased radionuclide uptake limited to the third phase
Temmerman et al ¹	2006	BS	THA(f)	S	Femoral: a mild or moderate increase in uptake of contrast in more than two zones or intense uptake in at least one zone
Granados et al ²	2015	BS	THA/TKA	M, H	Analyzing images of each phase (blood flow, blood pool and bone phase) of the BS independently, 2 categories (either positive or negative for periprosthetic infection) were considered. The GL was considered positive for infection when there was any extra-medullary periprosthetic uptake
Yoldas et al ³	2016	BS	THA	MSIS	increased uptake in all three phases
Arıcan et al ⁴	2015	BS-SPECT	THA	M, S	Focal or minimal linear increased periprosthetic and tip activity of prosthesis on all three phases of the planar bone scan and SPECT with a corresponding irregular periprosthetic radiolucency greater than 2 mm on CT
		BS-SPECT	TKA	M, S	Focal or minimal linear increased periprosthetic and tip activity of prosthesis on
		BS-SPECT/CT	TKA	M, S	all three phases of the planar bone scan and SPECT with a corresponding irregular periprosthetic radiolucency greater than 2 mm on CT

MSIS Musculoskeletal Infection Society for definitive diagnosing of periprosthetic infection. S surgery/intra operative findings. M = 2 or more positive peroperative samples that grew the same bacteria. H histopathology. 1 = 9/26 patients with PJI, 2 = 18/120 patients with PJI, 3 = 20/52 patients with PJI, 4 = number of PJI not reported

Table 5 The intra- and inter-observer agreement of leukocyte scintigraphy and combined techniques in diagnosing PJI

Study	Year	Imaging	Tracer	Doses	Prostheses	Observers	Intra-OA	Inter-OA
Pelosi et al	2004	LS	^{99m} Tc-HMPAO	740 MBq	THA / TKA	3(1)	NR	κ 0.55, 0.60, 0.74
Erba et al	2014	LS(SPECT)	^{99m} Tc-HMPAO	370–555 MBq	THA/TKA/TSA	2(1)	NR	DTC 11% and FT 19% disagreement ²
El Esper et al	2004	LS-BS	¹¹¹ In-oxine / ^{99m} Tc-HDP	185MBq/ 30MBq	THA / TKA	3(1)	NR	κ 0.40, 0.49, 0.55
El Esper et al	2004	LS-BMS	¹¹¹ In-oxine / ⁹⁹ Tc-SC ¹	185MBq/ 650MBq	THA / TKA	3(1)	NR	κ 0.95, 0.95, 1.00
Fuster et al	2008	LS-BMS	^{99m} Tc-HMPAO / ⁹⁹ Tc-SC ¹	185MBq / nr	THA	3*	NR	κ 0.74
Fuster et al	2011	LS-BMS/CFS	^{99m} Tc-HMPAO/ ^{99m} Tc-SC ¹ /CFS	370MBq	THA	3*	NR	κ 0.40
					TKA	3*	NR	κ 0.20

1 = ⁹⁹Tc-sulfur colloid, 2 = with lower agreement for hip and knee prosthesis (also OM and TSP) OA observer agreement, LS leukocyte scintigraphy, BMS bone marrow scintigraphy, CFS ciprofloxacin. ^{99m}Tc-DCP, ^{99m}Tc-dicarboxi-diphosphonate; ^{99m}Tc-HMPAO, ^{99m}Tc-hexamethylpropyleneamine oxime (1)*Three experienced nuclear medicine physicians, level of experience not reported. Level of experience and expertise was not defined

Table 6 Leukocyte scintigraphy and combined techniques in diagnosing symptomatic hip and knee replacements, index test, and reference standard

Study	Year	Imaging	Prostheses	Reference Standard (PJI)	Criteria
El Esper et al	2004	LS-BS	THA / TKA	M	Positive; when LS activity at the ROI exceeded that in the adjacent and contralateral region and corresponded to an area of increased bone tracer uptake. Negative; when no focal hyperactivity was identified on LS at the ROI
		LS-BMS	THA / TKA	M	Positive; when increased activity was observed on LS at the ROI without corresponding uptake on BMS (incongruent patterns). Negative; no increased activity on LS at the ROI or when the increased activity on LS was spatially congruent with an increased activity on BMS.
Pelosi et al	2004	LS	THA / TKA	M, S	QA Positive; positive when abnormal localized activity in the ROI in- creased in intensity or in extension in comparison with the contralateral region or with the ipsilateral adjacent bone segment. SQA Positive; When K increased with time (Klate > Kearly by at least 10%) any extramedullary periprosthetic focal uptake
Fuster et al	2008	LS-BMS	THA	M, H	NR
Fuster et al	2011	LS-BMS/CFS	THA / TKA/ TSA	M, P	at least one focus of abnormal uptake characterized by a time-dependent increase in radioactivity or an increase in size from the delayed to the late planar images (FT and DTC)
Erba et al	2014	LS(SPECT)	THA/ TKA/ TSA	M, H	
Total					

M = 2 or more positive peroperative samples that grew the same bacteria, ROI region of interest, QA qualitative analysis, SQA semiquantitative analysis, S surgery/peroperative findings, P macroscopic evidence of infection, H histopathology

Table 7 The intra- and inter-observer agreement of anti-granulocyte scintigraphy and combined techniques in diagnosing PJI

Study	Year	Imaging	Tracer	Doses	Prostheses	Observers	Intra-observer agreement	Inter-observer agreement
Gratz et al	2009	AGS	^{99m} Tc-monoclonal Fab' ¹	1110 ± 185 MBq	TKA	2(1)	NR	κ > 0.75, 0.49, 0.25 (severe-mild) ²
Sousa et al	2011	AGS	^{99m} Tc-sulesomab /	20 mCi	THA/TKA	3(2)	NR	κ 0.31, 0.50, 0.52 ³
		AGS-BMS	^{99m} Tc-rhenium sulfide colloid	20 mCi		3(2)	NR	κ 0.50, 0.55, 0.72 ³
Gratz et al	2012	AGS	^{99m} Tc-monoclonal Fab' ¹ /	555 – 925 MBq /	TKA/UKA	2(1)	NR	κ > 0.75
			^{99m} Tc-besilesomab ²	700 – 900 MBq			NR	

1 = ^{99m}Tc-sulesomab. 2 = ^{99m}Tc-besilesomab, 2 = qualitative/visual evaluation. 3 = inter-observer agreement between the three different pairs of readers (1) = two nuclear medicine physicians, > 5-year-experience. (2) = two nuclear medicine physicians, one orthopedic surgeon; level of experiences was not reported

Table 8 Anti-granulocyte scintigraphy and combined techniques in diagnosing symptomatic hip and knee replacements, index test, and reference standard

Study	Year	Imaging	Prostheses	Reference Standard (PJI)	Criteria
Gratz et al	2009	AGS	TKP	M, S, H	four-point scale as follows: 1, sulesomab uptake was similar to that in the bone marrow; 2, sulesomab uptake was increased minimally over that in bone marrow; 3, sulesomab uptake was distinctly higher than uptake in bone marrow; 4, sulesomab uptake was two or more times greater than uptake in bone marrow.
Sousa et al	2011	AGS-BMS	THP/TKP	M, H	activity on the sulesomab scan without corresponding activity on the bone marrow scan (the images are spatially incongruent). Any other pattern is negative for infection
Gratz et al	2012	AGS	TKP/UKP	M, S, H	1, uptake was similar to that in the bone marrow; 2, uptake was increased minimally over that in bone marrow; 3, uptake was distinctly higher than uptake in bone marrow; 4, uptake was two or more times greater than uptake in bone marrow
Total					

M intra-operative cultures, H intraoperative histological findings, S surgery/intra-operative findings

Table 9 Intra- and inter-observer agreement of FDG-PET/CT for diagnosing PJI

Study	Year	Imaging	Tracer	Doses	Prostheses	Observers	Intra-observer agreement	Inter-observer agreement
Stumpe et al	2004	FDG-PET/CT	¹⁸ F-FDG	300-400 MBq	THP	2(1)	NR	κ 0.47
Kumar et al	2016	FDG-PET/CT	¹⁸ F-FDG	0.14 mCi/Kg	THP	2*	NR	κ 0.67
		Fluoride-PET/CT	¹⁸ Fluoride	0.07 - 0.14 mCi/Kg				
Verberne et al	2018	FDG-PET/CT	¹⁸ F-FDG	156-351 MBq	THP	2(2)	NR	κ 0.85 ¹
						2(2)	NR	κ 0.81 ¹
						2(2)	NR	κ 0.77 ¹
						2(2)	NR	κ 0.79 ¹

1 = 4 different diagnostic criteria were investigated for inter-observer agreement, see Table 10 *Level of experience and expertise was not defined. (1) = two nuclear medicine physicians, >4-year-experience. (2) = one senior nuclear medicine physician, one nuclear medicine trainee, level of experience not reported

Table 10 FDG-PET/CT in diagnosing PJI, index test, and reference standard

Study	Year	Imaging	Prostheses	Reference Standard (PJI)	Criteria
Stumpe et al	2004	FDG-PET/CT	THP	M	Scale 0-5, uptake was low and comparable to that in inactive muscles and fat; a score of 2, that FDG uptake was moderate, clearly noticeable, and distinctly higher than the uptake in inactive muscles and fat; a score of 3, that FDG uptake was strong but was distinctly less than the physiologic uptake in the bladder; and a score of 4, that FDG uptake was very strong and was comparable to physiologic urinary uptake in the bladder
Kumar et al	2016	FDG/Fluoride-PET/CT	THP	H, M, S	one or more of any three criteria: (1) Periprosthetic FDG uptake around the femoral/ acetabular component along with FDG avid- associated periprosthetic soft tissue changes on CT images (2) Presence of sinus tract (3) Presence of regional lymph nodes or collection of pus.
Verberne et al	2018	FDG-PET/CT	THP	M, S, (MSIS)	(1) increased FDG uptake along the femoral bone-prosthesis-interface (2) Acetabulum uptake zone I - III (3) Periprosthetic uptake (4) Head zone (physiological)

M = 2 or more positive peroperative samples that grew the same bacteria, H histopathology, S surgery/peroperative findings, MSIS Musculoskeletal Infection Society for PJI

Recent meta-analyses demonstrated different diagnostic accuracies of nuclear imaging between hip- and knee arthroplasties. It is assumed that the interobserver agreement could vary between the location of the prostheses, due to different uptake patterns and physiology.^{103, 104, 115} In the interpretation of nuclear images, the type of implant (knee or hip) could be of influence to reproducibility, as demonstrated by several studies.^{64, 106, 118} Therefore, the reported reproducibility concerning both arthroplasties without differentiation of type and location should be interpreted with caution. Unfortunately, 5 of the included studies did not differentiate between hip- and knee arthroplasties. The degree of infection (chronic versus acute PJI) and the time between the implantation (last surgery) and performed imaging are also important factors in the interpretation of scans and were not described in most studies.

In the field of nuclear orthopedic imaging for painful prosthesis, concerns regarding the methodological quality and level of evidence has been previously been described¹²⁶. This systematic review depicts that the interpretation and reproducibility of nuclear imaging in the assessment of symptomatic joint replacements, an important aspect of clinical usability, has thus far been underreported. Moreover, it is important to note in general, that most studies reported the consensus results between two readers and therefore analyzing the intra- and interobserver agreement was not possible. Further investigation should report implant characteristics, time interval between imaging and surgery, degree of infection, and separately analyze hip- and knee arthroplasties.

Key points of the best available evidence according to this systematic review:

- Literature provide insufficient data regarding for intra-observer agreement when using nuclear imaging in the assessment of symptomatic joint replacements.
- Bone scintigraphy demonstrated a wide range of interobserver agreement.
- The comparison of images, as for combined leukocyte- and bone-marrow scintigraphy, could improve the level of interobserver agreement.
- The infection grade (mild versus severe) could directly influence the accuracy of interpretation.
- The interpretation and level of reproducibility for nuclear imaging could be different between hip- and knee arthroplasties.
- Although it is plausible that hybrid imaging improves interpretation for symptomatic joint replacements and could improve the level of interobserver agreement, there is limited data to support this assumption.
- The results of this systematic review should be interpreted with caution because of methodological concerns of the included studies with high risk of bias. Important variables that may influence the level of reproducibility as type of implant, time interval

between imaging and surgery, level of expertise of the observers, and degree of infection, were underreported.

- Further studies investigating the diagnostic performances of nuclear imaging in symptomatic orthopedic implants should report intra- and interobserver agreement and separately analyze hip- and knee arthroplasties.

Table 11 QUADAS-2, risk of bias

	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
El Esper et al	Unclear	Low	High	Unclear
Pelosi et al	Low	Low	Low	Unclear
Stumpe et al	Low	Low	Low	Low
Temmerman et al *	Low	Low	Low	Low
Temmerman et al *	Low	Low	Low	Unclear
Fuster et al	Low	Low	Low	Unclear
Gratz et al	Unclear	High	Low	Unclear
Fuster et al	Unclear	High	Low	Unclear
Sousa et al	Low	Low	Low	Unclear
Gratz et al	Low	Unclear	Low	Unclear
Erba et al	Unclear	Unclear	Low	Unclear
Arıcan et al *	Low	Low	Low	Unclear
Granados et al	Low	Low	Low	Low
Yoldas et al	Low	Unclear	Low	Unclear
Kumar et al	Low	Low	Low	Low
Verberne et al	Unclear	Low	Low	Unclear

*Study which investigated aseptic loosening

Table 12 QUADAS-2, applicability

	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
El Esper et al	Unclear	Low	High
Pelosi et al	Low	Low	Low
Stumpe et al	Low	Low	Low
Temmerman et al *	Low	Low	Low
Temmerman et al *	Low	Low	Low
Fuster et al	Low	Low	Low
Gratz et al	High	High	Low
Fuster et al	Low	High	Low
Sousa et al	Unclear	High	Low
Gratz et al	High	Unclear	Unclear
Erba et al	High	Unclear	Unclear
Arıcan et al *	Low	Low	Unclear
Granados et al	Low	Low	Low
Yoldas et al	Unclear	Low	Low
Kumar et al	Low	High	Low
Verberne et al	Low	Low	Low

*Study which investigated aseptic loosening

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Fluorodeoxyglucose Positron Emission Tomography Imaging for Diagnosing Periprosthetic Hip Infection: the Importance of Diagnostic Criteria

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ABSTRACT

Background

Fluorodeoxyglucose positron emission tomography (FDG-PET) is a novel method of assessing suspected periprosthetic hip infection. However, a heterogeneity of sensitivity and specificity using different diagnostic criteria across clinical studies has been published. The objective of this study is to evaluate the various diagnostic criteria using FDG-PET in diagnosing periprosthetic hip infection.

Methods

FDG-PET scans of patients suffering from painful hip prostheses between 2008 and 2015 were retrospectively reviewed. The PET images were considered positive for infection using five criteria: any increased uptake at the (1) bone-prosthesis-interface, (2) periprosthetic soft tissue (PST), or (3) both, (4) increased uptake in the bone-prosthesis-interface compared to the PST, and (5) increased uptake along the femoral bone-prosthesis-interface. The final diagnosis of infection was based on the pre-operative and intra-operative findings with clinical follow-up > 12 months.

Results

A total of 33 hip prostheses were evaluated in this study, of which 16 were determined to be infected and 17 uninfected. Any periprosthetic FDG uptake was found in all symptomatic prostheses (sensitivity 100%; specificity 0%). When increased uptake in the bone-prosthesis-interface (sensitivity 100%; specificity 65%) or PST (sensitivity 94%; specificity 59%) was considered infected, specificity increased. A higher intensity of uptake at the bone-prosthesis-interface than PST demonstrated only moderate specificity (sensitivity 44%; specificity 71%). The most specific criterion for infection was an increased FDG uptake along the femoral bone-prosthesis-interface (sensitivity 81%; specificity 94%).

Conclusions

Our results demonstrated that the accuracy of FDG-PET is highly dependent of the diagnostic criteria used for periprosthetic hip infection. Only an acceptable diagnostic accuracy (sensitivity 81%; specificity 94%) was found when increased FDG uptake along the femoral bone-prosthesis-interface was considered positive for infection.

Keywords Periprosthetic joint infection . Nuclear imaging . FDG-PET . Infected hip prosthesis . Positron-emission tomography . Infected hip arthroplasty . Prosthesis-related infections/diagnostic imaging . Prosthesis-related infections/microbiology

INTRODUCTION

Total hip arthroplasty is one of the most clinically successful and cost-effective surgical treatments of patients suffering from end stage hip disease, such as severe osteoarthritis, post-traumatic arthritis, developmental dysplasia, inflammatory arthritis, and osteonecrosis of the femoral head [1]. However, 10% of the treated patients eventually develop a significant painful hip prosthesis, the majority resulting from aseptic loosening [2]. Although less frequent, one of the most devastating complications is infection which can result in substantial morbidity and decline in functional outcome. Crucial for initiating the appropriate medical and surgical treatment is the timely identification and precise localization of a periprosthetic infection. A delay in diagnosing and treatment of a periprosthetic hip infection can have critical impact on loosening or maintaining the prosthesis and joint function.

Diagnosing periprosthetic hip infection, including a differentiation of mechanical loosening, remains challenging. The diagnostic algorithm is characterized by a multi-modality work-up including microbiologic, laboratory (elevated erythrocyte sedimentation rate [ESR], C reactive protein [CRP]), synovial marker, and histologic tests [3, 4]. In addition to these diagnostic tests, various imaging techniques including bone, leukocyte, bone marrow, antigranulocyte scintigraphy, and positron emission tomography (PET) can be used in the assessment of suspected periprosthetic infection, especially in the challenging diagnosis of a chronic or low-grade infection [5–7]. Currently, combined leukocyte and bone marrow scintigraphy is considered the preferred imaging modality in the evaluation of a suspected periprosthetic infection by most authors [8]. Although most studies indicate that this imaging technique is accurate, it is hampered by time-consuming procedures, technical difficulties, limited availability, and suboptimal spatial resolution. In recent literature, FDG-PET imaging has been proposed for detecting orthopaedic infections. This relative novel method of assessing periprosthetic infection has important advantages compared to combined leukocyte and bone marrow scintigraphy, such as increased resolution and time efficiency which results in a less inconvenient procedure for patients. Although most reports indicate that FDG- PET is highly accurate in the evaluation of infection associated with total hip arthroplasty, inconsistent results of diagnostic accuracy has been reported [7]. In literature, the sensitivity and specificity ranged between 33 and 95% and 62 and 96%, respectively. This heterogeneity may be explained by the use of different criteria in image interpretation for periprosthetic hip infection [7]. The present study was undertaken to evaluate the predefined diagnostic criteria in literature and determine the optimal criteria for diagnosing periprosthetic hip infection.

METHODS

Patient population

A cohort study was performed. The ICPC codes (International Classification of Primary Care) and operation codes were used to collect the patients with a painful hip prosthesis between 2008 and 2015 in two general teaching hospitals in the Netherlands. After this selection, all patients were screened whether FDG-PET imaging was used in the evaluation of symptomatic hip prostheses by the departments of orthopaedic surgery. The data were collected and these patients were allocated to the symptomatic group when the following inclusion criteria were met: (1) the diagnosis of the painful prosthesis was unclear before performing the FDG-PET imaging in the evaluation of infection; (2) the patients who underwent surgery were included when surgical exploration was performed within one year after performing the FDG-PET imaging; (3) a clinical follow-up of at least 12 months. Patients were excluded from this study if the imaging and clinical data were incomplete, such that retrospective analysis could not be performed. A priori, no differentiation was made regarding the stage of infection (acute or chronic), the sort of implant or the imaging time after surgery. When FDG-PET was not primarily used for the evaluation of symptomatic hip prosthesis or when patients had a bilateral, asymptomatic hip prosthesis, the data were also collected. These patients were allocated to the asymptomatic, control group. The study was performed according to the ethical and judicial guidelines of the Central Committee on Research Involving Human Subject (the Netherlands) and approved by the Ethical Committee.

Reference standard

The diagnosis of periprosthetic hip infection was based on one or more the following criteria: (1) a systemic infection with pain in the hip and purulent fluid within the joint and/or (2) a positive result on at least three tests (ESR, CRP, joint aspiration, and intra-operative culture) or (3) a sinus tract communicating with the joint [4]. A final diagnosis was given to each patient based on the interpretation of the clinical presentation and/or the pre-operative and intra-operative findings. For patients in which periprosthetic infection was excluded, the clinical follow-up was at least 12 months.

Imaging procedures

FDG-PET studies were performed with a Philips Gemini TF PET/CT scanner or a Siemens Biograph PET-CT 16 Truepoint. Patients fasted four hours prior to administering FDG. The images were obtained 60 minutes after the FDG injection of 156–351 MBq. Corrected and uncorrected transaxial images were acquired. Image reconstruction was performed with a multiplicative iterative reconstruction algorithm for improvement of image quality and reduction of computation time. Primarily, the PET images were used for the interpretation

of uptake patterns. The CT-portion, without a metal artifact reduction algorithm, was not used for the interpretation of periprosthetic soft tissue uptake.

Imaging interpretation

Two readers (one senior nuclear medicine physician and one nuclear medicine trainee) blinded to any clinical information, evaluated individual FDG studies. Each study was read once, and disagreement between the two observers was resolved with consensus. Any area of increased uptake was identified and the location of uptake was registered. The combination of non-attenuation and attenuation-correction images were used. The interpretation of images was generated using predefined criteria published in the literature. The femoral and acetabulum component of the hip prosthesis was divided into three zones (A, B, C and I, II, III, respectively) and the presence of FDG uptake in the bone-prosthesis-interface and soft tissue was documented (Fig. 1). The images were visual evaluated for infection using the following diagnostic criteria: (1) any increased uptake adjacent of the prosthesis [9, 10]; (2) uptake in the bone-prosthesis-interface (zone A–C, I–III) [10, 11]; (3) uptake in periprosthetic soft tissue [8]; (4) an increased uptake in the bone-prosthesis- interface compared to the periprosthetic soft tissue [12, 13]; and the (5) FDG uptake extending along the femoral bone-prosthesis-interface (zone B, Fig. 1), and involving more than one contiguous zone and not limited to only the femoral neck, head zone, or periprosthetic soft tissue [14–18] (Table 1).

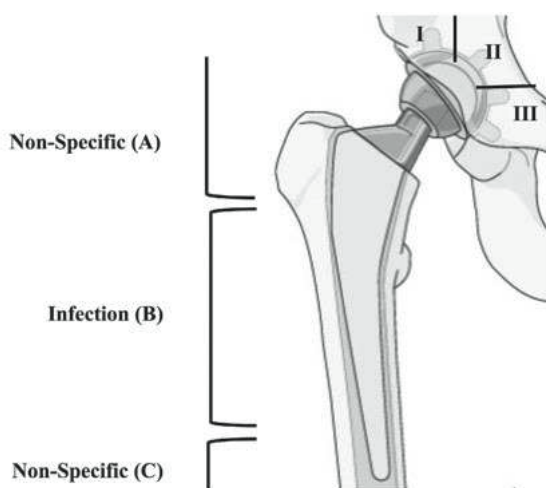


Fig. 1 Overview of the various regions that could demonstrate increased FDG uptake on FDG-PET imaging. An increased uptake in region A includes the femoral head and neck that could persist for years after implantation in both symptomatic and asymptomatic hip prostheses. An increased uptake or activity along the femoral bone-prosthesis-interface in region B is highly suggestive for infection. An increased uptake at the distal tip of the hip prosthesis in region C is not suggestive for infection (non-specific uptake)

Table 1 Literature overview of studies investigating the diagnostic accuracy of FDG-PET imaging in the assessment of periprosthetic hip infection

Study	Year	THP (infected)	Sn(%)	Sp(%)	Criteria for infection
Zhuang et al ¹⁶	2001	38(10)	90	89	Increased uptake in the BPI compared with adjacent soft tissue (increased uptake limited to an area around the femoral head or neck of the prosthesis but did not extend to the femoral shaft, loosening was considered likely)
Chacko et al ¹⁴	2002	41(12)	92	97	Increased FDG uptake at the BPI (FDG uptake in the soft tissue surrounding the prosthesis was considered negative for infection)
Vanquickenborne et al ¹⁹	2003	17(8)	88	78	Moderately or significantly higher uptake than contralateral distal femur
Love et al ¹⁹	2004	40(14)	100	0.1	Any periprosthetic activity, regardless of location or intensity
			52	44	Only activity in the BPI of the femoral component, regardless of intensity
Stumpe et al ¹⁹	2004	35(9)	43	96	Semi-Quantitative analysis of BPI activity in femoral with T/B ratio
Mumme et al ¹³	2005	70(46)	33	81	Diffusely increased uptake in BPI, less or comparable with bladder uptake
Reinartz et al ¹⁰	2005	92(33)	91	92	Increased uptake in the BPI and additionally in the PST
Pill et al ¹⁵	2006	92(21)	94	95	Uptake of FDG in the PST
			95	93	Abnormally increased FDG uptake at the BPI (uptake limited to the soft tissues or only adjacent to the neck of the prosthesis was not suggestive for infection)
García-Barrecheuren et al ¹²	2007	24(11)	64	62	FDG uptake in the BPI with intensity much higher than the synovial structures or adjacent soft tissues or fistulous tract uptake.
Chrysikos et al ¹⁷	2008	127(33)	85	93	Abnormally increased FDG uptake at the BPI (FDG uptake limited to the soft tissues adjacent to the neck of the prosthesis was not suggestive for infection)

Mayer-Wagner et al ¹¹	2010	15(8)	75	71	Increased uptake of FDG in the area of the BPI of the stem and/or acetabular cup was rated as pathologic process and according to its visual intensity regarded as loosening or infection (FDG uptake in the area of the femoral head, neck and at the end of the stem was judged as unspecific)
Basu et al ¹⁸	2014	134(33)	82	93	Increased FDG uptake at the BPI in the middle portion of the shaft of the hip prosthesis (FDG uptake limited to the soft tissues, synovium, or adjacent only to the neck of the prosthesis was considered negative for infection)

THP = Total Hip Prostheses, NR = not reported, AC = attention correction, NAC = non attenuation correction, Sn = Sensitivity, Sp = Specificity, BPI = Bone-Prosthesis Interface, T/B = target-to-background, PST = periprosthetic soft tissue

Analysis

The diagnosis of the FDG-PET studies, the consensus score, was compared to the reference standard in order to determine the sensitivity and specificity of the symptomatic group, with a 95% confidence interval (CI). The results were differentiated and analyzed regarding the stage of infection (acute or chronic), sort of implant, and time after surgery. The use of antibiotic treatment during FDG imaging was not analyzed, because it is assumed not to affect the sensitivity in delineating sites of infections, since uptake is independent of leukocyte migration. The Cohen's kappa (κ) coefficient was calculated in order to evaluate inter-observer reliability. Kappa's coefficient is a measure that adjusts for the agreement that is expected by chance and ranges between—1.0 and 1.0. Absolute agreement (100%) is represented with $\kappa = 1.0$ and $\kappa = 0.0$ is considered as random agreement. The interpretation of kappa coefficients was performed using the criteria of Landis and Koch and implies $\kappa = > 0.8$, $\kappa = 0.6–0.8$, $\kappa = 0.4–0.6$, $\kappa = 0.2–0.4$, and $\kappa = < 0.2$ as almost perfect, substantial, moderate, fair, and slight interobserver agreement, respectively [20]. Calculation was performed using computer calculated kappa statistics (Microsoft Office Excel 2007, Redmon, Washington USA) and the web-based statistical tool http://www.hslls.pitt.edu/medcalc/Kappa_MC.htm.

RESULTS

Inclusion

A total of 43 hip prostheses were included for evaluation (age ranges 54–92 years, mean 76.4 year). Of these patients, 33 prostheses were allocated to the symptomatic group. This group comprised 21 primary (15 uncemented, 6 cemented) and 12 revised hip prostheses (7 uncemented, 5 cemented). The main reason for implantation of the primary prostheses was osteoarthritis, while revision surgery was performed after mechanical loosening. The time between implantation and imaging ranged between one and 415 months (mean 47.0). Details of the patient characteristics, infection, and implants are detailed in Table 2. Of the symptomatic hip prostheses, 16 were determined to be infected. No sinus tract or open wound was found in this group. These patients demonstrated elevated CRP and/or ESR and no signs of loosening or infection on plain radiographs. Of the remaining 17 prostheses, infection was excluded based on either surgical and aspiration findings or clinical follow-up. A total of ten asymptomatic hip prostheses were used as control group. The reason for total hip arthroplasty in this group was osteoarthritis. All prostheses were primary implants (two were cemented, eight uncemented). The time between implantation and imaging was three to 108 months.

Evaluation of control group

Of the ten asymptomatic hip prostheses in the control group, eight prostheses demonstrated some uptake of FDG adjacent to the prosthesis (Tables 3 and 4). Uptake in

the head zone was found in eight cases. One hip prosthesis, implanted less than one year before imaging, demonstrated uptake in periprosthetic soft tissue adjacent to the femoral component. No increased uptake was found in the femoral bone-prosthesis-interface. The time after implantation ranged between three and 108 months (Table 2).

Uptake areas in the symptomatic group

The FDG-PET studies demonstrated any increased uptake (zone A, B, or C) at the bone-prosthesis-interface in all 16 infected cases (Table 4), located at the middle portion of the femoral component in 13 cases (zone B). Any uptake in the periprosthetic soft tissue was observed in 15 prostheses. Of the 17 uninfected hip prostheses, any uptake at the bone-prosthesis-interface was observed in six cases. Five of these six cases demonstrated (not extended) uptake involving zone A and/or zone C (Fig. 1), not considered to represent an increased uptake to zone B. In one case, there was increased uptake at zone B (Fig. 1). Uptake in the periprosthetic soft tissue around the femoral component was found in seven cases, all within one year after implantation. Without exception, uptake in the neck and head zone was observed in all symptomatic cases.

Comparison of diagnostic criteria

In the comparison of the different diagnostic criteria (Table 3), the most accurate interpretation was FDG uptake extending along the femoral bone-prosthesis-interface (zone B), not limited to only the femoral neck, head zone, or periprosthetic soft tissue (Fig. 2), with a sensitivity of 81% and specificity of 94%. Any FDG accumulation adjacent to the prosthesis resulted in a sensitivity of 100% and a specificity of 0%. Only uptake at the bone-prosthesis-interface demonstrated comparable sensitivity of 100% and higher specificity of 65%. A sensitivity of 94% and specificity of 59% was found when only uptake in the periprosthetic soft tissue was used as criterion for infection. When the diagnostic criterion was used that uptake of the bone-prosthesis-interface was relatively more than uptake in the periprosthetic soft tissue, sensitivity decreased to 44% and specificity increased to 71%.

Inter-observer agreement

The inter-observer agreement between the two readers demonstrated substantial to almost perfect agreement. In the interpretation of uptake in bone-prosthesis-interface zone B, disagreement was found in four of the 33 symptomatic hip prostheses, which resulted in an almost perfect inter-observer agreement ($\kappa = 0.85$). This disagreement was only found in four infected cases. In the acetabulum component, periprosthetic soft tissue and head zone uptake, inter-observer agreement was substantial to almost perfect ($\kappa = 0.81$, $\kappa = 0.77$, and $\kappa = 0.79$ respectively).

Table 2 Details of the included patients, diagnoses and FDG uptake in the symptomatic and control group

Study no.	Male/ Female	Age Patient	Implant	Age Patient Implant	TAI (months)	Diagnosis (MB)	CRP/ESR	Work-up	CFU (months)
1	F	76	P(c)	76	1	I.ac (S. Aureus)	+/+	X, USA, TPBS, S, H	16
2	F	92	P(c)	73	173	I.ch (S. Aureus)	+/+	X, USA, S, H	62
3	F	63	P(u)	26	415	I.ch (S. Epidermis)	+/+	X, USA, TPBS, S, H	21
4	M	54	R(c)	44	9	I.ch (S. Epidermis)	+/+	X, USA, MRI, S, H	48
5	F	90	P(c)	80	26	I.ch (S. Aureus)	+/+	X, TPBS, ART, S, H	97
6	M	77	P(u)	76	6	I.ch (S. Epidermis)	+/+	X, TPBS, ART, S, H	10
7	M	75	P(u)	63	41	I.ch (Neg. Staph.)	+/-	X, USA, TPBS, S, H	107
8	M	69	P(u)	66	3	I.ac (S. Aureus)	+/+	X, USA, ART, MRI, S, H	35
9	M	69	R(u)	66	0	I.ac (Prop. Acnes)	+/+	X, USA, TPBS, S, H	21
10	F	72	P(u)	61	61	I.ch (S. Aureus)	+/+	X, USA, S, H	70
11	F	72	P(u)	61	67	I.ch (S. Aureus)	+/+	X, USA, S, H	65
12	M	79	P(u)	76	1	I.ac (S. Aureus)	+/-	X, USA, S, H	28
13	M	74	P(u)	62	102	I.ch (S. Aureus)	+/+	X, USA, S, H	40
14	F	79	R(u)	70	3	I.ac (Hem. Strept.)	+/+	X, TPBS, ART, USA, S, H	71
15	F	79	P(u)	70	38	I.ch (Streptoc.)	+/+	X, USA, ART, TPBS, S, H	69
16	M	85	R(c)	83	10	I.ch (S. Epidermis)	+/+	X, USA	9
17	M	65	P(u)	57	52	NI	+/+	X, USA, S, H	41
18	F	88	R(u)	65	145	NI.OLF	-/+	X, TPBS	16
19	F	88	R(u)	66	33	NI. OLS	+/-	X, TPBS	16
20	F	78	R(u)	70	74	NI.AL(F)	+/-	X, TPBS	17
21	F	80	P(u)	78	10	NI	+/-	X, USA	14
22	M	76	R(u)	65	0	NI	+/+	X, USA, S, H	68
23	M	79	P(c)	64	145	NI.WC	+/-	X, USA, MRI	37
24	F	60	P(u)	54	29	NI	+/-	X, USA, MRI, TPBS	42

25	M	73	P(u)	69	9	NI,AL(F)	+/+	X, MRI, USA, S, H	37
26	F	75	R(c)	69	35	NI,AL(F)	+/+	X, TPBS, S, H	40
27	F	82	P(c)	78	10	NI	+/+	X, TPBS, USA	39
28	M	68	P(u)	61	22	NI	+/+	X, USA, S, H	52
29	F	74	R(u)	68	13	NI,AL(A)	+/-	X, USA	30
30	F	89	P(c)	87	11	NI	-/+	X, MRI, USA	12
31	F	83	R(c)	68	6	NI	+/+	X, USA, TPBS, S, H	59
32	M	79	R(c)	59	1	NI	+/-	X, USA	33
33	F	81	P(u)	80	3	NI,OM	+/+	X, MRI, USA	14
34	F	77	P(u)	69	36	C	-/-	CFU	65
35	F	79	P(u)	72	43	C	-/-	CFU	47
36	M	79	P(u)	70	77	C	-/-	CFU	29
37	F	60	P(u)	55	26	C	-/-	CFU	42
38	M	68	P(u)	55	99	C	-/-	CFU	52
39	F	79	P(c)	71	55	C	-/-	CFU	37
40	F	57	P(c)	48	74	C	-/-	CFU	26
41	F	63	P(u)	57	03	C	-/-	CFU	67
42	M	75	P(u)	60	76	C	-/-	CFU	107
43	M	54	P(u)	41	108	C	-/-	CFU	48

F female, M male, P primary implant, R revised implant, (u) uncemented, (c) cemented, TAI imaging time after implantation, I acute (ac) or chronic (ch) infection, NI no periprosthetic hip infection, WC wear of the cup, OL osteolysis proximal femur (F) or sacrum (S), AL aseptic loosening of the femoral (F) or acetabulum (A) component, OM osteomyelitis, MB microbiological cultures (organism), CFU clinical follow-up, X X-ray negative for septic loosening, USA (ultrasound guided) aspiration with negative results of culture or dry tap, TPBS triple-phase bone scintigraphy with inconclusive results, ART arthrography with no positive aspiration results, H negative histological results, CRP: - = < 10 mg/L, + = > 10 mg/L, ECRP: - = < 30 mm/h, + = > 30 mm/h

Table 3 Sensitivity and specificity of FDG-PET using different criteria for periprosthetic infection

Criteria	TP/FN (Sensitivity)	95-CI	TN/FP (Specificity)	95-CI
1) Any increased uptake adjacent to the prosthesis	16/0 (100%)	0.75 - 1.00	0/17 (0 %) [0%]	0.00 - 0.24
2) Any uptake in the BPI	16/0 (100%)	0.75 - 1.00	11/6 (65%) [78%]	0.38 - 0.86
3) Any uptake in the PST	15/1 (94%)	0.62 - 0.98	10/7 (59%) [70%]	0.28 - 0.77
4) Uptake in the BPI was more than uptake in the PST	7/9 (44%)	0.20 - 0.70	12/5 (71%) [77%]	0.44 - 0.90
5) Uptake in the BPI, not limited to the femoral neck, headzone or PST	13/3 (81%)	0.54 - 0.96	16/1 (94%) [96%]	0.72 - 1.00

Specificity calculated with the control group included (x) and excluded [x]. The criteria 1–5 are demonstrated in Fig. 2 BPI bone-prosthesis interface, PST periprosthetic soft tissue, 95-CI 95% confidence interval, TP true positive, FN false negative, TN true negative, FP false positive

DISCUSSION

In the evaluation of suspected periprosthetic hip infection, various diagnostic tests including blood laboratory tests, aspiration results and synovial fluid, and microbiologic and histopathological analysis can be used. However, inconsistent diagnostic accuracies with these various tests across studies have been published and accurate diagnosis of periprosthetic hip infection remains challenging, especially in chronic- or low-grade infections. Because of that, imaging tests remain important, and could contribute in the diagnosis. FDG-PET is a novel method of assessing suspected periprosthetic hip infection; however, a heterogeneity of sensitivity and specificity using different diagnostic criteria across clinical studies have been published [7]. The objective of this study was to evaluate the predefined diagnostic criteria when FDG-PET was used in the assessment of periprosthetic hip infection. Our results demonstrated that accumulation of FDG along the bone-prosthesis-interface, not limited to only the femoral neck, head zone, or periprosthetic soft tissue was the most accurate diagnostic criterion with a sensitivity of 81% and specificity of 94%.

FDG-PET has been successfully used the evaluation patients with both malignant and infectious disorders [21]. Subsequently, this imaging modality was introduced as potential useful tracer in detecting periprosthetic infections. Although differentiation between inflammatory uptake resulting from mechanical loosening and periprosthetic infection was presumed difficult [19, 22], the first clinical investigations demonstrated specific uptake pattern in infected hip prostheses. The visual interpretation of site and pattern of FDG uptake appeared more important and reliable than intensity of uptake, standardized uptake

values (SUV), in the region of interest. However, the sequential published investigations demonstrated heterogeneity in diagnostic accuracies across clinical studies, with sensitivity and specificity ranging between 33 and 95% and 62 and 96%, respectively (Table 1) [7]. A possible explanation for the heterogeneity may lie in the use of different diagnostic criteria for periprosthetic infection.

Various diagnostic criteria for infection were used in previous investigations (Table 1). When any periprosthetic uptake was considered as infection, Love et al. reported sensitivity of 100% and specificity of 0.1%, similarly to our results (Table 3) [19]. However, any uptake was also found in our control group, which illustrates the lack of efficacy of this criterion [12, 22]. Specificity increased when more specific uptake patterns were used as criterion for infection. Reinartz et al. evaluated exclusively the accuracy of uptake in the periprosthetic soft tissue, with a reported sensitivity of 94% and specificity of 95% [10]. Our results demonstrated similar sensitivity but lower specificity of 59%. When using the criterion of an increased uptake in the bone-prosthesis-interface compared to the periprosthetic soft tissue, Garcia et al. found a sensitivity of 64% and a specificity of 62% [12]. In our study, sensitivity was lower with 44% and specificity was more or less equivalent with 71%. The most specific criteria for diagnosing periprosthetic hip infection in previous studies was found to be an increased uptake along the bone-prosthesis- interface, not limited to only the femoral neck, head zone, or periprosthetic soft tissue (Fig. 1). Our results demonstrated a sensitivity of 81% and specificity of 94%, which is comparable with the pooled sensitivity of 86% and pooled specificity of 93% found in a recently performed meta-analysis [7].

When periprosthetic uptake of FDG is absent, a periprosthetic hip infection can be excluded (Table 3). However, in case uptake is observed, it is important to differentiate in uptake patterns, as mentioned above. The asymptomatic group showed non-specific uptake around the head and neck in 80% (Fig. 3), as described by previous reports [15, 23]. Similar to conventional tracers, the post-operative remodeling conditions after implantation results in non-infectious uptake patterns around the neck and/or head of the asymptomatic prosthesis for years after surgery. This non-specific postsurgical inflammation pattern does not affect the ability of FDG-PET to diagnose or exclude infection associated with total hip arthroplasty. It is assumed that the uptake at the femoral component provides a larger area that facilitates the possibility to differentiate between non-specific and infection uptake patterns. Uptake at the femoral component is not necessarily a sign of progression of infection from the acetabulum, area A or C. Therefore, in this setting, recognition of the commonly increased FDG uptake pattern (area A) is important and should not be interpreted as a finding suggestive of infection. In only one case, the interpretation of

uptake in the head and neck zone was different between the two readers, which resulted in a substantial inter-observer agreement ($\kappa = 0.79$).

In the evaluation of suspected periprosthetic infection, the diagnosis relies on a combination of clinical judgment, pre-operative hematologic testing, information obtained from aspiration, and microbiologic as well as histopathologic testing of tissue or fluid obtained at the time of surgery. Although important developments have been described [3], there is not yet a single gold standard diagnostic test for identification of a periprosthetic infection. It is not recommended to use nuclear imaging as isolated diagnostic; however, imaging can contribute in the challenging diagnosis of a periprosthetic infection [6, 7, 24]. In clinical practice, when there is a low suspicion of an infected hip implant, a highly sensitive imaging modality can rule out an infection. For this purpose, bone scintigraphy could be the preferred imaging modality because it is widely available with low costs. Unfortunately, this technique lacks the specificity needed to differentiate between various conditions causing periprosthetic uptake and is of limited use in the first post-operative years because of increased bone turnover after surgery. When prior diagnostic tests are inconclusive, especially in case of a low-grade or chronic infection (Fig. 2), including inconclusive periprosthetic uptake on a bone scan (Fig. 4), a more specific imaging modality can contribute in diagnosing infection. For this purpose, most authors reported that combined leukocyte and bone marrow scintigraphy is the preferred imaging modality [8]. However, a recent meta-analysis compared the diagnostic accuracies of all currently used imaging modalities in the assessment of periprosthetic hip infection and concluded that FDG-PET could potentially be used as preferred imaging modality [7]. Compared to combined bone marrow and leukocyte scintigraphy, FDG-PET has important advantages as time efficiency, increased resolution, and the use of low-dose computed tomography. However, in the setting of assessing periprosthetic infection, FDG-PET is often depicted as an expensive and complicated imaging modality, and therefore gained limited popularity in clinical daily practice. In the perspective of combined costs of multiple diagnostic tests including the use of conventional nuclear medicine methods, clinical investigating is needed to evaluate the cost-effectiveness and exact role of FDG-PET in the diagnostic algorithm of a periprosthetic infection. Our results demonstrated that, when the appropriate diagnostic criteria were used, this imaging modality could provide additional value in more complex clinical patients using relatively simple and visual interpretation.

Table 4 Details of the FDG uptake in the symptomatic and control group (x). Results of the consensus score after disagreement between readers 1 and 2

Study no.	Extended F.BPI ¹ (zone B) R1/R2 ²	BPI Zone A,C ³ R1/R2	Acetabulum Zone I,II,III ³ R1/R2	PST ⁴ R1/R2	Headzone R1/R2
Infected					
1	+/+(+)	A,C/A	-/(-)	+/+(+)	+/+(+)
2	-/+(-)	A,C/A,C	+/+(+)	+/+(+)	+/+(+)
3	+/+(+)	A,C/A,C	+/+(+)	+/+(+)	+/+(+)
4	+/+(+)	A,C/A,C	-/(-)	+/-(-)	+/+(+)
5	+/+(+)	A,C/A,C	+/+(+)	+/+(+)	+/+(+)
6	+/+(+)	A/A	+/+(+)	+/+(+)	+/+(+)
7	+/+(+)	A/A	+/+(+)	+/+(+)	+/+(+)
8	-/+(-)	A/A	-/(-)	+/+(+)	+/+(+)
9	+/+(+)	A/A	+/+(+)	+/+(+)	+/+(+)
10	+/+(+)	A,C/A,C	+/+(+)	+/+(+)	+/+(+)
11	-/(+)	A,C/A	+/+(+)	+/+(+)	+/+(+)
12	+/+(+)	A/-	-/(-)	+/+(+)	+/+(+)
13	+/+(+)	C/A,C	+/+(+)	+/+(+)	+/+(+)
14	-/+(-)	A,C/A,C	-/(-)	+/+(+)	+/+(+)
15	+/+(+)	A,C/A	+/-(+)	+/+(+)	+/+(+)
16	+/+(+)	A,C/A,C	+/+(+)	+/+(+)	+/+(+)
Non-Infected					
17	-/(-)	-/-	+/-(-)	-/(-)	+/+(+)
18	-/(-)	A/A	+/+(+)	-/(-)	+/+(+)
19	-/(-)	A/A	+/+(+)	-/(-)	+/+(+)
20	+/+(+)	A,C/A,C	-/(-)	-/(-)	+/+(+)
21	-/(-)	A/-	-/(-)	+/+(+)	+/+(+)
22	-/(-)	A/A	+/-(+)	+/+(+)	+/-(+)
23	-/(-)	A/A	+/+(+)	-/(-)	+/+(+)
24	-/(-)	-/-	-/(-)	-/(-)	+/+(+)
25	-/(-)	-/-	-/(-)	+/-(+)	+/+(+)
26	-/(-)	-/-	-/(-)	-/(-)	+/+(+)
27	-/(-)	-/-	-/(-)	+/+(+)	+/+(+)
28	-/(-)	-/-	-/(-)	-/(-)	+/+(+)
29	-/(-)	-/A	+/+(+)	+/+(+)	+/+(+)
30	-/(-)	-/-	-/(-)	+/+(+)	+/+(+)

Table 4 Continued

Study no.	Extended F.BPI ¹ (zone B) R1/R2 ²	BPI Zone A,C ³ R1/R2	Acetabulum Zone I,II,II ³ R1/R/2	PST ⁴ R1/R2	Headzone R1/R2
31	-/-(-)	-/-	-/-(-)	-/-(-)	+/+(+)
32	-/-(-)	-/-	+/-(+)	+/+(+)	+/+(+)
33	-/-(-)	C/A	+/+(+)	+/-(-)	+/+(+)
Control					
34	-/-(-)	-/-	-/-(-)	-/-(-)	+/+(+)
35	-/-(-)	-/-	-/-(-)	-/-(-)	-/-(-)
36	-/-(-)	-/-	-/-(-)	-/-(-)	+/-(+)
37	-/-(-)	-/-	-/-(-)	-/-(-)	+/+(+)
38	-/-(-)	-/-	-/-(-)	-/-(-)	+/+(+)
39	-/-(-)	-/-	+/+(+)	-/-(-)	+/+(+)
40	-/-(-)	-/-	-/-(-)	-/-(-)	-/-(-)
41	-/-(-)	-/-	-/-(-)	+/-(+)	+/+(+)
42	-/-(-)	-/-	-/-(-)	+/-(-)	+/+(+)
43	-/-(-)	-/-	-/-(-)	-/-(-)	+/+(+)
IOA	$\kappa = 0.85$		$\kappa = 0.81$	$\kappa = 0.77$	$\kappa = 0.79$

¹ F.BPI extended uptake at the middle portion of the femoral bone-prosthesis-interface (BPI), defined as zone B in 2 R1 reader 1, R2 reader 2. ³ Femoral zone A, B, C; acetabulum zone I, II, III = zones as defined in Fig. 1 ⁴ PST periprosthetic soft tissue. ⁵ IOA interobserver agreement, Cohen's kappa

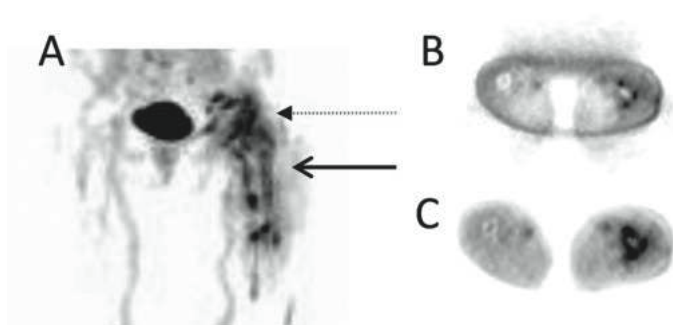


Fig. 2 Example of infection. This 84-year-old patient had left hip replacement 10 months previously. He suffered from increasing pain at the prosthesis. The laboratory blood tests showed elevated CRP and ESR. Clinical findings and prior diagnostic tests, including negative arthrography, did not demonstrate signs of loosening or infection. A variety of uptake patterns are demonstrated in the FDG-PET images. All the different criteria, as showed in Table 3, are positive in this example: (1) there is some increased uptake adjacent to the prosthesis; (2) there is increased uptake at the bone-prosthesis-interface of the femoral and acetabulum component; (3) any increased uptake in the periprosthetic soft tissue (dotted arrow); (4) uptake at the femoral bone- prosthesis-interface is more than the surrounding soft tissue; and (5) an increased FDG uptake along the bone-prosthesis-interface of the femoral shaft, not limited to the femoral head, neck of periprosthetic soft tissue. The arrow points at the region that reflects the most specific uptake pattern for infection. a PET coronal image; b PET transverse non- attenuation-correction image; c PET transverse attenuation-correction image. After FDG-PET imaging, cultures samples taken from the proximal and distal femur, grew *Staphylococcus epidermidis*

Our investigation is a blinded study that involves a sufficient cohort of patients; however, there are several limitations. (1) Based on routine practice with multiple diagnostic tests including laboratory tests, radiographs, and aspiration results, the diagnosis of infection was initially not clear in the symptomatic group before performing FDG-PET imaging. Subsequently, these symptomatic patients represent a group in which the diagnosis was more complex compared to patients with more obvious signs of infection. Therefore, our results should be interpreted with caution when applying to all patients with painful hip prostheses. (2) This study defined test performance of FDG-PET as an isolated diagnostic test. Because we performed a retrospectively study, the influence of FDG-PET on the diagnostic decisions in the algorithm could not properly be analyzed. It is important to note that this technique can be used in concert with other elements of other diagnostic tests to arrive at a more precise diagnosis than is possible with imaging testing alone. Further, prospective studies should investigate the exact role of FDG-PET in the multi-modality work-up of a periprosthetic infection. (3) Although we used stringent criteria for periprosthetic hip infection and we were convinced of the diagnosis, the universally lack of a golden standard could potentially distort some results due to a reference test bias [4]. For

obvious reasons, surgery with microbiologic evaluation was not performed in all patients with a painful hip prosthesis, and clinical follow-up sometimes had to be used as the method for the final diagnosis. Potentially, this could have resulted in more false-negative results. (5) Although we observed no influences of the stage of infection and time after surgery, more patient data and members are needed in order to analyze these variables properly. These variables are often insufficient described in published investigations. In our study, the majority of the included patients were not considered acute infections. The differentiation between acute and chronic infection is important because nuclear imaging is presumed more useful when there are less obvious signs of infection, which is more likely in chronic infections.

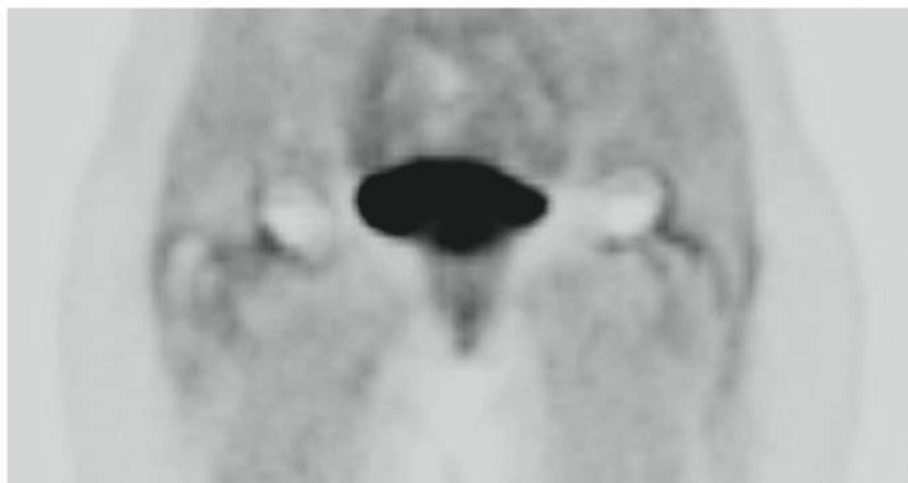


Fig. 3 Example of non-specific uptake. This 54-year-old patient had bilateral hip replacement. Total hip arthroplasty (uncemented) on the right side was performed 2 years before FDG-PET imaging. This prosthesis was not painful and asymptomatic. The FDG-PET image demonstrated non-specific uptake which is the result of postoperative remodeling. The (uncemented) hip replacement on the left side was performed 3 years before performing FDG-PET imaging. One year after implantation, the patient suffered from ongoing pain in the left hip region. The prior diagnostic tests, including radiographs, laboratory blood tests, aspiration results, and bone scintigraphy were inconclusive. FDG-PET imaging was performed to rule out a low-grade periprosthetic infection. The FDG-PET scan demonstrated a non-specific periprosthetic uptake pattern, not suggestive for infection

The most used classification systems defined periprosthetic joint infection either as acute or chronic, or as early (occurring within 3 months postoperatively), delayed (3–24 months), and late (> 24 months) [25]. Of the 33 included patients, only two patients developed symptoms within four weeks and three patients within three months after implantation (early infection). The remaining patients were considered chronic infection

and developed symptoms within three to 24 months (delayed) or after 24 months (late infection). Therefore, our results should be interpreted with caution when applying to patients with acute infected hip prostheses. (4) Furthermore, in our study, we defined the interobserver variability of the interpretation using FDG imaging, and a substantial to almost perfect inter-observer agreement was found. However, we only investigated two observers with a limited number of patients and disagreement between the two observers was found in four of the 16 infected cases. The diagnostic results in clinical practice could be potentially be hampered by a larger inter-observer variability. A larger number of patients and observers are needed to properly define the reproducibility of FDG imaging in the assessment of periprosthetic infection including the influences of experience of the observers and diversity of periprosthetic uptake patterns.

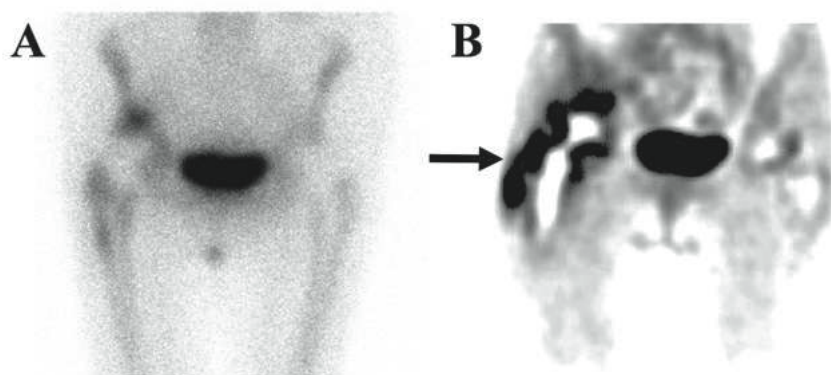


Fig. 4 Example of infection. Because of osteoarthritis, this 90-year-old patient underwent hip replacement in 2000 on the left side (cemented) and in 2005 on the right side (cemented). Two years after implantation of the right hip prosthesis, the patient complained about pain in the right hip region. Radiographs did not show any signs of loosening or infection. Laboratory blood results demonstrated elevated ESR. A triple-phase bone scintigraphy a was performed to rule out infection. However, periprosthetic uptake was found in all three phases, suggestive for infection. To confirm a chronic periprosthetic infection, FDG-PET imaging b was performed. The FDG-PET images demonstrated periprosthetic uptake in the lateral soft tissue region and an extended uptake at the femoral bone-prosthesis-interface, specific for infection on the right side. The arrow defines the extended uptake from zone A to zone B. The intraoperative findings and the culture samples separately taken from the distal femur, were positive for *Staphylococcus epidermidis*. The asymptomatic left prosthesis demonstrated uptake in the head and neck region, not specific for infection

In conclusion, FDG-PET can be used as a sensitive and specific imaging modality in diagnosing periprosthetic hip infection. Our results demonstrated that the accuracy of FDG-PET is highly dependent of the diagnostic criteria used for periprosthetic infection. Only an acceptable diagnostic accuracy was found using increased FDG uptake along

the femoral bone-prosthesis-interface, not limited to only the femoral neck, head zone, or periprosthetic soft tissue as a criterion for infection.

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**Reimplantation or Interval Prolongation? FDG-PET/
CT as a Tool to Identify Infection after Resection
Arthroplasty in Periprosthetic Hip Infection**

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ABSTRACT

Background

In the treatment of periprosthetic joint infection (PJI) of the hip, the diagnosis of infection eradication after resection arthroplasty is a crucial determinant before performing second-stage re-implantation. FDG-PET/CT could contribute in diagnosing complicating infectious foci and/or local eradication of infection, especially when CRP and ESR remain elevated. The aim of this study is to evaluate the usefulness of FDG-PET/CT in identifying patients in need of additional treatment or delayed re-implantation after resection arthroplasty.

Methods

From 2005-2015, the FDG-PET/CT scans of patients with persistently elevated CRP and/or ESR after resection arthroplasty for the treatment of hip PJI were retrospectively reviewed. The FDG-uptake patterns were analyzed to identify possible specific uptake patterns at the resection arthroplasty area. Secondary, the effect of the FDG-PET/CT findings on the two-stage revision management in terms of identifying patients in need of additional medical treatment or delayed re-implantation were reviewed.

Results

A total of 16 patients with 17 resection arthroplasties were included in this study. All patients demonstrated increased local FDG-uptake. Specific local FDG-uptake patterns that could suggest persistent infection at the resection area were not found. Additional foci that could cause persistent elevated ESR and CRP were found in 59% of the cases (n =10). The FDG-PET/CT findings resulted in additional medical treatment and/or altered re-implantation management in all included patients.

Conclusion

This study demonstrated that FDG-PET/CT is a feasible tool for identifying patients in need of additional treatment or delayed re-implantation after resection arthroplasty for the treatment of hip PJI. It can be reserved for patients with dilemmatic conditions and persistence of elevated CRP and/or ESR serum levels. FDG-PET/CT may not be the preferred imaging modality for diagnosing persistent infection at the local resection area.

Keywords:

Periprosthetic Infection - Periprosthetic Hip Infection - Infected Hip Arthroplasty - Two-stage-revision - Girdlestone - Resection Arthroplasty - Prosthesis Related Infection - FDG-PET/CT - Nuclear Imaging

INTRODUCTION

Failure of total hip replacement (THR) can result in resection arthroplasty as a result of the management of periprosthetic joint infection (PJI) ¹²⁷. Two-stage revision is generally considered the gold standard for treatment of PJI and involves removal of all associated components with radical debridement of all possible infected tissue and bone, followed by a long period of (intravenous) administration of anti-biotics. The reported rate of failure to eradicate infection after a two-stage revision is up to 30% ^{128, 129}. Moreover, the treatment of re-current infection after two-stage revision may have lower success rates than the first attempt in terms of infection recurrence and functional outcomes. Therefore, in cases of suspected residual infection after resection arthroplasty, the identification and localization of an infection is crucial for initiating the appropriate medical and/or surgical treatment. It can have critical impact on the discussion for re-implantation, and therefore on joint function and patient quality of life¹³⁰.

The interval time between resection arthroplasty and re-implantation can be used to evaluate for residual infection by clinical assessment and laboratory tests¹³¹. Currently, there is no metric available that can determine the optimal timing of re-implantation¹³². There is limited information available to the treating physician to determine if the infection has been successfully eradicated or controlled at the time of attempted re-implantation¹³³. A prerevision sedimentation rate (ESR) and C-reactive protein levels (CRP) are recommended, although persistently elevated ESR and CRP levels may not be accurate in predicting infection persistence after resection arthroplasty¹³³⁻¹³⁵. In selected cases, other diagnostic tests can be used to evaluate the eradication of infection. Some investigators advocate the use of joint aspiration, synovial fluid examination, and other serum markers. However, it is assumed that these tests are of inadequate diagnostic validity and cannot reliably detect or rule out infection ^{133, 135-137}. Imaging can be used in the assessment of persistent infection, including Computed tomography (CT), Magnetic Resonance Imaging (MRI) and ultrasound (US). Unfortunately, these imaging modalities are less suitable as screening methods, especially when clues for specific site of infection (additional than the resection site) are absent. In short, so far, no accurate test is available to evaluate infection persistence and the optimal re-implantation moment after resection arthroplasty. Fluorodeoxyglucose positron emission tomography (FDG-PET/CT) is increasingly used for detection of (orthopedic) infections ^{104, 138-144}. This sensitive imaging technique is suitable as a screening modality for complicating infectious foci ¹⁴⁵ and might be helpful in identifying patients in need of prolonged antibiotic treatment or delayed re-implantation.

To the best of our knowledge, no previous study investigated the use of FDG-PET/CT in the assessment of residual infection after resection arthroplasty and the timing of second-stage re-implantation. Therefore, the present study was undertaken to identify possible specific FDG-uptake patterns that could suggest persistent infection at the resection

arthroplasty area. Secondary, the FDG-PET/CT findings were evaluated for usefulness in identifying patients in need of additional treatment or delayed re-implantation after resection arthroplasty in the two-stage revision treatment of hip PJI.

METHODS

Patient population

A retrospective cohort study was performed. The ICPC codes (International Classification of Primary Care) and surgical codes were used to identify patients who underwent a resection arthroplasty of the hip between January 2008 and December 2015, in a general teaching hospital in the Netherlands. Patients who underwent resection arthroplasty for other reasons than PJI were excluded. Anti-biotic impregnated spacers were not used. After this selection, all patients were screened for use of FDG-PET/CT imaging in the evaluation of infection persistence by the departments of orthopedic surgery. Patients were included when the following criteria were met: 1) the diagnosis of periprosthetic hip infection was confirmed using the criteria of Parvizi et al ¹⁴⁶. 2) resection arthroplasty was performed in the context of two-stage revision management in the treatment of periprosthetic infection 3) there was persistently elevated ESR and/or CRP levels during the interval period before the attempted second-stage re-implantation. 3) FDG-PET/CT imaging was performed within one year after resection arthroplasty. 4) a follow-up of at least 12 months after FDG-PET/CT imaging was possible.

A priori, no differentiation was made regarding the implant or fixation type, micro-organism or acute or chronic PJI. Patients were excluded if imaging or clinical data were incomplete, and therefore no complete analysis could be performed.

Imaging procedures and interpretation

FDG-PET/CT studies were performed with a Philips Gemini TF PET/CT scanner or a Siemens Biograph PET-CT 16 Truepoint. Patients fasted 4 hours prior to administering FDG. The images were obtained 60 minutes after the FDG injection of 156-351 MBq. Corrected and uncorrected transaxial images were acquired. Image reconstruction was performed with a multiplicative iterative reconstruction algorithm for improvement of image quality and reduction of computation time. Primarily, the PET-images were used for the interpretation of uptake patterns. The CT portion was used to depict periprosthetic bone and soft-tissue abnormalities. The images were read by at least one senior nuclear medicine physician (WB). With exception of the date of surgery, the physician was blinded to any clinical information. Any area of increased uptake was identified and the location of uptake was registered. The region of interest (ROI), the resection arthroplasty area, was primarily visual evaluated for persistent infection in the former bone-prosthesis interface and surrounding soft tissue with registration of the maximum standardized uptake value (SUVmax). Literature

lacks criteria for the definition of persistent infection in the ROI, so no predefined criteria could be used. Secondly, the full body scans were analyzed for complicating infectious foci other than the ROI. A combination of non-attenuation and attenuation-correction images were used. The use of antibiotic treatment during FDG imaging was assumed not to affect the sensitivity in delineating sites of infections ⁷⁴.

RESULTS

Inclusion

A total of 16 patients were included for this study (age ranges 55 - 87 years, mean 77.9 year). Resection arthroplasty was performed in 17 hips (one patient underwent resection arthroplasty of both hips) because of PJI of the hip (Table 1). Patients underwent regular follow-up, and serum CRP and ESR levels were checked routinely. Patients were evaluated with FDG-PET/CT imaging because of persistent elevation of CRP (n=12) or increasing CRP (n=5) (mean 98 mg/L) after resection arthroplasty. No open sinus tract to the hip joint was found. All included patients had at least one underlying medical condition possibly affecting serum CRP and ESR levels. Patient characteristics and implants details are shown in Table 1. Causative micro-organisms were identified by cultures. The most common organism was *Staphylococcus epidermidis* (47%), followed by *Staphylococcus aureus* (41%) (Table 2). Hematogenous spreading of the micro-organism from a known source was found in 2 patients, both with *Staphylococcus aureus*. According to our protocol, systematic antibiotics were given in the interval period, specifically targeted to the causative micro-organisms. Additional antibiotic-loaded spacers were not used. The interval period between resection arthroplasty and re-implantation varied between 4 and 41 months.

Table 1: Subject Characteristics

	TOTAL [range]
Number of subjects	16
Male:Female (% male)	11:5 (69%)
Primary arthroplasty (% cemented)	9 (38%)
Revised arthroplasty (% cemented)	8 (75%)
Mean age at implantation (y)	67.41 [50 - 81]
Mean age at resection (y)	74.9[55 - 87]
ASA Classification	
	I 0
	II 1
	III 14
	IV-VI 1

Table 1: Continued

	TOTAL [range]
BMI	
BMI < 30 kg/m ²	8
BMI > 30 kg/m ²	8
Comorbidities	
Cardiovascular	7
Pulmonary	5
Diabetes Mellitus	4
Clinical follow-up (m)	38.4 [13 - 67]
Deceased (%)	5 (31%)

Table 2 Details of periprosthetic infection (PJI), FDG-PET/CT findings and re-implantation

	TOTAL [range]
PJI	
Occurrence of PJI after initial implantation (y)	3 [0.1 - 6]
Acute : Chronic (%)	6% : 94%
CRP (at resection)	128 [38 - 232]
ESR (at resection)	73 [34 - 176]
Culture	
<i>Staphylococcus epidermidis</i>	n = 8
<i>Staphylococcus aureus</i>	n = 7
<i>Enterococcus faecalis</i>	n = 2
Bacteremia (%) ²	13%
FDG-PET/CT	
Time after resection arthroplasty (w)	4.3 [4 - 44]
CRP (at FDG-PET/CT)	98 [10 - 398]
ESR (at FDG-PET/CT)	64 [13 - 125]
SUV max ROI	[2.0 - 8.6]
Increased uptake femoral bone	n = 13
Increased uptake acetabulum	n = 4
Increased uptake soft tissue	n = 7
Exclusion of other infectious foci	n = 10
RE-IMPLANTATION	
Number (success)	10 (7)
Negative cultures during re-implantation	10

FDG-PET/CT findings

FDG-PET/CT imaging was performed 1 to 11 months after resection arthroplasty (mean 4.8 months). All resection arthroplasties demonstrated local (ROI) increased uptake with a SUVmax that ranged between 2.8 - 8.6 (mean 4.7). An increased FDG-uptake in femoral bone, acetabulum and surrounding soft tissue was found in 13, 4, and 7 cases, respectively. The visual analyzation of the uptake patterns did not identify specific, distinctive increased uptake for infection persistence at the ROI that could differentiate between inflammatory processes or postsurgical uptake.

In 5 cases, the uptake at the ROI demonstrated increased SUVmax between 3.2 and 8.6 with an additional increased uptake at the surrounding soft tissue, including fluid and/or gas collections on the CT-portion. Extended FDG uptake along the femoral bone was found in 3 cases. The FDG-PET/CT findings in these 5 cases could be suggestive for persistent local infection (Fig. 1-3, Table 3). The time of imaging after surgery ranged between 1 and 6 months. In 3 of these patients the local infection could not be controlled and re-implantation was canceled (definitive resection arthroplasty). Re-implantation was performed in the 2 other cases after 11 and 12 months. Of these, one patient developed an acute re-current infection which was successfully treated with a debridement, antibiotics, irrigation and retention of the arthroplasty (DAIR protocol). There was no recurrent infection in the other patient.

Table 3: Details of the included patients, sort of implant, the diagnosis of PJI and FDG-PET/CT findings.

No.	Male/ Female	Age (1)	Implant	Culture	CRP/ESR (2)	Imaging TAR (m)	CRP/ESR (3)	FDG-PET/CT ROI [Uptake] [SUVm] [F] [ST]	FDG-PET/CT other foci	Interim Time	PJI recurrence	FU (m)
1	M	76(58)	P (u)/L	SE	232/176	1	170/124	1 4.5 + 2	arthritis	NS	X	13
2	F	87(85)	R (c)/R	SA	38/72	1	120/125	2 8.6 + 1	-	11m	+	15
3	M	56(54)	P (c)/L	SA	132/52	1.5	87/122	1 3.2 + 2	-	NS	X	15
4	M	55(50)	R (h)*/R	SE	83/34	10	31/13	1 4.2 + 0	abscess	15m	+	36 (†)
5	M	70(64)	P (u)/R	SE	130/120	4	10/23	1 3.9 + 0	-	6m	-	46
6	M	76(62)	P (u)/L	SA	99/110	6	67/82	1 2.0 + 0	prostatitis, THA right	41m	-	36(†)
		76(63)	P (u)/R	SA	104/106	5	14/24	2 5.0 + 0	prostatitis	20m	-	48(†)
7	M	80(68)	P (c)/L	SA	259/116	11	14/51	1 5.2 + 0	diverticulitis, pneumonia	4m	+	67
8	M	81(76)	P (c)/L	SA	46/46	1	224/72	1 3.3 0 0	spondylodiscitis	NS	X	63
9	F	85(80)	P (u)/L	SA	120/60	11	7/19	1 3.2 + 0	thyroiditis, esophagus ca.	NS	X	60(†)
10	M	69(60)	P (u)/R	SE	138/37	5.5	398/45	1 5.5 + 0	-	10m	-	62
11	F	77(59)	R (c)/R	SE	80/36	8	70/40	1 7.8 + 1	-	39m	-	84
12	M	78(76)	R (c)/R	EF	62/25	6	144/70	1 4.6 0 2	-	12m	-	12
13	M	84 (81)	R (h)/R	SE	244/103	1	130/80	1 2.8 0 0	OM	NS	X	14(†)
14	F	71 (65)	R (u)/R	EF	205/44	4	108/104	1 3.2 + 2	pneumonia, abscess	NS	X	24(†)
15	M	72 (68)	R (u)/R	SE	77/77	3	40/42	1 4.2 + 0	pneumonia	6m	-	32
16	F	84(77)	R (c)/R	SE	134/55	2	28/50	2 6.3 0 1	-	NS	X	25

(u) uncemented, (c) cemented, (h) hybrid, (1) age patient during implantation, P / R = primary or revision arthroplasty, R / L = left or right side, SE = *Staphylococcus epidermidis*, SA = *Staphylococcus aureus*, EF = *Enterococcus faecalis*, CRP/ESR (2) at resection arthroplasty, CRP/ESR (3) at FDG-PET/CT, TAR = Time After Resection Arthroplasty, ROI = Region of Interest, area of resection arthroplasty, uptake at ROI [0] no increased uptake, [1] moderate increased uptake [2] substantial increased uptake, SUVm = SUVmax, ST = uptake at the surrounding soft tissue, NS = second stage re-implantation is not performed, ca = carcinoma, OM = osteomyelitis of the foot, FU = follow-up, † = deceased during FU, m = months. In bold = FDG-PET/CT findings suggestive for infection.

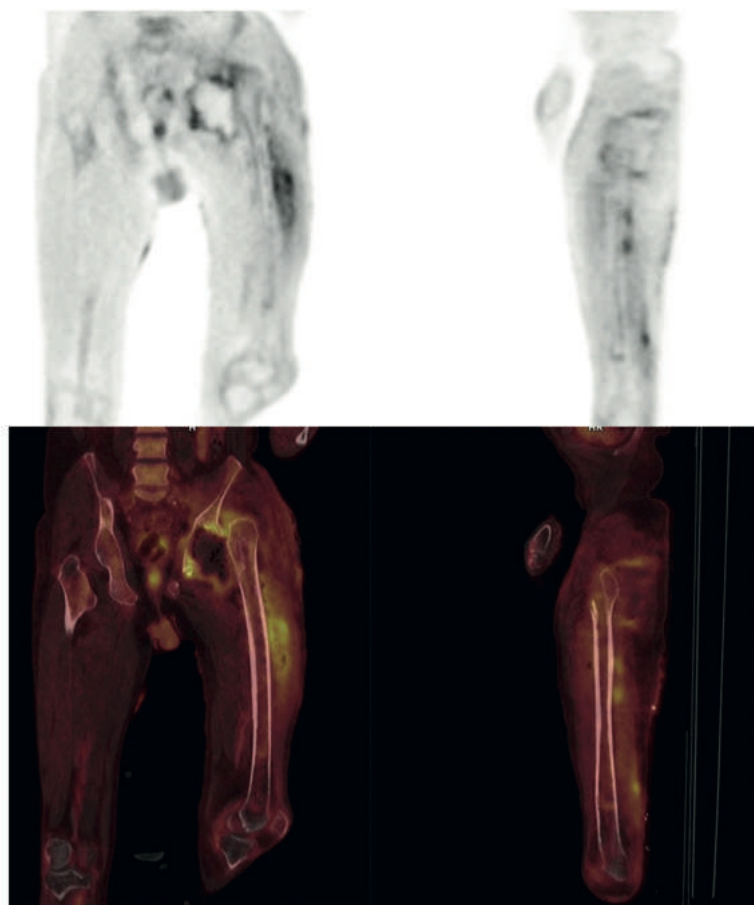


Figure 1: Example of FDG-PET/CT findings suggestive for infection persistence. This 87-year-old patient (Table 3, study number 2), ASA 3, had right cemented hip replacement 2 years previously. She underwent resection arthroplasty of hip PJI with *Staphylococcus aureus*. One months after this resection, FDG-PET/CT imaging was performed because CRP and ESR increased despite targeted antibiotic treatment. There were no clinical signs of infections. The FDG-PET/CT demonstrated increased uptake at the resection arthroplasty area with a SUVmax of 8.6. The FDG uptake was also increased along the surrounding soft tissue, femoral bone (SUVmax 2.1) and acetabulum (SUVmax 3.3). These findings were suggestive for infection persistence at the ROI without other infectious foci. The second stage-re-implantation was delayed because of these findings. The ROI was monitored with MRI and bone scintigraphy. After normalization of CRP and ESR and negative findings on MRI and bone scintigraphy, the THR was re-implanted after 11 months. Cultures samples taken from the proximal and distal femur were negative. Unfortunately, this patient was subject to acute infection recurrence and successfully treated with DAIR.

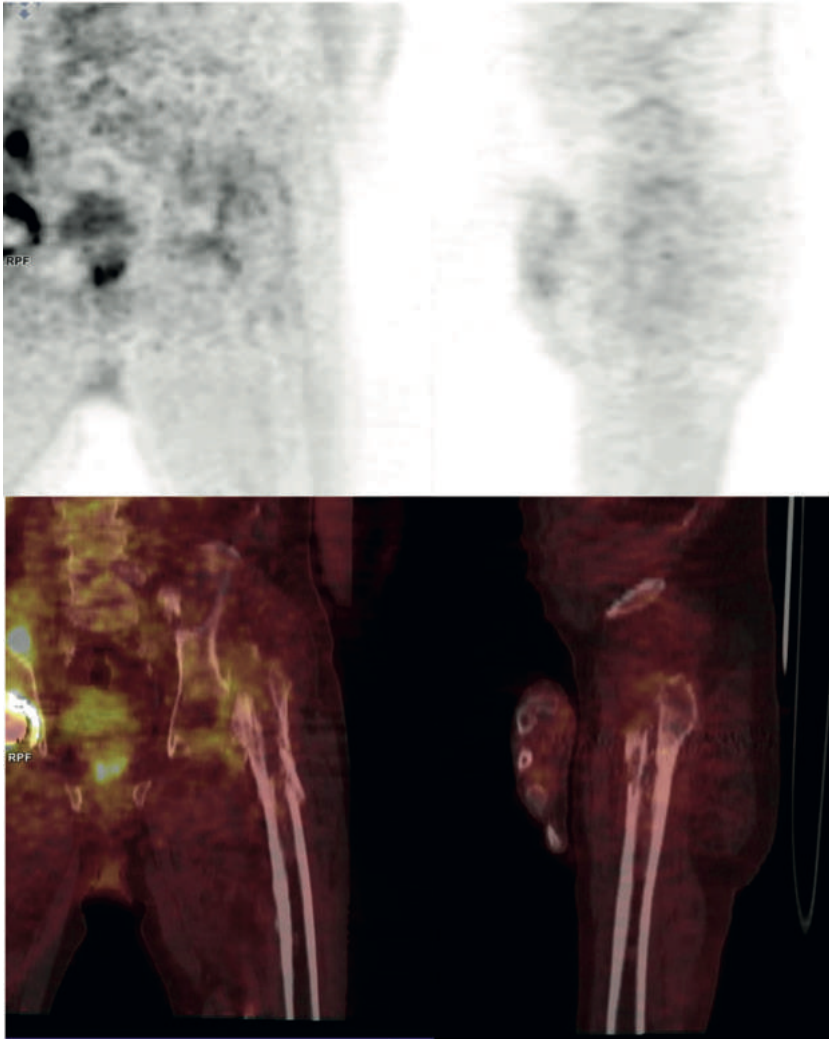


Figure 2: Example of FDG-PET/CT findings of other infectious foci than the ROI. This 76-year-old patient (Table 3, study number 6), ASA 3, had uncemented hip replacement of both sides 6 years previously. Six months after resection arthroplasty of the left hip replacement (*Staphylococcus aureus*), CRP and ESR remained elevated without clinical signs of infection. The FDG-PET/CT demonstrated increased FDG uptake at the ROI (SUVmax 2.0), femoral bone, and acetabulum. This increased uptake was not suggestive for infection persistence. However, there was periprosthetic uptake at the contra-lateral hip replacement suggestive for hip PJI that could explain the elevated CRP and ESR. Second stage re-implantation (cultures negative for growths) was delayed for 41 months because of treatment of the PJI at the contralateral side. There was no recurrence of periprosthetic infection on both sides. The patient deceased after 48 months follow-up, not caused by the PJI (carcinoma).

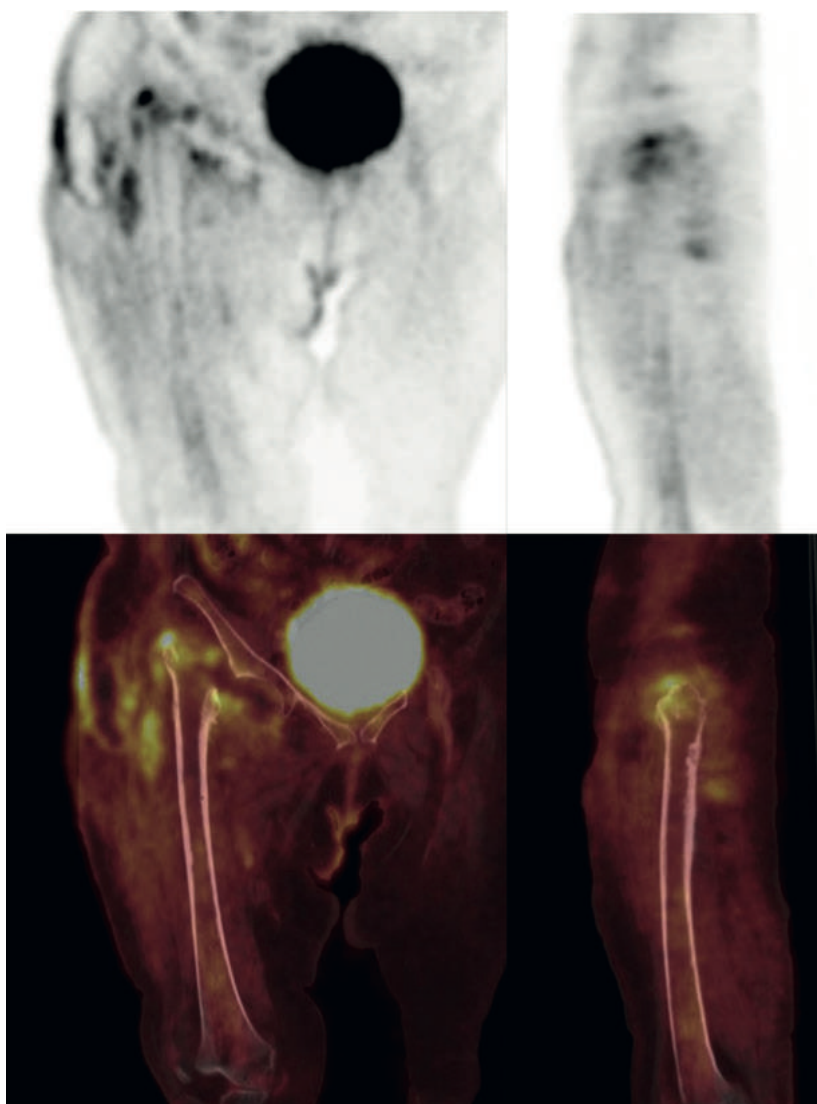


Figure 3: Example of FDG-PET/CT findings suggestive for infection persistence. This 78-year-old patient (Table 3, study number 12), ASA 3, had cemented right hip replacement 2 years previously. 6 months after resection arthroplasty because of periprosthetic infection with *Enterococcus faecalis*, FDG-PET/CT was performed. The CRP and ESR serum levels increased after targeted antibiotic treatment. There were no clinical signs of infection. FDG-PET/CT demonstrated increased uptake at the ROI and surrounding soft tissue, suggestive for infection persistence. No other infectious foci were found. The local area was monitored with bone scintigraphy and SPECT scans. After 6 months, re-implantation (culture sample were negative for growths) was successfully performed, without recurrence of infection.

In 12 patients, the SUVmax of local FDG-PET/CT findings ranged between 2.0 and 7.8. Only two of these cases demonstrated increased uptake and some fluid collections in the surrounding soft tissue, which was found not suggestive for infection. Increased uptake at the femoral bone and acetabulum was found in 10 and 2 patients, respectively. Of these patients, 8 of them underwent delayed re-implantation. Two of these patients were subject to recurrence of (acute) infection and treated successfully with the DAIR protocol. Re-implantation was canceled in 4 patients because of treatment for other medical conditions than the infection persistence at the ROI. The time between FDG-PET/CT imaging and resection arthroplasty ranged between 1 and 11 months.

Second stage re-implantation

Additional infectious foci, other than the ROI, that could explain the elevated CRP and ESR serum levels were found in 10 patients. The second-stage re-implantation was delayed in these patients because of additional treatment for infection persistence at the resection area ($n = 5$) or treatment for other infectious foci including diverticulitis, pneumonia, prostatitis, and (contralateral) periprosthetic infection ($n = 5$). Re-implantation was performed 4 to 41 months after resection arthroplasty. At the time of re-implantation, histology was negative for infection, and tissue cultures showed no bacterial growths ($n=10$). After re-implantation, 3 patients were subject to infection recurrence (or persistence), all successfully treated with DAIR. The re-implantation was canceled in 7 patients because of infection persistence that could not be controlled ($n = 4$) or complicating comorbidities such as multiple arthritis ($n = 1$), spondylodiscitis ($n=1$) and carcinoma with limited life expectancy ($n = 1$). Because of these complicating comorbidities, 3 patients deceased during follow-up. In the re-implantation group, 2 patients deceased because of other reasons than the consequences of PJI. The mean follow-up period was 38.4 months (range 12 - 67 months).

DISCUSSION

The diagnoses of infection persistence or recurrence after resection arthroplasty following antibiotic treatment remains complex. Various diagnostic tests including serum markers, and synovial fluid testing can be used. However, some studies demonstrated that these parameters are not accurate markers for confirming or ruling out infection persistence after resection arthroplasty^{133-135,137}. Although not recommended in current guidelines¹³¹, FDG-PET/CT could be useful as a sensitive imaging technique suitable for detection of infectious foci, especially in patients with other underlying medical conditions. The results of this study demonstrated that FDG-PET/CT is useful in identifying patients in need of additional treatment and thus can contribute in the difficult decision for (delayed) re-implantation if CRP and ESR levels remain elevated. However, a specific uptake pattern at the resection area that could identify infection was not found.

There is limited information available to the treating physician to determine if the infection has been successfully eradicated at the time of attempted re-implantation. The most commonly used indicators include clinical signs (e.g., decrease in pain, improvement in wound condition, absence of systemic or local infection signs) and, as recommended in current guidelines¹³¹, normalization of serum CRP and ESR levels. However, these markers often fail to normalize after eradication and poorly predict infection persistence or resolution^{133-135, 147}. Moreover, these values may fluctuate in patients with underlying inflammatory disease, malignancy, or other medical conditions. Little is known about alternative diagnostic tests in resection arthroplasty. Two recent studies investigated the role of synovial aspiration and concluded that synovial fluid cultures and synovial fluid white blood cell count seem to be poor parameters to exclude persistent infection^{137, 147}. Only Interleukin-6 (IL-6) seemed to perform reasonably well, as reported by Hoell et al¹⁴⁸. However, this test is hampered by limited availability and its utility has not yet been confirmed by other studies. Alternative diagnostic tests, such as alpha-defensin immunoassay and leukocyte esterase colorimetric strip^{35, 104, 149, 150} have recently been identified as useful indicators of PJI, but their utility in the setting of an attempted re-implantation is unknown.

In the assessment of infection persistence after resection arthroplasty, the role of imaging modalities has not been investigated in previous reports. CT, MRI and ultrasound can be used to assess for residual local infection, but the diagnostic accuracy in this setting has not been studied. Moreover, these imaging modalities are less suitable as screening methods when clues for specific sites of infection are absent¹⁵¹, especially in clinically complex patients.

In complex cases, such as included in the current study, FDG-PET/CT may be helpful in identifying patients in need of additional medical treatment or delayed re-implantation. 18F-FDG accumulates in metabolically active cells, including activated leukocytes at the site of infection, enabling imaging of inflammatory processes¹⁵². FDG-PET/CT is a useful imaging modality in detecting orthopedic infections^{24, 43, 54, 104, 138-142, 153-155} because specific uptake patterns were found which identifies periprosthetic infection and differentiates with inflammatory processes¹⁴⁴. The current role of FDG-PET/CT after resection arthroplasty is unknown and has only been described in patient with interim spacers^{156, 157}. This study was the first to investigate the additional value of FDG-PET/CT after resection arthroplasty. Unfortunately, the results of this investigation did not depict specific infectious uptake patterns at the resection arthroplasty to differentiate with inflammatory or postsurgical processes. Increased uptake at the ROI was found in all patients. In some cases (n= 5), the combination with increased uptake at the surrounding bone and soft tissue was suggestive for infection but it remained difficult to differentiate between persistent local infection and postsurgical uptake.

FDG-PET/CT findings directly influenced the two-stage revision management by either diagnosing other infectious foci (41%) or excluding them. Additional findings led to canceled re-implantation in 7 patients. Ruling out other infectious foci suggested that elevated CRP and/or ESR levels were caused by infectious or inflammatory processes at the resection arthroplasty area. In those 10 cases, the ROI was further monitored with other imaging techniques (ultrasound, MRI, CT, leukocyte- or bone scintigraphy) or clinical observation. In current literature, no information exists about the preferred modality to assess the local development of the infectious or inflammatory processes at the ROI. It is important to note that for local monitoring, FDG-PET/CT may not be the preferred imaging modality because differentiation between infection and inflammation is difficult. Moreover, FDG-PET/CT is more expensive compared to other imaging modalities for this purpose.

Our results illustrated that FDG-PET/CT may be able to identify patients in need for additional treatment and can exclude other infection loci. A negative FDG-PET/CT for other foci may guide the clinical physician to monitor the local resection area because it suggests that the ROI is main focus for the elevated CRP and ESR levels. Although FDG-PET/CT results directly influenced the clinical decision-making process in all described patients, it is not recommended for routine use. It is assumed most useful in clinically complex patients with absence of local infection signs. It is important to note that our results demonstrated recurrence of hip PJI in 37.5% of the cases without any predicting clues on the FDG-PET/CT. However, FDG-PET/CT can be complementary to other diagnostic tests to arrive at a more-precise evaluation, especially in selected, complex cases. FDG-PET/CT is often depicted as an expensive and complex imaging modality with limited availability in some countries, and therefore gained limited popularity in clinical practice for orthopedic infections. However, FDG-PET/CT could add to the decision-making process in selected cases. More clinical investigation is needed to evaluate the cost-effectiveness and exact role of FDG-PET/CT in the diagnostic algorithm for evaluation of residual infection^{74, 138, 143, 158}. In our opinion, the role of FDG-PET/CT in the algorithm of periprosthetic infection after resection arthroplasty should be limited to exclusion or diagnosis of other infectious foci during the interim period in patient with persistence of elevated CRP and/or ESR serums levels, and not for local monitoring of the resection areas.

This study had several limitations. Our investigation is a retrospective study that involves a small cohort of patients. Although all cultures after re-implantation were negative, there was a lack of a true reference standard to determine infection persistence at the ROI. However, the aim of this study was not to investigate the diagnostic accuracy of FDG-PET/CT in the assessment of infection after resection arthroplasty. Our investigation investigated preliminary findings to depict possible specific uptake infectious patterns at the ROI and the effect on the two-stage management of hip PJI in patients with a clinical dilemma after resection arthroplasty. Important variables such as the influence of the type of PJI (acute or chronic), the type of organism, type of implant, cost-effectiveness,

and inter- and intraobserver agreement could not properly be analyzed because of an insufficient number of patients. Furthermore, it is important to note that these findings are the outcome of a small study group with a variety in postsurgical period. With the retrospective nature of the cohort, undoubtedly selection bias has occurred, so we aimed to only describe our results for a group of complex patients with elevated CRP and/or ESR levels. Further, prospective studies should investigate the exact role of FDG-PET/CT after resection arthroplasty, especially to analyze the postsurgical uptake patterns with sequential FDG-PET/CT imaging.

In conclusion, FDG-PET/CT may not be the preferred imaging modality for diagnosing persistent infection at the resection arthroplasty area. However, a negative FDG-PET/CT study for other complicating infectious foci could be used as an important surgery reference for local diagnostic follow-up of the resection area before second stage re-implantation. FDG-PET/CT could be a feasible tool in identifying patients in need of additional treatment or delayed re-implantation in patients with dilemmatic conditions with persistence of elevated CRP and/or ESR serum levels.

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PART II

The Contribution of Alpha-Defensin in Diagnosing Periprosthetic Joint Infection



Does the Alpha Defensin ELISA Test Perform Better Than the Alpha Defensin Lateral Flow Test for PJI Diagnosis? A Systematic Review and Meta-analysis of Prospective Studies

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ABSTRACT

Background

Periprosthetic joint infection (PJI) following total joint arthroplasty is a serious complication that causes severe morbidity and adds a major financial burden to the healthcare system. Although there is plenty of research on the alpha-defensin (AD) test, a meta-analysis consisting of only prospective studies investigating AD's diagnostic efficacy has not been performed. Additionally, some important subgroups such as THA and TKA have not been separately analyzed, particularly regarding two commonly used versions of the AD test, the laboratory-based (ELISA) and lateral-flow (LF).

Questions/purposes (1

Does the AD ELISA test perform better in the detection of PJI than the AD LF test, in terms of pooled sensitivity and specificity, when including prospective studies only? (2) Are there differences in sensitivity or specificity when using AD ELISA and AD LF tests for PJI diagnosis of THA or TKA PJI separately?

Methods

Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines, we included prospective studies describing the use of either AD test in the workup of pain after total joint arthroplasty (primary or revision, but not after resection arthroplasty). Fifteen studies (AD ELISA: 4; AD LF: 11) were included, with 1592 procedures. Subgroup data on THA and TKA could be retrieved for 1163 procedures (ELISA THA: 123; LF THA: 257; ELISA TKA: 228; LF TKA: 555). Studies not describing THA or TKA, those not using Musculoskeletal Infection Society (MSIS) criteria as the standard for determining the presence or absence of PJI, those not clearly reporting data for the AD test for the total cohort, and those describing data published in another study were excluded. Studies were not excluded based on follow-up duration; the MSIS criteria could be used within a few weeks, when test results were available. Quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 criteria. Study quality was generally good. The most frequent sources of bias were related to patient selection (such as unclear inclusion and exclusion criteria) and flow and timing (uncertainty in place and time of aspiration, for example). Heterogeneity was moderate to high; a bivariate random-effects model therefore was used. To answer both research questions, sensitivity and specificity were calculated for AD ELISA and LF test groups and THA and TKA subgroups, and were compared using z-test statistics and meta-regression analysis.

Results

No differences were found between the AD ELISA and the AD LF for PJI diagnosis in the pooled cohorts (THA and TKA combined), in terms of sensitivity (90% versus 86%; $p = 0.43$) and specificity (97% versus 96%; $p = 0.39$). Differences in sensitivity for PJI diagnosis were found between the THA and TKA groups for the AD ELISA test (70% versus 94%; $p = 0.008$); pooled AD LF test sensitivity did not differ between THA and TKA (80% versus 87%; $p = 0.20$). No differences in specificity were found in either subgroup.

Conclusions

Both the AD ELISA and AD LF test can be used in clinical practice because both have high sensitivity and very high specificity for PJI diagnosis. The lower sensitivity found for diagnosis of PJI in THA for the AD ELISA test must be carefully interpreted because the pooled data were heterogenous and only two studies for this group were included. Future research should analyze TKAs and THAs separately to confirm or disprove this finding.

Level of Evidence

Level II diagnostic study.

INTRODUCTION

Periprosthetic joint infection (PJI) is a devastating complication of total joint arthroplasty that often leads to additional surgical procedures and prolonged intravenous antibiotic administration [36, 53]. Because of its importance, and because of the difficulty of diagnosing it, many novel diagnostic biomarkers for PJI have recently been developed [1]. One of the best-described biomarkers in the past 5 years has been alpha-defensin (AD). AD is produced by neutrophils in synovial fluid. Higher levels indicate local infection [10]. AD levels can be measured in a laboratory with an ELISA test developed by CD Diagnostics (Claymont, DE, USA). As a fast alternative, a point-of-care test using a lateral flow (LF) device (Synovasure®, Zimmer-Biomet, Warsaw, IN, USA) was developed. This LF test gives a result within 10 minutes.

According to the many meta-analyses performed in the last few years, the ELISA test performs extremely well (sensitivity 95% to 100%, specificity 95% to 97%) [1, 6, 16, 27–29, 50, 55–57], whereas the LF test appears not to be as good (sensitivity 71% to 85%, specificity 89% to 96%) [1, 6, 16, 29, 50, 57]. However, most of these meta-analyses included multiple studies that seemed to count the same patients more than once, studies that used different criteria to diagnose PJI, and retrospective studies, which are more prone to bias. Furthermore, several relevant new studies have been published [26, 37, 39, 45, 51], and so a repeat meta-analysis is necessary. Also, most included studies mention both THA and TKA procedures, but possible differences in diagnostic accuracy in the tests between TKA and THA have not been separately analyzed.

We therefore performed a meta-analysis of all prospective studies comparing the AD ELISA test with the AD LF test for PJI in THA and TKA. We sought to determine: (1) Does the AD ELISA test perform better in the detection of PJI than the AD LF test, in terms of pooled sensitivity and specificity, when including prospective studies only? (2) Are there differences in sensitivity or specificity when using AD ELISA and AD LF tests for diagnosis of THA or TKA PJI separately?

MATERIALS AND METHODS

Search Strategy and Criteria

We designed a search to include all cohort studies on the diagnostic accuracy of the AD test (either ELISA or LF) in patients with PJI. A PubMed and EMBASE search was performed in August 2019, with the terms synovasure OR defensin AND infect* OR PJI AND prosth* OR peri-prosth* OR arthroplast*, according to the Preferred Reporting Items for Systematic reviews and Meta- Analyses (PRISMA) statement [33]. Titles and abstracts were screened, full-text articles were assessed, data were extracted by two authors (JWPK, SJV), and conflicts were resolved by consensus. If needed, we contacted the study authors to provide details on their data.

Inclusion and Exclusion Criteria

All studies describing patient groups in which AD (either ELISA or LF) was used to evaluate pain after total joint arthroplasty were assessed (primary and revision but not resection arthroplasty). The exclusion criteria were symposium abstracts, studies solely describing joints other than the hip or knee, retrospective studies, studies using diagnostic criteria other than the original or modified Musculoskeletal Infection Society (MSIS) criteria as the gold standard for the presence or absence of PJI, and studies that did not provide data on the total cohort (that is, we could not retrieve correct data on the number of true positives, false positives, true negatives, and false negatives). If studies described possibly overlapping cohorts, the study with the larger cohort was included; of the 11 previous meta-analyses, 10 included studies with cohorts we believe may have had the same patients. If AD was only used in a subgroup or as a second step in a classification tree, we excluded the study because of evident selection bias.

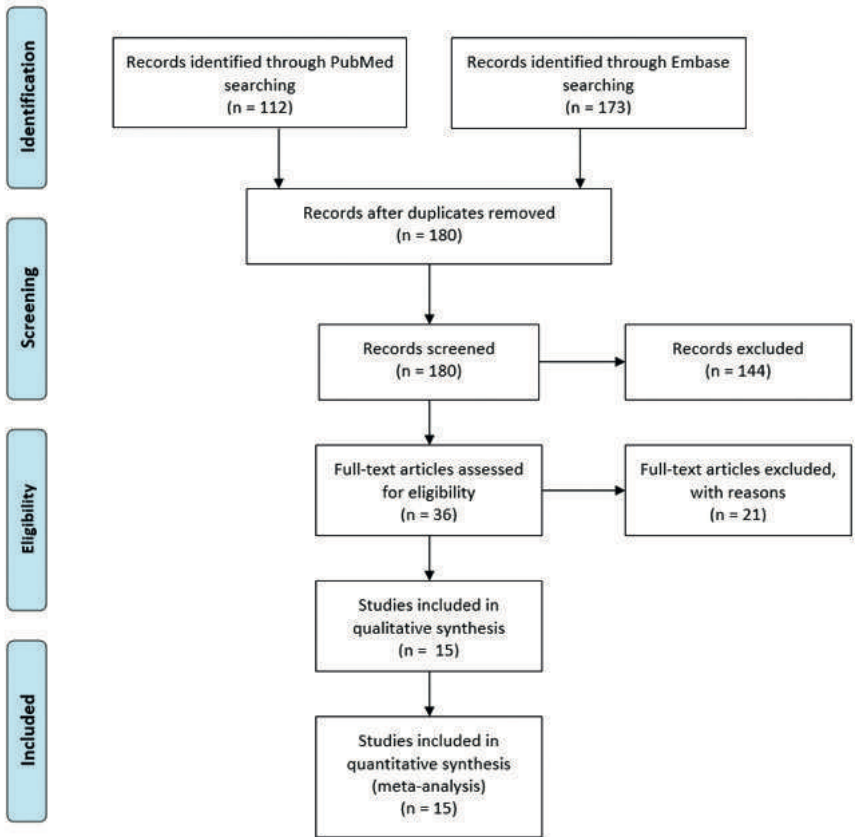


Fig. 1 This PRISMA flowchart shows the studies that were included in this meta- analysis [32].

Data Extraction

Two reviewers (JWPK, SJV) independently extracted relevant data including demographic, joint, and index test characteristics. Important variables such as antibiotics, comorbidities such as inflammatory conditions and the presence of metallosis, methods for obtaining synovial fluid samples, microbiological results, and data regarding diagnostic performance indexes (that is, sensitivity and specificity) were analyzed in detail to form subgroups, if possible. Cutoff or range definitions of the test, and whether these were predetermined by the study authors or derived with the use of receiver operating characteristic curves, were also noted.

Search Results

The search identified 180 unique studies (Fig. 1). After screening, 36 studies were selected for full-text review. No other studies were extracted from the reference lists of these studies. Of these 36, 21 were excluded: 13 retrospective studies [4, 8, 12, 14, 23, 25, 31, 35, 42, 43, 46–48], two studies solely on total shoulder arthroplasty [15, 19], one study using other diagnostic criteria [52], two studies with a different cohort selection (one only included revision for aseptic loosening, excluding clear diagnoses of PJI [41], and one study describing data on AD for only low-grade PJI with synovial C-reactive protein levels higher than 2 mg/L [17]), and three studies describing a cohort in another, larger study [9, 11, 44].

Fifteen studies were included in the final analysis, with a total of 1592 procedures (Table 1): four studies described the use of AD ELISA (Table 2) [5, 10, 18, 26], and 11 of AD LF (Table 3) [2, 3, 7, 21, 24, 37–39, 45, 49, 51]. Subgroup data on THA and TKA could be retrieved for 1163 procedures (ELISA THA: 123; LF THA: 257; ELISA TKA: 228; LF TKA: 555). There was no disagreement between the reviewers regarding the definitive inclusion of the studies.

Quality Assessment

To assess the quality of the included studies, we used Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria [54]. This methodologic evaluation was independently performed by two authors (JWPK, SJV). Studies were not excluded from the systematic review based on methodologic quality. Quality of the included studies was generally good (Figure 2). Possible bias in patient selection (for example, unclear inclusions and exclusions) and flow and timing was seen in some studies, such as differences regarding aspiration location (outpatient clinic, operating room or radiology department) and the period between aspiration and revision (aspiration directly before revision surgery, or during diagnostic work-up). The possible use of lavage to obtain material was mentioned as an exclusion criterion only once specifically [38], but an insufficient amount of fluid was an exclusion criterion in almost all studies.

Statistical Methods

To answer the two research questions, we calculated summary statistics for each study: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). To assess which model should be used for further analysis, between-study heterogeneity was assessed using the I^2 statistic. An I^2 value lower than 40% was considered low heterogeneity and a value of 0% meant that all variability in the effect size estimate was the result of sampling error within studies. We considered the following possible sources of heterogeneity a priori, and defined possible subgroups accordingly: affected joint (THA versus TKA), time from the index operation, use of antibiotics, and concomitant inflammatory diseases. Only the affected joint could be investigated; data on other possible sources of heterogeneity were insufficient. As heterogeneity was moderate to high, sensitivity, specificity, and respective 95% confidence intervals (CI) were calculated using the bivariate random-effects model suggested by DerSimonian and Laird [13].

For the first question, data were pooled for the ELISA (Table 2) and LF groups (Table 3) and sensitivity and specificity were calculated. For the second research question, the same calculations were performed on the ELISA (Table 4) and LF data (Table 5) for THA and TKA separately. For both questions, as the main study endpoint, sensitivity and specificity were pooled independently and were weighted by the inverse of the variance with the use of MetaDiSc 1.4 (Hospital Universitario Ramon y Cajal, Madrid, Spain) [58]. The logit-transformed sensitivity, specificity, and corresponding 95% CIs of the index tests were compared using z-test statistics. A p value of < 0.05 was considered significant. We performed a meta-regression analysis using STATA 13.0 (StataCorp, College Station, TX, USA).

Table 1. Characteristics of the included studies

Author	Year	Joints	AB	Test	n	n	%	TP	FP	TN	Aspiration	PJI criteria	Blinding	Metallosis	Sinus tract
Deirmengian <i>et al</i> [11]	2014	THA/TKA	10	ELISA	149	37	24.8	36	5	1	107	MSIS	None	17/112, 3/5 FP	5/37
Frangiamore <i>et al</i> [18]	2016	THA/TKA	^a	ELISA	78	24	30.8	24	1	0	53	MSIS	None	excluded	4/24 (4 TP, 0 FN)
Kasperek <i>et al</i> [24]	2016	THA/TKA	^a	LF	40	12	30.0	8	2	4	26	Modified MSIS	None	excluded	
Balato <i>et al</i> [2]	2017	TKA	0	LF	51	16	31.4	14	1	2	34	Modified MSIS	None	0	4/16
Berger <i>et al</i> [3]	2017	THA/TKA	^a	LF	121	34	28.1	33	3	1	84	OR/OP MSIS	None	1/3 FP	
Bonanzinga <i>et al</i> [5]	2017	THA/TKA	≥ 2	ELISA	156	29	18.6	28	4	1	123	Modified MSIS	MB, PA	2/4 FP	7/29 (6 TP, 1 FN)
Suda <i>et al</i> [49]	2017	THA/TKA	PO	LF	30	13	43.3	10	3	3	14	Modified MSIS	None	^a	
de Saint Vincent <i>et al</i> [7]	2018	THA/TKA/ TFA ^b	1	LF	39	8	20.5	7	4	1	27	MSIS	None	1/4 FP	
Gehrke <i>et al</i> [21]	2018	THA/TKA	Excluded	LF	195	76	39.0	70	0	6	119	MSIS	None	excluded	3/76 (0 TP, 3 FN)
Plate <i>et al</i> [37]	2018	TKA/THA	Excluded	LF	109	20	18.3	18	7	2	82	Modified MSIS	MB, OS	1 TN	1/20 (0 TP, 1 FN)
Renz <i>et al</i> [38]	2018	THA/TKA	PO	LF	212	45	21.2	38	6	7	161	Modified MSIS	None	^a	12/45 (7 TP, 5 FN)
Riccio <i>et al</i> [39]	2018	THA/TKA/ TSA ^b	9	LF	71	38	53.5	32	1	6	32	MSIS	None	0	
Tahta <i>et al</i> [51]	2018	TKA	Excluded	LF	38	17	44.7	16	0	1	21	MSIS	None	0	
Sigmund <i>et al</i> [45]	2019	THA/TKA	≥ 2	LF	101	29	28.7	20	4	9	68	Modified MSIS	PA	^a	1/29 (1 TP, 0 FN)
Kleiss <i>et al</i> [26]	2019	THA/TKA	^a	ELISA	202	55	27.2	43	5	12	142	Modified MSIS	None	5 (all TN)	14/55 (9 TP, 5 FN)

^aNot mentioned. ^bProcedures other than THA and TKA excluded. TFA = total femur arthroplasty; TSA = total shoulder arthroplasty; PO = perioperative; TP = true positive; FP = false positive; FN = false negative; TN = true negative; OR = operating room; OP = outpatient clinic; DR = dedicated room; RD = radiology department; MB = microbiologist; PA = pathologist; LS = laboratory staff; OS = orthopaedic surgeon.

Table 2. Characteristics of the studies on the ELISA-based AD test

Study	Year	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Deirmengian <i>et al.</i> [10]	2014	36	5	1	107	0.97 (0.86-1.00)	0.96 (0.90-0.99)
Frangiamore <i>et al.</i> [18]	2016	24	1	0	53	1.00 (0.86-1.00)	0.98 (0.95-1.00)
Bonanzinga <i>et al.</i> [5]	2017	28	4	1	123	0.97 (0.82-1.00)	0.97 (0.92-0.99)
Kleiss <i>et al.</i> [26]	2019	43	5	12	142	0.78 (0.65-0.88)	0.97 (0.92-0.99)
Pooled		131	15	14	425	0.90 (0.84-0.95)	0.97 (0.94-0.98)

TP = true positive; FP = false positive; FN = false negative; TN = true negative.

Table 3. Characteristics of studies on the LF AD test

Study	Year	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kasperek <i>et al.</i> [24]	2016	8	2	4	26	0.67 (0.35-0.90)	0.93 (0.76-0.99)
Suda <i>et al.</i> [49]	2016	10	3	3	14	0.77 (0.46-0.95)	0.82 (0.57-0.96)
Berger <i>et al.</i> [3]	2017	33	3	1	84	0.97 (0.85-1.00)	0.97 (0.90-0.99)
Balato <i>et al.</i> [2]	2017	14	1	2	34	0.88 (0.62-0.98)	0.97 (0.85-1.00)
Gehrke <i>et al.</i> [21]	2018	70	0	6	119	0.92 (0.84-0.97)	1.00 (0.97-1.00)
Renz <i>et al.</i> [38]	2018	38	6	7	161	0.84 (0.71-0.94)	0.96 (0.92-0.99)
de Saint Vincent <i>et al.</i> [7]	2018	7	4	1	27	0.88 (0.47-1.00)	0.87 (0.70-0.96)
Riccio <i>et al.</i> [39]	2018	32	1	6	32	0.85 (0.70-0.94)	0.97 (0.84-1.00)
Tahta <i>et al.</i> [51]	2018	16	0	1	21	0.94 (0.71-1.00)	1.00 (0.84-1.00)
Plate <i>et al.</i> [37]	2018	18	7	2	82	0.90 (0.68-0.99)	0.92 (0.84-0.97)
Sigmund <i>et al.</i> [45]	2019	20	4	9	68	0.69 (0.49-0.85)	0.94 (0.86-0.98)
Pooled		266	31	42	668	0.86 (0.82-0.90)	0.96 (0.94-0.97)

TP = true positive; FP = false positive; FN = false negative; TN = true negative.

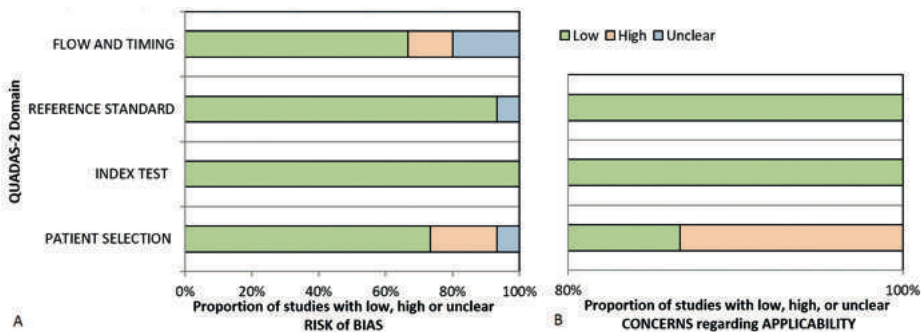


Fig. 2 A-B Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) scores for (A) risk of bias and (B) concerns regarding applicability of the included studies.

We could not investigate publication bias because tests addressing this type of bias require at least 10 studies and lower heterogeneity to be valid [22]. We calculated Spearman's correlation coefficient to assess a possible threshold effect because different studies might have used other thresholds, such as another cutoff value for a positive result of the ELISA based test, which greatly influenced the estimation of summary points (sensitivity and specificity). The threshold for the ELISA-based reference test was mentioned in all four studies (5.2 mg/L [18] or signal-to-cutoff ratio 1.0 [5, 10, 26]). No threshold effect (suggested by a strong positive correlation) was found (Spearman's correlation coefficient: -0.40; $p = 0.60$) [34].

Table 4. Characteristics of included studies with data on THA

Study	Year	Test	TP	FP	FN	TN
Deirmengian <i>et al.</i> ¹⁰	2014	ELISA	2	3	0	28
Kleiss <i>et al.</i> ²⁶	2019	ELISA	19	2	9	60
Combined			21	5	9	88
Kasperek <i>et al.</i> ²⁴	2016	LF	4	0	1	6
Suda <i>et al.</i> ⁴⁹	2016	LF	4	2	0	5
Berger <i>et al.</i> ³	2017	LF	12	1	1	22
Renz <i>et al.</i> ³⁸	2018	LF	15	2	4	40
de Saint Vincent <i>et al.</i> ⁷	2018	LF	4	1	0	9
Riccio <i>et al.</i> ³⁹	2018	LF	14	1	5	2
Plate <i>et al.</i> ³⁷	2018	LF	14	3	2	30
Sigmund <i>et al.</i> ⁴⁵	2019	LF	11	3	6	33
Combined			78	13	19	147

LF = lateral flow; TP = true positive; FP = false positive; FN = false negative; TN = true negative.

Table 5. Characteristics of included studies with data on TKA

Study	Year	Test	TP	FP	FN	TN
Deirmengian <i>et al.</i> ¹⁰	2014	ELISA	34	2	1	79
Kleiss <i>et al.</i> ²⁶	2019	ELISA	24	3	3	82
Combined			58	5	4	161
Kasperek <i>et al.</i> ²⁴	2016	LF	4	2	3	20
Suda <i>et al.</i> ⁴⁹	2016	LF	6	1	3	9
Berger <i>et al.</i> ³	2017	LF	21	2	0	62
Balato <i>et al.</i> ²	2018	LF	14	1	2	34
Renz <i>et al.</i> ³⁸	2018	LF	23	4	3	121
de Saint Vincent <i>et al.</i> ⁷	2018	LF	3	3	1	18

Table 5. Continued

Study	Year	Test	TP	FP	FN	TN
Riccio <i>et al.</i> ³⁹	2018	LF	18	0	1	30
Tahta <i>et al.</i> ⁵¹	2018	LF	16	0	1	21
Plate <i>et al.</i> ³⁷	2018	LF	4	4	0	52
Sigmund <i>et al.</i> ⁴⁵	2019	LF	9	1	3	35
Combined			118	18	17	402

LF = lateral flow; TP = true positive; FP = false positive; FN = false negative; TN = true negative.

RESULTS

AD ELISA Versus AD LF Test (THA and TKA Data Combined)

After pooling data from studies on PJI in THA and TKA combined, we found no differences in sensitivity between the AD ELISA and LF tests: 90% (95% CI 84 to 95) versus 86% (95% CI 82 to 90; $p = 0.43$) (Fig. 3). Likewise, we identified no differences in specificity between the two tests: 96% (95% CI 94 to 97) versus 97% (95% CI 94 to 98). ($p = 0.39$) (Table 6). We found that PPV was 90% for the AD ELISA and 90% for the AD LF test; NPV was 97% for the AD ELISA test and 94% for the AD LF test.

AD ELISA Versus AD LF Test When Assessing THA and TKA Data Separately

We found no differences between the AD ELISA test and AD LF test in terms of sensitivity for PJI diagnosis in THA: 70% (95% CI 51 to 85) versus 80% (95% CI 71 to 88; $p = 0.30$). Likewise, for specificity, we found no differences: 95% (95% CI 88 to 98) versus 92% (95% CI 86 to 96; $p = 0.40$) (Table 6). For THA, PPV was 81% for ELISA, and 86% for LF; NPV was 91% for ELISA and 89% for the AD LF test.

For PJI diagnosis in TKA, AD ELISA and LF tests showed no differences in sensitivity: 94% (95% CI 84 to 98) versus 87% (95% CI 81 to 93; $p = 0.18$). For specificity, we identified no differences: 97% (95% CI 93 to 99) versus 96% (95% CI 93 to 97; $p = 0.60$). The PPV for TKA subgroups was 92% for ELISA and 87% for the AD LF test, and NPV was 98% for ELISA, and 96% for LF.

When comparing THA and TKA, we found the AD ELISA test was more sensitive in diagnosing PJI in TKA than in THA: 94% (95% CI 84 to 98) for TKA versus 70% (95% CI 51 to 85) for THA ($p = 0.008$). The specificity of the AD ELISA test was not different between THA and TKA: 95% (95% CI 88 to 98) versus 97% (95% CI 93 to 99; $p = 0.45$).

For the AD LF test, we saw no differences in sensitivity between THA and TKA: 80% (95% CI 71 to 88) versus 87% (95% CI 81 to 93; $p = 0.20$). The specificity also showed no differences: 92% (95% CI 86 to 96) versus 96% (95% CI 93 to 97; $p = 0.076$).

DISCUSSION

PJI is a substantial problem in orthopaedic practice, and consequently, new diagnostic biomarkers are constantly being developed [1]. AD has been described in many clinical studies and meta-analyses, but they all have shortcomings: some included multiple studies with (partly) the same cohorts; others included studies using different criteria to diagnose PJI, risking increased heterogeneity. In addition, all meta-analyses included retrospective studies, which are often of lower quality and more at risk for confounding and bias [1, 6, 16, 27-29, 40, 50, 55-57]. In this meta-analysis, we found no differences between the AD ELISA and AD LF tests in terms of sensitivity and specificity. In subgroup analysis, the ELISA test demonstrated higher sensitivity for diagnosing PJI in TKA compared with THA. However, some nuance on this result is essential: the pooled group is small (only two included studies) and heterogeneous. Also, differences in diagnostic workup between TKA and THA are likely, but data were insufficient to study this.

Although only prospective studies were included and strict inclusion and exclusion criteria were applied, the heterogeneity of the included studies is one of the major shortcomings of this meta-analysis. Small differences in patient cohorts of the included studies, such as differences in aspiration location, aspiration techniques, possible use of lavage, and the period between aspiration and revision, probably are the main reason for this heterogeneity. For example, differences in aspiration techniques between THA (operating room or radiology department) and TKA (usually done in the outpatient clinic) are very likely. Unfortunately, as full specifics were not given, pooling heterogeneous data was unavoidable. It is therefore possible that the absence of differences between the ELISA and LF test found in this study only applies for this selection of (heterogeneous) studies. Although this is a substantial limitation, differences between hospitals in daily practice are also considerable, rendering the described results applicable to orthopaedic practice in general, with careful interpretation.

We also raise a concern about publication bias of studies on this subject: more than half of the included studies reported conflicts of interest concerning the AD test. We hope there will be more studies in the future from authors not directly connected to manufacturers of the tests being studied.

Furthermore, the lower sensitivity for THA PJI diagnosis for the AD ELISA-based test alone is largely based on the results of a single study [26]. Separate data on THA and TKA could only be retrieved for two studies describing the AD ELISA test [10, 26], resulting in a fairly small pooled group (Table 4 and Table 5). Several differences between these studies exist, such as the use of biopsy to obtain cultures in cases of borderline PJI criteria fulfillment (21%) in one study [26], which was not described in the other study [10]. Hematoma formation after biopsy, and subsequent dilution, for example, may be a reason for false negative results, but this has never been described in any study. Because only two studies could be included, the greater sensitivity of the AD ELISA test in TKA compared with THA should be interpreted with great caution.

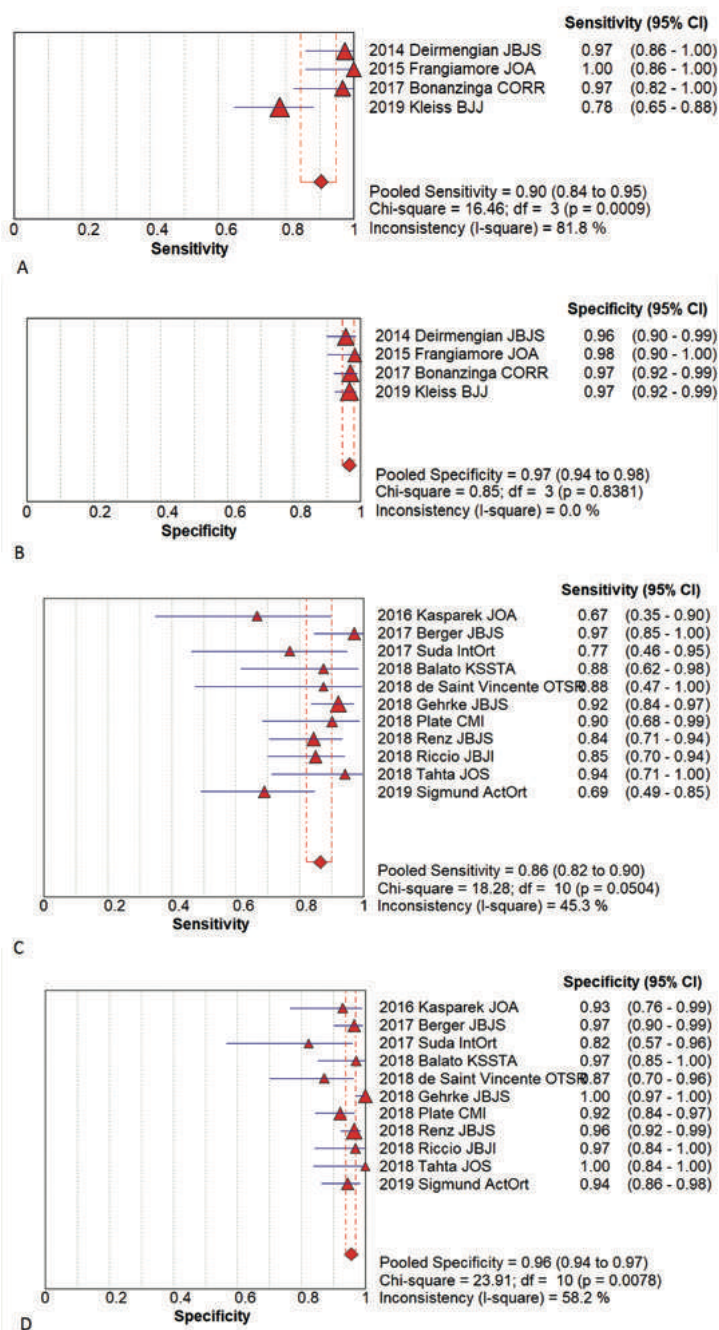


Fig. 3 A-D These forest plots show (A) sensitivity and (B) specificity for the ELISA-based AD test and (C) sensitivity and (D) specificity for the AD LF test.

Table 6. Comparison of results for ELISA versus LF tests and THA versus TKA, combined and separately

Pooled group	Pooled group	Sensitivity (95% CI)	Sensitivity (95% CI)	Comparison	Specificity (95% CI)	Specificity (95% CI)	Comparison
Test 1	Test 2	Test 1	Test 2	p value	Test 1	Test 2	p value
LF: THA & TKA	ELISA: THA & TKA	86% (82 to 90)	90% (84 to 95)	0.43	96% (94 to 97)	97% (94 to 98)	0.39
LF: THA	LF: TKA	80% (71 to 88)	87% (81 to 93)	0.20	92% (86 to 96)	96% (93 to 97)	0.076
ELISA: THA	ELISA: TKA	70% (51 to 85)	94% (84 to 98)	0.008*	95% (88 to 98)	97% (93 to 99)	0.45
LF: THA	ELISA: THA	80% (71 to 88)	70% (51 to 85)	0.30	92% (86 to 96)	95% (88 to 98)	0.40
LF: TKA	ELISA: TKA	87% (81 to 93)	94% (84 to 98)	0.18	96% (93 to 97)	97% (93 to 99)	0.60

Table 7. Meta-analyses describing pooled results for ELISA-based and (in some studies) LF and AD tests

Author	Year	Included studies (n)	Included studies	Sensitivity ELISA	Specificity ELISA	Sensitivity LF	Specificity LF
Wyatt <i>et al.</i> ⁵⁵	2016	6	[4,9-12,19]	100%	96%		
Li <i>et al.</i> ²⁸	2017	4	[4,10,11,18]	98%	97%		
Xie <i>et al.</i> ⁵⁶	2017	6	[4,9,10,12,18,19]	96%	95%		
Lee <i>et al.</i> ²⁷	2017	7	[4,5,9-11,18,42]	97%	96%		
Yuan <i>et al.</i> ⁵⁷	2017	11	[4,5,9-12,18,19,24,44,49]	97%	96%	8%	89%
Eriksson <i>et al.</i> ¹⁶	2018	7	[4,5,10,18,24,44,49]	96%	96%	71%	90%
Suen <i>et al.</i> ⁵⁰	2018	10	[4,5,9-11,18,19,24,44,49]	95%	97%	77%	91%
Ahmad <i>et al.</i> ¹	2018	10	[4,5,9-11,18,19,24,44,49]	97%	97%	80%	89%
Marson <i>et al.</i> ²⁹	2018	11	[2-5,10,11,18,21,24,44,49]	95%	97%	85%	90%
Carli <i>et al.</i> ⁶	2019	16	[2-5,7,9-11,18,21,24,25,30,38,44,49]	97%	97%	82%	96%
Current study	2020	15	[2,3,5,7,10,18,21,24,26,37-39,45,49,51]	90%	97%	86%	96%

AD ELISA VERSUS AD LF TEST (THA AND TKA DATA COMBINED)

In terms of sensitivity and specificity, we found no differences between the AD ELISA and LF test, when we pooled THA and TKA data. Both tests showed high sensitivity and very high specificity for PJI diagnosis. These test characteristics make either test a useful addition to the array of diagnostic tools currently available for PJI; the ELISA-based test results take a day but allow a more nuanced interpretation with continuous values, and the lateral flow test provides a yes/no result within 10 minutes. However, one must keep the above-mentioned limitations in mind when interpreting AD tests for individual patients. When comparing these results with previous studies, the sensitivity of the ELISA test is slightly lower than previously described, and the LF test performed slightly better in terms of sensitivity and specificity than reported in most earlier studies (Table 7). The publication of new studies included in this meta-analysis is probably the most important explanation for these differences.

AD ELISA VERSUS AD LF TEST WHEN ASSESSING THA AND TKA DATA SEPARATELY

When pooling data for THA and TKA separately, we found a lower sensitivity of the AD ELISA test alone for THA PJI diagnosis compared with TKA. We found no other differences. For clinical practice, when interpreting the results of the AD ELISA test for THA PJI, one should keep in mind that sensitivity may be lower than for TKA. Recognizing the caveats mentioned in the limitations section, these findings may also partly be explained by differences between THA and TKA PJI. Hypothetically, the type of joint should not influence the results of the AD test (ELISA-based or LF) because these patients all have the same immune response. However, differences in joints exist. First, they have different volumes, thus possibly influencing the AD concentration. Furthermore, PJI in different joints has different causative organisms, at least for shoulder versus hip and knee PJI [20]. AD is known to be less sensitive in diagnosing shoulder PJI: two studies on the ELISA-based AD test for PJI in shoulder arthroplasty found comparable high specificities (95% to 96%) but lower sensitivities (63% to 75%) [15, 19]. Considering our findings, we would recommend authors describe test results for THA and TKA separately in addition to overall results, which should help confirm or disprove the difference in sensitivity that was found.

CONCLUSIONS

We found no differences in sensitivity or specificity between the ELISA and LF AD test after pooling all included studies, and we did not find that the AD ELISA test was superior. For

THA and TKA subgroups, sensitivity was found to be lower for THA PJI diagnosis than for TKA PJI diagnosis when using the AD ELISA test. For clinical practice, this study confirms that both tests have good sensitivity and specificity, and implementation in diagnostic routines is justifiable. This study provides no arguments to favor the AD ELISA test over the AD LF test. However, with the heterogeneity of the pooled groups, and the availability of only two studies with separate THA and TKA data for the AD ELISA test, these results must be considered carefully. Further studies are indispensable for a more thorough assessment of differences between THA and TKA, and analysis of different subgroups may provide information about patients in whom the AD test will be most useful. We encourage researchers to specify which joint(s) is/are being studied, the criteria used to determine PJI (including the presence or absence of a sinus tract), timing of the possible infection (acute or chronic), pretreatment with antibiotics (if any), the presence or absence of metallosis, and the location and method of aspiration (including management of dry taps).

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**Are Accuracy Studies for Periprosthetic Joint Infection
Diagnosis Inherently Flawed? And What to Do with
Schrödinger's Hips? A Prospective Analysis of the
Alpha Defensin Lateral-Flow Test in Chronic Painful Hip
Arthroplasties**

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ABSTRACT

Purpose: The most recent diagnostic criteria for periprosthetic joint infection (PJI) include the use of the alpha-defensin (AD) lateral-flow (LF) test, but hip and knee arthroplasties were usually combined in previous studies. This prospective study was designed to examine the accuracy of the AD-LF test for diagnosis of PJI in chronic painful total hip arthroplasties (THA).

Materials and Methods: Patients with chronic painful hip arthroplasties were prospectively enrolled between March 2018 and May 2020. Exclusion criteria included acute PJI or an insufficient amount of synovial fluid. The modified Musculoskeletal Infection Society (MSIS) criteria were primarily used for PJI diagnosis. Fifty-seven patients were included in the analysis group. Revision surgery was not performed in 38 patients, for different reasons (clinical group); these patients remain “Schrödinger’s hips”: in such cases PJI cannot be excluded nor confirmed until you “open the box”.

Results: The result of the AD-LF test was positive in nine patients and negative in 48 patients. Six patients were diagnosed with PJI. AD-LF sensitivity (MSIS criteria) was 83% (95% confidence interval [CI] 36-100%) and specificity was 92% (95% CI 81-98%). The positive and negative predictive value were 56% and 98%, respectively.

Conclusion: The AD test is useful in addition to the existing arsenal of diagnostic tools, and can be helpful in the decision-making process. Not all patients with chronic painful THA will undergo revision surgery. Consequently, in order to determine the reliable diagnostic accuracy of this test, future PJI diagnostic studies should include a second arm of “Schrödinger’s hips”.

Key Words: Hip, Arthroplasty, Prosthesis-related infections, Diagnosis, Alpha-defensin

INTRODUCTION

Periprosthetic joint infection (PJI), one of the most severe complications after arthroplasty, has a significant impact on the patient and on health care costs (1,2). Since strategies for treatment of septic prosthetic failure differ considerably from treatments for other causes of arthroplasty failure, an accurate and prompt diagnosis of PJI is of the utmost importance.

PJI cannot be confirmed or excluded based on the result of a single diagnostic test. Several definitions have been proposed in recent years (1,3-6); of which the modified MSIS criteria, which include two major and several minor sub-criteria, are the most commonly used definition⁵⁾ (Supplementary Table 1). The modified 2018 International Consensus Meeting (ICM) (Supplementary Table 2) and European Bone and Joint Infection Society (EBJIS) 2021 criteria (Supplementary Fig. 1), which were recently published, include alpha-defensin (AD), an antimicrobial peptide released by neutrophils in response to pathogens (7). Two different AD tests are available: the ELISA test, which requires performance of analysis in a laboratory, and the lateral-flow (LF) test, which has the practical advantages of providing a result within 10 minutes and that the analysis can be performed virtually anywhere (7). Differences in diagnostic accuracies between various joints have been reported^{7,8)}; a recent meta-analysis reported sensitivity and specificity for THA separate from TKA: pooled sensitivity for THA PJI diagnosis using the LF test was 80%, and specificity was 92%, slightly lower than its accuracy for TKA (87% and 96%, respectively) (7).

No previous prospective study investigating the diagnostic accuracy of the AD-LF test for diagnosis of PJI exclusively in chronic painful hip arthroplasties has been reported in the literature. The SWAG study (Synovasure and White blood cell count after Aspiration compared to the Gold standard) was designed for prospective evaluation of the diagnostic performance of AD-LF testing in this challenging (and heterogenous) group of patients. The aim of the study was to provide answers to the following questions:

- 1) What is the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the AD-LF test for diagnosis of PJI for chronic painful THA?
- 2) Which subgroups in which AD-LF testing is more (or less) accurate (e.g., metallosis) can be identified?

MATERIALS AND METHODS

This single center prospective cohort study was conducted in a large secondary teaching hospital and PJI referral center. Approval for the study was granted by the ethics committee of Noordwest Hospital Group in February 2018 (No. L-018-009) and the informed consent was waived by the ethics committee.

Patients (range, 18-99 years) who underwent joint aspiration as part of the diagnostic work-up for evaluation of painful or poorly functioning total hip arthroplasty (THA) between March 2018 and May 2020 at Noordwest Hospital Group were included in a prospective database. A total of 151 consecutive patients underwent joint aspiration during this period. Exclusion criteria for this study were as follows: suspicion of an acute PJI (joint aspiration performed within three months of index surgery), insufficient amount of fluid for AD testing (dry tap, <1 mL), and aspiration performed after resection arthroplasty. A priori, antibiotic use and suspected metallosis were not regarded as exclusion criteria. Data regarding aspirations performed for painful hip hemi-arthroplasties (HHA) were collected separately. The modified MSIS criteria were used to define PJI (5). For the purpose of comparison, the modified 2018 ICM criteria (6) and EBJS criteria were also described (9).

Aspiration of the hip was performed in the operating room under sterile conditions using fluoroscopy. A (temporary) diagnosis was then made, and patients were selected for aseptic revision, septic two-stage revision, wait-and-see policy, or antibiotic suppression therapy. Two-stage revision was performed in cases where there was suspicion of PJI. In cases where the results indicated aseptic pathology, one-stage revision was performed or a wait-and-see policy was used in subclinical or improving patients. Antibiotic suppression therapy was considered in high-risk patients in terms of substantial co-morbidities with suspicion or evident PJI. Six tissue cultures were collected during performance of revisions surgery. Samples were cultured for at least 14 days.

The patient's history, clinical findings, laboratory tests including serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, and results of synovial tests from joint aspiration were documented. The AD-LF test (Synovasure; Zimmer Biomet, Warsaw, IN, USA) was performed according to manufacturer guidelines: after aspiration, the synovial fluid was added to the sample cup, and the microsafe tube was placed horizontally in the cup. Once the fluid had reached the black line on the tube, the contents were transferred to the pre-filled dilution bottle. After mixing, three drops of fluid were dispensed on the lateral flow device, and the results were read after 10 minutes. When a sufficient amount of synovial fluid could be obtained, the remaining fluid was used for culture in blood culture bottles (aerobic and anaerobic), WBC count and polymorphonuclear neutrophil percentage (PMN%), and leukocyte esterase (LE) dipstick testing.

Calculation of sensitivity, specificity, PPV, and NPV of the AD-LF test was performed in the group of patients who underwent revision surgery. Except for age, the scale variables were described using the median and the range regarding a non-normal distribution measured using the one-sample Kolmogorov-Smirnov test. 95% Confidence intervals (CI) were calculated and are described. Statistical analysis was performed using IBM SPSS Statistics (ver. 19.0; IBM, Armonk, NY, USA).

RESULTS

A total of 151 patients underwent aspiration of hip arthroplasty; of these, 56 patients were excluded. Exclusion criteria included HHA ($n=9$), acute PJI ($n=5$), or an insufficient amount of synovial fluid for performance of the AD test ($n=42$). Ninety-five aspirations of THA were included. These were split into two groups: the analysis group, with sufficient data to confirm or rule out PJI, and the clinical group: patients who did not meet criteria for diagnosis of PJI, but who did not undergo surgery and therefore remain cases where PJI cannot be excluded. A flowchart is shown in Fig. 1.

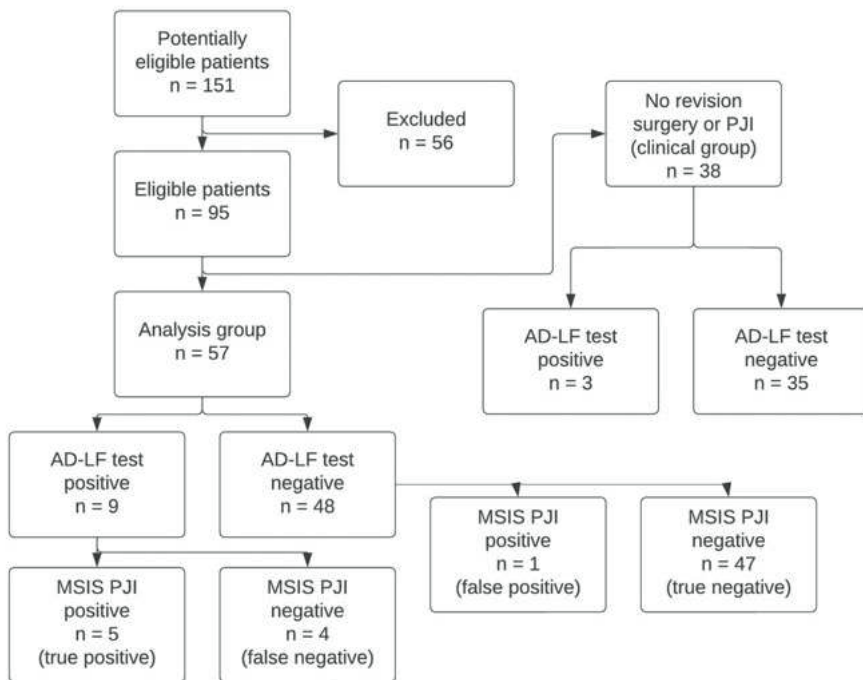


Fig. 1. Flowchart of patients, index test, and reference standard.

PJI: periprosthetic joint infection, AD-LF: alpha-defensin lateral flow, MSIS PJI: Musculoskeletal Infection Society criteria for PJI diagnosis.

Table 1. Patient, Initial Operation, and Test Characteristics

	Analysis group (median and range, or occurrence) n=57	Clinical group (median and range, or occurrence) n=38
Demographics		
Age (years)	71 (mean: 69.9, range 38 – 89)	74.5 (mean: 71.2, range 49 – 90)
Sex: male	n=17	n=12
Sex: female	n=40	n=26
ASA: I	n=1	n=0
ASA: II	n=40	n=15
ASA: III	n=15	n=14
ASA: IV	n=1	n=1
ASA: unknown	n=0	n=8
BMI (kg/m ²)	26.8 (21.4 – 34.6)	28.0 (21.4 – 42.0)
Deceased	n=0	n=0
Initial operation		
Time interval after THA implantation (months)	69 (4 – 587)	31 (5 – 232)
Primary THA	n=35	n=33
Revision THA	n=22	n= 5
Cemented / Hybrid	n=21	n=10
Uncemented	n=36	n=28
Metal on metal	n=3	n=2
Blood tests		
CRP (mg/L)	2.7 (1 – 25) (n=48)	4.4 (1 – 171) (n=34)
ESR (mm/hr)	11.0 (2 – 94) (n=43)	14.5 (2 – 115) (n=32)
WBC (/nL)	7.1 (4.1 – 12.4) (n=47)	7.4 (3.6 – 11.6) (n=33)
Aspiration results		
1/ AD test	n=57	n=38
AD-LF test: negative	n=48	n=35
AD-LF test: positive	n=9	n= 3
2/ Aspiration cultures	n=52	n=33
Aspiration culture positive	n=2	n=0
3/ WBC count	n=52	n=31
WBC Count: < 3000	n=40	n=23
WBC Count: > 3000	n=12	n=8
PMN % > 80	n=6	n=4
4/ LE test	n=36	n=21
LE Test: negative	n=10	n=1

Table 1. Continued

	Analysis group (median and range, or occurrence)	Clinical group (median and range, or occurrence)
	n=57	n=38
LE Test: trace	n=17	n=15
LE Test: 1+	n=2	n=3
LE Test: 2+	n=3	n=2
LE Test: 3+	n=1	n=0
LE Test: unreadable	n=3	n=0
Intraoperative tests		
Cultures	n=54	
Two or more positive	n=1	
One positive	n=9	
-	n=44	
Histology	n=27	
Positive	n=3	
Negative	n=24	

Values are presented as median (range) or number only.

ASA: American Society of Anesthesiologists score, BMI: body mass index, THA: total hip arthroplasty, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell, AD: alpha-defensin, AD-LF: alpha-defensin lateral flow, PMN%: polymorphonuclear neutrophil percentage, LE: leukocyte esterase.

The analysis group included 57 cases of THA aspiration: 55 patients underwent hip revision surgery (seven positive AD test results), and two patients treated with suppression had definitive PJI. Both patients had a positive result for the AD test and were the only patients in the cohort with a positive culture of aspiration fluid (*Staphylococcus epidermidis* in both cases). Characteristics are shown in Table 1. None of the patients were taking antibiotics prior to, or at the time of, aspiration. Positive cultures from intraoperative samples were found in nine patients. Positive histology was observed in three cases (of 27 cases where histology was performed). Three patients had metallosis: one patient with a false positive AD-LF test result, and two patients who had a true negative AD-LF test result. The clinical group consisted of 38 patients who did not undergo surgery because of subclinical aseptic loosening with decreasing pain/wait-and-see policy (n=15) or aseptic loosening excluded/other diagnosis than PJI (n=23). All patients were excluded for analysis of AD test performance. Three patients in this clinical group had a positive result for the AD-LF test; one of these patients had metallosis. Differences in the results of aspiration and intra-operative tests between the analysis group and the clinical group are shown in Table 2.

Table 2. Comparison of Aspiration and Intraoperative Results between the Analysis Group (in Which PJI Could Be Confirmed or Ruled Out) and the Clinical Group (PJI Not Confirmed nor Ruled Out but Treated according to Symptoms)

Analysis group				Clinical group			
	Work up PJI confirmed (fistula or 3 MSIS minor criteria)	Work up PJI suspected (1-2 MSIS minor criteria)	Work up PJI not suspected (0 MSIS minor criteria)	Work up PJI confirmed (fistula or 3 MSIS minor criteria)	Work up PJI suspected (1-2 MSIS minor criteria)	Work up PJI not suspected (0 MSIS minor criteria)	
N:	2	14	41	0	16	22	
Lab							
CRP >10 mg/L	1 (median: 15)	0 (median: 2)	4 (median: 2.7)		5 (median: 7)	3 (median: 3.8)	
ESR >30 mm/hour	1* (94)	1 (median: 7.5)	3 (median: 11)		6 (median: 20)	1 (median: 9)	
Aspiration							
AD-LF +	2	5	2 (dubious)		2	1 (MoM)	
WBC > 3000 cells/μl	1* (87000)	11 (median: 5500)	0 (median: 1200)		8 (median: 3100)	0 (median: 1600)	
PMN% > 80%	1* (97%)	5 (median: 77)	0 (median: 30)		4 (median: 59)	0 (median: 28)	
LE ++	1*	3	0		2	0	
Blood culture +	2	0	0		0	0	
Intra operative							
	Suppression: 2	Two-stage: 7 One-stage: 7	One-stage: 41		Suppression: 1† Extra-articular pathology: 11 No diagnosis, clinically better in time: 4	Extra-articular pathology: 13 No diagnosis, clinically better in time: 9	
Cultures	-	> 2 positives: 1 1 positive: 2	> 2 positives: 0 1 positive: 6				
Histology +	0	3	0				
PJI + post operative	2 (2/2 AD pos)	4 (3/4 AD pos)	0				

PJI: periprosthetic joint infection, MSIS: Musculoskeletal Infection Society, CRP: C-reactive protein, ESR: erythrocyte sedi- mentation rate, AD-LF: alpha-defensin lateral flow, MoM: metal-on-metal, WBC: white blood cell, PMN%: polymorphonu- clear neutrophil percentage, LE: leukocyte esterase, AD: alpha-defensin, pos: positive.

* Only performed in one case.

+ Pragmatic treatment based on micro-organisms found during the DAIR (debridement, antibiotics, irrigation, and retention) procedure three years prior to inclusion.

Table 3. Diagnostic Accuracy of the Alpha-Defensin Lateral-Flow Test for Total Hip Arthroplasty

	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
MSIS									
All patients	5	4	1	47	83% (36-100)	92% (81-98)	56% (31-77)	98% (89-100)	91% (81-97)
Modified 2018 ICM									
1: All patients (inconclusive treated as infected)	9	0	8	40	53% (28-77)	100% (91-100)	100%	83% (75-89)	86% (74-94)
2: All patients (inconclusive treated as non-infected)	6	3	1	47	86% (42-100)	94% (83-99)	67% (39-86)	98% (88-100)	93% (83-98)
3: Exclusion of 'inconclusive' results	6	0	1	40	86% (42-100)	100% (91-100)	100%	98% (87-100)	98% (89-100)
EBJIS									
1: All patients (likely treated as infected)	9	0	11	37	45% (23-68)	100% (91-100)	100%	77% (69-83)	81% (68-90)
2: Exclusion of 'likely' results	9	0	10	37	47% (24-71)	100% (91-100)	100%	79% (71-85)	82% (70-91)

MSIS: Musculoskeletal Infection Society, ICM: International Consensus Meeting, EBJIS: European Bone and Joint Infection Society, TP: true positive, FP: false positive, FN: false negative, TN: true negative, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value.

In the analysis group, AD-LF sensitivity (MSIS criteria) was 83% (95% CI 36-100%) and specificity was 92% (95% CI 81-98%). PPV and NPV were 56% and 98%, respectively. The number of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN) and a comparison with the other diagnostic criteria are shown in Table 3.

DISCUSSION

This prospective study that included patients with chronic painful THA was conducted in order to evaluate the results of the AD-LF test; according to our findings, sensitivity and specificity were comparable to those reported in other studies on the AD-LF test (7). To the best of our knowledge, this is the first prospective study investigating the AD-LF test exclusively for hip arthroplasty, which is important, because PJI of the hip and PJI of the knee are probably not exactly the same⁷). For example, in this study, exclusion of one quarter of all aspirated patients was required because of an insufficient amount of fluid; in our experience, such “dry taps” are more common in hip aspirations, compared to knee aspirations. In addition, in this study the clinical group reflects the decisions and uncertainties of daily orthopedic practice: not all chronic painful THAs continue to be painful, warranting revision, especially if PJI is not confirmed in the diagnostic workup.

Question 1: What is the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for PJI diagnosis of the AD-LF test for chronic painful THA?

In the analysis group, AD-LF sensitivity (MSIS criteria) was 83% (95% CI 36-100%) and specificity was 92% (95% CI 81-98%). PPV and NPV were 56% and 98%, respectively.

PJI was defined according to the modified MSIS criteria (5). The other two criteria described obviously render different numbers for (mainly) test sensitivity, because more cases are regarded as (possibly) infected. Unfortunately, using the modified 2018 ICM criteria, many cases were considered ‘inconclusive’. Although these cases were neither definitively infected nor not infected, excluding them would be a form of bias. Therefore, we chose to report the numbers considering these cases as infected, as not infected and excluding them. When using the EBJIS criteria and 2018 ICM criteria, there is another caveat: the alpha defensin test is the studied test, but also part of the definition. Thus, a positive result on the AD test enables easier fulfilment of the definition “infected”. This positive feedback is a form of bias, producing fewer false positive test results.

Definitions of PJI have been revised in the last decade and now contain more criteria for use in diagnosis of PJI. It appears that the categories “inconclusive” (2018 ICM) or “infection likely” (EBJIS 2021) were added in order to make it less likely that absence of PJI is incorrectly stated. However, not every chronic painful THA will (or should) undergo revision. According to the current definitions of PJI, intra-operative cultures and histology are required for

exclusion of a diagnosis of PJI. Because (multiple) positive intra-operative cultures result in a positive diagnosis of PJI according to each definition used, these hips can be regarded as “Schrödinger’s hips”. They are infected and not infected at the same time; however, we cannot be certain until we “open the box”. These “Schrödinger’s hips” remain an uncertain factor, leading to bias. To the best of our knowledge, most investigations of the diagnostic performances of PJI tests have been conducted with this bias. Differential verification might be a solution to this problem. Differential verification involves the use of different reference standards between patients (10). One reference standard could be the modified MSIS PJI criteria for patients who undergo revision (so that these patients have a complete reference standard), while the other reference standard could be long-term follow-up for patients selected for a “wait-and-see” approach. With this, it would be expected that PJI patients in the cohort would eventually be identified in the long-term follow-up, therefore the follow-up is used as a proxy to obtain information regarding the true status during performance of the studied test.

Question 2: Which subgroups can be identified in which AD-LF testing is more (or less) accurate (e.g., metallosis)?

Several studies concluded that the presence of metallosis could be a misleading factor, increasing the potential for false-positive AD results (11-14). Of the three patients with a MoM THA in the analysis group, one patient had a false positive result (MSIS not infected, 2018 ICM inconclusive due to a positive AD test result and EBJS infected due to a positive AD test result) and two were true negative. Therefore, despite being a very small subgroup, in this study, one out of three patients with MoM had false positive results. We would advise refraining from use of the AD test in the diagnostic workup of chronic painful hip arthroplasties for MoM patients, at least until studies including larger MoM groups have been conducted.

A second possible variable is the administration of antibiotics before performing the AD-LF test. Based on the best available evidence, administration of antibiotics does not lead to a decrease of the AD level in synovial fluid (15). Antibiotic use was not an exclusion criterion in this study; however, none of the included patients received treatment with antibiotics in the weeks prior to aspiration.

Nine patients with a HHA underwent aspiration and AD testing during the study period. A negative result was obtained for all nine patients (six patients underwent revision surgery and were definitely true negative); however, unfortunately, the sample size was too small to draw any conclusions.

A doubtful positive AD-LF test result was obtained for two patients (Fig. 2). The WBC count was 2,000-2,500 cells/ μ L for both patients. This study is the first in the literature to describe cases where such a doubtful positive test result was obtained. After consulting with the manufacturer, the authors decided that the results of both AD tests should be

regarded as positive for PJI. A one-stage revision, including a very thorough debridement, was performed in both cases. According to the modified MSIS criteria, both cases were not infected, and were only considered infected when the 2018 ICM criteria (1/2, the other being inconclusive) and EBJIS criteria (2/2) were used because of the positive results of the AD tests. When the result of the doubtful AD-LF test was considered negative, these two border line cases would be regarded as not infected and inconclusive, respectively (2018 ICM criteria), and likely but not confirmed (EBJIS, both), demonstrating the bias we anticipated in advance. If borderline test results are the only sign of infection, they should be considered with caution and should be used as a “guide value” rather than a “cut-off value”. If revision is indicated in these cases, apart from the test results, a one-stage revision with thorough debridement and intraoperative cultures and histology could be considered, especially since obtaining positive cultures during revision surgery is not associated with inferior survival in the short-term (up to two years)¹⁶. Follow-up or repeat aspiration would be an alternative approach in cases where revision is not indicated.

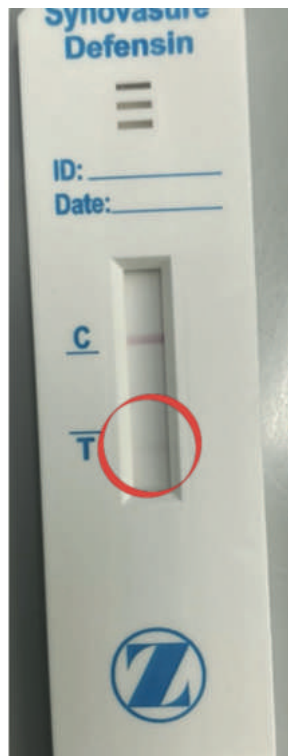


Fig. 2. Example of a doubtful positive alpha-defensin lateral-flow test (Synovasure; Zimmer Biomet).

The main caveat of this study is that not every patient underwent all possible tests: due to the hospital infrastructure, histology was not performed in all cases, and sonication was not possible. The LE test was not performed in some cases because of low yields. In addition, due to the patient centered design of this study, not all patients underwent revision surgery. It should be noted that selecting the revision cases does introduce bias. If, understandably, such a selection is made, the use of follow-up or repeat aspirations is advised as the second arm for differential verification of these “Schrödinger’s hips”, in order to ultimately determine the true accuracy of tests for diagnosis of PJI and their role in the diagnostic work up of patients with chronic painful arthroplasties.

CONCLUSION

The AD test, which is a useful addition to the arsenal of tests available for diagnosis of PJI, can be helpful to the surgeon and patient in the decision-making process. Because not all patients will undergo revision surgery, we suggest incorporating differential verification for the accuracy of PJI testing in groups of patients with painful arthroplasties. One reference standard (PJI definition) is used for verification of all patients with a positive index test result and a second reference standard (follow-up or repeat aspirations) is used for verification of all patients with a negative result.

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10

General Discussion

The diagnosis and treatment of periprosthetic joint infection (PJI), especially a low-grade periprosthetic infection, remain a significant challenge and often requires multiple diagnostic tests. A painful prosthesis may result from a low-grade infection; however, differentiating this from aseptic problems can be challenging. To effectively distinguish between these two conditions, it is essential to have a comprehensive understanding of the available and supportive diagnostic tools. In this chapter, the challenges in diagnosing PJI will be discussed how to enhance the knowledge of supportive diagnostic tests, specifically focusing on the use of nuclear imaging and the Alpha-Defensin (AD) novel synovial biomarker.

The definition of Periprosthetic Joint Infection

This thesis investigated the accuracies of nuclear imaging and AD testing in diagnosing PJI. An essential aspect in these investigations is a reliable reference standard for diagnosing PJI. The diagnostic standard for PJI have been the modified MSIS criteria in the last decade. These criteria were the result of expert consensus meetings, lacking real validation studies. This has led to concerns about its sensitivity¹. Since then, the ICM 2018 definition has been developed and validated which was reported with increased sensitivity to 97.7% (compared to the 86.9% sensitivity of the modified MSIS criteria) and specificity of 99.5% for diagnosing PJI¹. In 2019, another validation study was published which confirmed the higher sensitivity for the ICM 2018 criteria (94.9%) compared to the modified MSIS criteria (53.1%). The specificity was almost similar (95.2% and 97.7%, respectively)^{2,3}. Another validation study, in 2020, reported a sensitivity of 96% and specificity of 86% (for hip PJI) using these modified criteria⁴. The validation of these criteria, however, remain problematic, mainly due to the use of different “gold standards”. The EBJS also published a new set of criteria for diagnosing PJI in 2021. A recent study (2021) was performed comparing 4 different criteria sets for diagnosing PJI: MSIS, IDSA, ICM and EBJIS. The conclusion was clear; the use of different criteria for PJI significantly influences the rate of diagnosed PJIs at THA revision⁵.

There are several treatment options for PJI, depending on several factors, but the diagnosis is essential for choosing the best treatment option. The treatment options are: Debridement, Antibiotics and Implant Retention (DAIR), Revision (one- or two staged re-implantation), Suppression Therapy and, in the worst-case scenario, definitive Resection Arthroplasty. The main goal is to offer the least debilitating treatment option for patients. In clinical practice, the choice for treatment is depending on several factors. When the diagnosis is not conclusive for PJI (‘inconclusive’ PJI), it leads to several possible treatment options. For reliable comparison of results, the same definition for PJI should be used in every case. Ideally, a diagnostic test should be 100% specific, 100% sensitive and useful in clinical practice. Unfortunately, this not realistic at the moment. As mentioned above, the ICM 2018 criteria has incorporated a ‘inconclusive’ PJI group and using a number of

different tests. The latest EBJIS criteria also incorporated a ‘infection likely’ PJI group. These two middle groups are not ideal for research purposes, because treatment option can vary because of the unclear diagnosis. In the future, the ICM group and the EBJIS will optimize their definitions, in line with the newest research data. In order to create essential uniformity in research and clinical practice, it would be a major positive development when ICM and EBJIS develop a single definition for PJI. In 2019, an expectant development was seen when a joint paper by the EANM, EBJIS, and ESR (consensus document for the diagnosis of PJI) was published⁶. In the meantime, it may be best to report and investigate all three definitions for comparison. Both clinicians and researchers should be aware of the lack of a golden standard for diagnosing PJI and that accuracy studies are flawed because of “Schrödinger’s hips and knees”, as described in Chapter 9 for the hip.

The prospective study in Chapter 9 reported results of the alpha-defensin lateral flow (AD-LF) test for PJI diagnosis of the hip with good sensitivity (83%) and specificity (92%), using the Musculoskeletal Infection Society (MSIS) criteria. These test characteristics are comparable (within the statistical margins) to the sensitivity and specificity found in Chapter 8 for the AD-LF test (80% and 92%, respectively). However, using the EBJIS criteria for diagnosing PJI, the AD-LF test becomes perfectly specific, but sensitivity decreased to 45%, meaning that a lot of negative AD-LF tests are considered false-negative with this definition. The same issue arises when the ICM 2018 criteria were used. Excluding the inconclusive cases, the AD-LF test demonstrated high sensitivity (86%, Chapter 9) and perfect specificity (100%, Chapter 9) using the ICM 2018 criteria. An important remark, however, is that the most difficult cases (the ‘inconclusive’ cases) should not be excluded from analysis. The inclusion of ‘inconclusive’ cases into the PJI group (most of these cases will probably be treated as such), the sensitivity decreased (91% and 53%, respectively). Unfortunately, these numbers are biased: with a positive AD test, the EBJIS criteria are fulfilled for PJI, and three (out of six) points for PJI diagnosis are received in the modified ICM 2018 criteria. The 100% specificity should be considered bearing this in mind. Another flaw with these PJI accuracy studies is described in Chapter 9. The conservative treated patients, the “Schrödinger’s hips”, are not included, meaning that potential PJI patients may be missed. The results could be extrapolated to other PJI patient undergoing revision surgery, but not to patients with a non-functional arthroplasty in general.

The role of nuclear imaging in diagnosing PJI

The issue of different reference standards, various index criteria using the same imaging technique, as well as the quality of the studies were important limitations in the studies that used nuclear imaging for diagnosing PJI.

In the meta-analyses (Chapter 4 and 5) pooled results were reported to get more clarity of the diagnostic accuracies of the different nuclear imaging modalities and their tracers. There was significant heterogeneity in the data concerning diagnostic accuracy

in studies assessing PJIs. Although a valid reference test (at least 1 positive culture) was an inclusion criterion in the meta-analyses, the explanation for the heterogeneity may lie in the use of different criteria for diagnosing PJI in the included studies. Although a valid reference standard with microbiologic confirmation was a stringent inclusion criterion in the meta-analyses and systematic reviews, there is a risk of false-positive diagnosis of infection, which potentially could decrease specificity. Only studies with a clinical follow-up of at least 6 months were included. For obvious reasons, surgery with microbiologic evaluation could not be performed in all patients (patients believed to be without infection did not always undergo surgery). Again, an issue that can be addressed to the ‘Schrödinger’s hips and knees’. This could result in more false-negative results and potentially decrease the reported sensitivity in the meta-analyses when an infection is found after the final diagnosis, especially in the case of a low-grade infection. The analyses of studies investigating nuclear imaging for diagnosing PJI was also more complicated because of the extended use of different index test criterion for the same imaging technique for diagnosing PJI. For example, using LS for diagnosing PJI of the hip, all included studies used different criteria. The analysis of sources for heterogeneity for LS diagnosing PJI demonstrated a statistically significant effect of the image review procedure. The diversity of interpretation criteria used for the index tests and the insufficient details regarding implants and imaging procedures reduced the statistical power.

Moreover, the meta-analyses defined test performance for the various imaging modalities when used in isolation for diagnosing PJI. However, in clinical practice, nuclear imaging should not be used in isolation for diagnosing PJI because additional tests, including synovial and serum tests, will be required for diagnosing PJI. Another important limitation of the included studies is the lack of uniform criteria for diagnosis PJI. This was also a concern in our systematic review to investigate the reproducibility of the various nuclear imaging modalities (Chapter 5). The inclusion criteria could not be restricted to studies using the MSIS because many of the included studies were performed before the development of these criteria. The meta-analyses included reports from 1988; the unmodified 2011 MSIS criteria were published much later, no consensus meeting had been held yet, and the latest EBJIS criteria didn’t arrive until years later (2021).

It is important to note that the most challenging patient subgroup are the patients suffering from chronic problems after TJA in which nuclear imaging can significantly impact clinical decisions on patient management. However, the diagnostic approach for PJI in this subgroup is variable between countries and centers⁶ and is usually guided by diagnostic criteria for PJI and available imaging techniques⁷. Advanced nuclear imaging techniques such as ^{99m}Tc-HDP BS, radiolabeled leukocyte scintigraphy (LS) with or without combined with SPECT, CT or FDG PET/CT can be used to evaluate suspected PJI. However, the choice of the most accurate imaging procedure and optimal radiopharmaceutical remains controversial as described in Chapter 2, 3, and 4. The literature search reveals different

diagnostic accuracies using the same imaging techniques, with consecutive agreement that there is no single nuclear imaging modality to date that is able to diagnose all possible disorders with satisfactory accuracy⁸. Therefore, a combination of modalities remains necessary in many cases. This thesis confirmed in Chapter 2, 3 and 4 that BS (including three-phase BS) is the most widely used screening modality for diagnosing PJI. BS is very sensitive for bone remodeling and no significant differences were found between the various radiopharmaceutical tracers. However, the role of BS is limited in the first 12-24 months after THA and up to 5 years after TKA (also depending on the type of prostheses)⁹. The most important contribution of the modality is its very high negative predictive value (NPV) when performing BS (with SPECT/CT) so unnecessary (additional) nuclear scans can be avoided⁶⁻⁸. It is considered strong evidence against the presence of an infection. Conversely, after a positive bone scan, a more specific imaging modality will be needed. The reported isotope distribution patterns on bone scans are less specific for infection and a bone scan is not recommended as a single modality. The choice of this additional imaging technique remains one of the most interesting research questions. However, this decision will also be dependent on local availability, time, cost, expertise and the possibilities for multidisciplinary approaches (which is recommended). The possible options for additional imaging are LS, LS-BMS, AGS (combined with SPECT/CT) or FDG-PET/CT.

A more specific imaging modality is radiolabeled LS with ^{99m}Tc-HMPAO or ¹¹¹In-oxine, which can confirm or rule out infection with high diagnostic accuracy. Interpretation of LS can potentially be hampered by the accumulation physiologically in the bone marrow. To reduce false-positive results, LS is therefore often combined with BMS. In Chapter 3 and 4, a significant heterogeneity was reported, related to interstudy differences of interpretation criteria. However, when the appropriate interpretation criteria are used, LS can be a specific and accurate imaging modality. It is highly recommended to use standardized criteria for labeling procedure, acquisition, and interpretation. In future research investigation the role of LS in diagnosing PJI, the European Association of Nuclear Imaging (EANM) criteria could be a valid option⁶⁻⁸. Interesting, for the more patient-friendly alternative with in vivo labeling of leukocytes (AGS) only a moderate pooled specificity of 75% for hip PJI was found, contrary to the high specificity of 95% for knee PJI. The differences between the hip and knee joint, on a theoretical basis, is that the knee joint is a complex structure with multiple compartments and a relatively smaller soft tissue envelope compared to the hip. In TKA, infections may localize more closely to the surgical site, potentially allowing for more precise localization through AGS. The hip joint is encapsulated within a larger area of surrounding soft tissue and musculature. In THA, the potential for infection extends beyond the joint itself, which may complicate the interpretation of scintigraphy results due to the added challenge of distinguishing infection from other inflammatory processes in the surrounding tissues. After reviewing the literature in Chapter 2 the conclusion was that this technique is not the preferred modality at the moment and therefore has not

gained wide acceptance. The findings of the meta-analysis in Chapter 4 suggest a need to reassess this conclusion regarding knee PJI, although further investigation will be required.

The FDG-PET/CT could be a choice for additional, more specific imaging for diagnosing PJI. In the period 2001 - 2014, the role for this imaging modality was not clear. The nonspecific mechanism of 18F-FDG uptake has been shown to be beneficial in terms of high sensitivity and high negative predictive value, but FDG-PET/CT could have a limitation of a low specificity for imaging inflammation and infection after TJA. In literature we found a variety of diagnostic criteria in studies investigating the role of FDG-PET/CT for diagnosing PJI. The highest diagnostic accuracy was found using a specific criterion for infection that was related to the location of the FDG uptake in the bone-prosthesis interface (pattern) of hip PJI. For diagnosing knee and hip PJI with FDG-PET/CT, the EANM/SNMMI guidelines reported an overall sensitivity of 96% and a specificity of 98% for diagnosing knee and hip PJI in 2013¹⁰. In later studies, different diagnostic accuracies were reported, as reported in Chapter 3, 4 and 6. In Chapter 6, we confirmed the high sensitivity (85%) and high specificity (94%) for hip PJI. Important to note is that the scans were analyzed as an isolated diagnostic test. In our opinion, nuclear imaging should not (or seldom) be used in isolation but in concert with the other elements of diagnostic evaluation. For TKA, as described in Chapter 4, FDG-PET/CT may not be the preferred imaging modality because of the inferior specificity compared to other imaging modalities.

The diagnostic performance of FDG PET/CT in detecting hip PJI has been increasingly proven not be inferior to labeled LS. However, the exact role of FDG-PET/CT and the diagnostic accuracies in diagnosing PJI remains subject for debate¹¹⁻¹³. As the role of BS as a sensitive screening tool is established, which additional imaging modality should be chosen by the clinician after a positive bone scan? Are there decisive and defining differences between the imaging modalities so that the clinician can choose the best option? The answer is not that simple. This decision will firstly be dependent on local availability, time, cost, expertise and the possibilities for multidisciplinary approaches. Not only these potential practical limitations make the answers to these questions difficult. In research, neither one of the nuclear imaging modalities is superior. In various reports, the comparison between FDG-PET/CT and LS (-BMS) was investigated. In 2022 a study was published in which the two imaging modalities were directly and prospectively compared in patients with chronic problems after TJA¹⁴. The conclusion of this study was illustrative (and in line with our results in Chapter 3 and 4); LS-BMS SPECT/CT was confirmed highly accurate in confirming chronic PJI, while FDG PET/CT has an appropriate accuracy, but the utility of its use in the clinical diagnostic algorithm of suspected PJI needs further evidence.

In conclusion, there is no superior nuclear imaging modality with the desired specificity to confirm the diagnosing of hip or knee PJI. As screening tool (with high sensitivity), the role of BS is established, although limited in the first postoperative years after implantation. When a clinician needs more additional imaging, with higher specificity, both LS-BMS

(SPECT/CT) and FGD-PET/CT can be selected but this choice can be dependent of other factors including availability, expertise and local rules.

The role FDG-PET/CT after resection arthroplasty in the treatment of PJI

In the two-stage revision treatment of PJI, resection arthroplasty of the infected hip prosthesis is the first step for the eradication of the infection. Two-stage revision is generally considered the gold standard for treatment of PJI and involves removal of all associated components with radical debridement of all possible infected tissue and bone, followed by a long period of (intravenous) administration of anti-biotics. The reported rate of failure to eradicate infection after a two-stage revision is up to 30%¹⁵⁻¹⁶. Moreover, the treatment of re-current infection after two-stage revision may have lower success rates than the first attempt in terms of infection recurrence and functional outcomes. Therefore, in cases of suspected residual infection after resection arthroplasty, the identification and localization of an infection is crucial for initiating the appropriate medical and/or surgical treatment. It can have critical impact on the discussion for re-implantation, and therefore on joint function and patient quality of life¹⁷. The role of FDG-PET/CT after resection arthroplasty in complex PJI cases was investigated in Chapter 7. This patient subgroup is complex, as treatment has failed to improve their clinical condition. There was no available literature that reported the use of FDG-PET/CT in the assessment of residual infection after resection arthroplasty of the hip and the timing of second-stage re-implantation. Unfortunately, there was no specific uptake pattern or specific intensity of uptake at the resection area. However, the FDG-PET/CT findings directly influenced the two-stage management in the majority of these complex cases. In our opinion, the role of FDG-PET/CT after resection arthroplasty should be limited to the exclusion or diagnosis of other infectious foci during the interim period in patient with persistence of elevated CRP and/or ESR serums levels, and not for local monitoring of the resection areas. In Chapter 7, we illustrated multiple cases, also cases in which the BS was negative, but the FDG-PET/CT demonstrated a crucial and different finding that influences the treatment options directly. It is important to be aware that BS is only useful in bone remodeling, not suitable for the detection of infectious foci, especially in patients with (multiple) underlying medical conditions.

The reproducibility of hybrid imaging

In the field of nuclear orthopedic imaging for painful prosthesis, concerns regarding the methodological quality and level of evidence has been previously been described in this thesis¹⁸. An important aspect of clinical usability of nuclear imaging is the interpretation and reproducibility of the scan. Remarkably enough, this important aspect was clearly underreported in the studies investigating the role of nuclear imaging in the assessment of PJI. Most of the studies reported the consensus results between two readers and therefore analyzing the intra- and interobserver agreement was not possible, as described in Chapter 5.

The reported diagnostic accuracies of the nuclear imaging modalities in the assessment of symptomatic TJA reflects the agreement of the interpretation of the scan (index test) with the reference standard. However, understanding the variables which are of influence to the interpretation of a scan is important for the outcome of (false) positive or (false) negative results. These variables are related to several domains such as the index test, the references standard and observer related factors. Important variables related to the subject (the painful arthroplasty) are the time interval between imaging and surgery, location and type of implant, and severity of the infection. For example, the interpretation of a low grade PJI could be more challenging for the observer and could lead to more false negative results compared to diagnosing an acute PJI. The type of imaging modality (index test), the performed imaging protocol, and the used diagnostic criteria could also affect the interpretation and outcome. For example, a variety of diagnostic criteria was reported for various nuclear imaging modalities which could lead to different diagnostic accuracy outcomes regarding the investigated imaging modality^{19,20}. Finally, in the interpretation of the scans, the background of the observer such as the level of expertise and experience may also affect the diagnostic outcome. These factors could not only affect the reported diagnostic accuracy, but may also introduce variations in intra- and interobserver agreement. These variations are important and potential compromising factors for the reproducibility and therefore the clinical application of the imaging modalities in the assessment of symptomatic TJA. We recommend future investigations to report implant characteristics, time interval between imaging and surgery, degree of infection, and separately analyze hip- and knee arthroplasties.

Can the same criteria be used for knee and hip PJI?

Hip and knee PJI have been analyzed in the same group in the ICM 2018 guidelines²¹. In 2018, 63% of the members of the international meeting disagreed that the same criteria can be used for both joints²². In the same year, a study validating the modified ICM 2018 criteria reported slightly higher diagnostic performance for hip PJI, compared to knee PJI (and different cutoff level seem)⁴.

The hip and knee joint are two different entities for several reasons. A critical aspect that warrants attention is the synovial fluid and its associated properties within the hip and knee joints. The compositions of synovial fluid vary significantly between these two joints, influencing inflammatory responses and healing processes post-surgery. The knee joint, with its larger surface area and increased mobility, tends to experience different synovial fluid dynamics compared to the hip joint. For example, the knee typically has a higher concentration of inflammatory markers and cytokines in pathological conditions, which can affect recovery and the occurrence of PJI. Conversely, the hip joint may exhibit a different profile, potentially related to its more stable anatomical structure and weight-bearing function. Given these inherent differences in synovial properties, it becomes

even more crucial to analyze the problems that arise after total hip arthroplasty (THA) and total knee arthroplasty (TKA) independently. Such an approach helps to mitigate potential biases in future research, ensuring that the unique characteristics of each joint are adequately considered. For instance, hormonal differences, such as the presence or absence of osteoarthritic change, may lead to different synovial fluid responses that ultimately impact clinical outcomes. Moreover, the microbiome is different in the various parts of the human skin and the soft tissue coverage is significantly different between the joints. There are also surgical and implant related differences; for example, the use of bone cement, tourniquet, coatings and the surgical approach. Another difference is the causative microorganisms for PJI, which is definitely the case for shoulder versus hip and knee PJI²³. In 2017, a study was performed to identify and compare the causative bacteria of prosthetic knee and hip joint infections²⁴. A similar etiology of hip and knee PJIs was found, however, bacteria isolated from knee showed higher resistance rates when compared with those isolated from the hip.

Another important dissimilarity is the aspiration, which is much easier for the knee joint. For hip aspiration, the use of fluoroscopy or ultrasound is often needed. Despite these supportive imaging tools, a dry tap is more often the case for the hip compared to aspiration of the knee²⁵, which can affect the diagnostic accuracies. Blood contamination is more often seen with hip aspiration which can result in more false-negatives, a possible explanation for the lower sensitivity of AD testing after hip aspiration (Chapter 8 and 9).

The use of nuclear imaging for diagnosing PJI was separately investigated in Chapter 3 and 4 because of the described differences between the hip and knee joint. It was already obvious that postoperative physiological bone remodeling after hip versus knee implantation, which induces accumulation of radiopharmaceutical in asymptomatic prostheses, was different between the two joints. Physiological tracer uptake in a bone scintigraphy after THA is observed up to 12–24 months after implantation, while postoperative uptake after TKA is observed up to 5 years^{26,27}. This is an important limitation in using bone scintigraphy after TJA. This underlines that THA and TKA should be investigated separately. The pooled results for diagnosing PJI of the hip versus the knee was also different in the use of FDG-PET/CT for diagnosing PJI. This imaging modality may not be the preferred imaging technique for TKA, while a satisfactory diagnostic accuracy was found for diagnosing hip PJI. In Chapter 6 the diagnostic accuracy of FDG-PET/CT was investigated after THA and, indeed, when using the right diagnostic criteria, an acceptable diagnostic accuracy was found (sensitivity 81% and specificity 94%). After the results of the meta-analyses for the knee, the conclusion was that the use of FDG-PET/CT for diagnosing PJI of the knee was less useful, because of the inferior diagnostic results. For AGS, there were also important differences in diagnostic accuracies between the two joints. Regarding hip PJI, a relatively modest pooled specificity of 75% was found, while a high specificity was reported for knee PJI.

In conclusion, this thesis investigated and reported various important differences in diagnosing PJI for the knee versus the hip joint after TJA, including the different diagnostic accuracies when using nuclear imaging and the alpha defensin synovial biomarker. Future investigations should focus on the specific challenges and complications associated with THA and TKA as separate entities. By doing so, researchers can achieve a clearer understanding of the risk factors, outcomes, and effective interventions pertinent to each joint. This focused approach may not only improve the reliability of research findings but also enhance clinical decision-making and patient care strategies in orthopedics.

The incidence of low-grade Periprosthetic Joint infection

A significant limitation of our investigations, as well as those conducted by others in the field of PJI, is the low incidence of patients developing a low-grade PJI. Infection complicates only 1-2% of primary prostheses. Even in a large regional clinical Centre, this would lead to no more than 10 to 20 hip and knee PJIs on a yearly basis. As a result, the studies and analyzes had to be performed with small cohorts (Chapter 6,7 and 9). As a result, most studies tend to be retrospective cohorts. Prospective cohorts (Chapter 9) usually take a long time, and still often yield small cohorts. Systematic reviews (Chapter 5) and meta-analyses (Chapter 3,4 and 8) are considered the highest level of evidence, but the majority of the included studies that investigated PJI demonstrated limited quality. For that reason, only prospective studies were included in Chapter 8, but the resulting data was still heterogeneous. Although only prospective studies were included and strict inclusion and exclusion criteria were applied, the heterogeneity of the included studies is one of the major shortcomings of this meta-analysis. Small differences in patient cohorts of the included studies, such as differences in aspiration location, aspiration techniques, possible use of lavage, and the period between aspiration and revision, probably are the main reason for this heterogeneity. As described above, these important variables were mostly not sufficiently reported so pooling heterogeneous data was unavoidable. Although future, high quality, and prospective investigations are needed to achieve more comprehensive understanding of the available and supportive diagnostic tools for diagnosing PJI, this will not be easy because of the low incidence of low-grade PJI.

CONCLUSION

Diagnosing PJI remains an interesting and challenging research topic, especially for the subgroup of patients with chronic problems after TKA and THA who might be suffering from low-grade PJI. During the years, important developments have been described in the diagnosis of PJI including the introduction of AD and other synovial fluid tests. When the diagnostic evaluation using synovial fluid markers clearly indicates infection, there is little or no need for additional nuclear imaging tests. However, if those tests cannot be

obtained or are inconclusive, nuclear imaging can be used in concert with other elements of diagnostic evaluation, including microbiologic analysis, serum and synovial testing, to arrive at a more-precise diagnosis than is possible with imaging or laboratory testing alone. We believe that nuclear imaging seldom is used in isolation, and probably should not be used that way. On the other hand, the most challenging patient subgroup are the patients suffering from chronic problems after TJA in which nuclear imaging can significantly impact clinical decisions on patient management. As illustrated in this thesis, nuclear imaging can have also crucial impact on patient management who appeared therapy resistant after resection arthroplasty in the treatment of PJI. In this context, it is important that the orthopedic surgeon is aware of the nuclear imaging options and has some understanding of the drawbacks and added value of the most used nuclear imaging modalities. The first goal of this thesis was to create an overview and outline all possible nuclear imaging modalities for diagnosing or excluding PJI. However, the choice of additional imaging should be done in strong collaboration with the nuclear physician (and if possible as a part of multidisciplinary approach).

This thesis investigated the diagnostic accuracies of the various imaging modalities for diagnosing PJI. In literature, heterogenous data was found with a variety of index- and reference standards and relative limited quality of studies. With a sufficient and complete analyses for knee and hip PJI separately, we believe that this thesis may be initiating new studies with improved methodology. However, performing high quality studies, prospectively in design, with large or sufficient enough included patients is not easy. Especially the subgroup of low-grade PJI patients is challenging and multicenter studies are probably necessary. Furthermore, it is important that patients should be studied with diagnostics in a standardized matter (algorithm). There are developments with the collaboration and consensus meetings between the EANM, EBJIS, and ESR which are of potential interest. Moreover, for future study of the diagnostic accuracies of tests it is crucial to use the same reference standard. The lack of a golden standard remains problematic for PJI research. The development of novel biomarkers, and the development of more specific radiopharmaceuticals is important and more studies are needed to improve the outcome of the patient with a suspected prosthesis infection.

This thesis discusses the most difficult group of patients for diagnosing PJI in which infection was possible, but uncertain. This uncertain group of patients are defined as 'inconclusive' (ICM 2018) and 'infection likely' (EBJS). Diagnostic accuracies are dependent on a variety of factors, including valid index test criteria and a valid reference standard with the highest sensitivity and specificity as possible. However, this specific group of 'inconclusive' or 'infection likely' for diagnosing PJI reflects a limitation in the reported diagnostic accuracies of investigation (including nuclear imaging and AD testing) of tests for diagnosing PJI. When the diagnosing for PJI is unclear, the outcome can be dependent of the orthopedic surgeon preferences and the treatment agreed on with the patients.

This means that when a 'wait and see' policy is agreed on with the patient, a potential low-grade PJI can be missed and potentially more false negative results can be reported. The absence of a universally accepted gold standard for PJI diagnosis over the years, combined with the application of various diagnostic criteria sets, represents a critical limitation affecting the reliability of reported findings.

This thesis highlighted the distinct differences between the hip and knee joints following total joint arthroplasty (TJA). The differences were theoretically outlined in various aspects and the research findings of this thesis further substantiate the necessity of treating these two joints separately in clinical studies and analyses. The evidence presented in this thesis emphasized that hip and knee prostheses are subjected to different biomechanical aspects and synovial characteristics, which can lead to varying rates and types of complications associated with each joint. This underscores the importance of individualized analyses that consider the unique anatomical, biomechanical, and synovial fluid characteristics of each joint.

Finally, this thesis emphasize that advanced hybrid imaging is increasingly used and it is important to keep investigating the diagnostic value of the different imaging techniques so the best technique can be incorporated in the diagnostic workups for diagnosing PJI. Nuclear imaging can be crucial for patient management in PJI and incorporation of nuclear imaging should be considered in the international workup for diagnosing PJI, following up on the EBJs. Unfortunately, we were not able to find enough evidence to support strict recommendation for using either LS-BMS (SPECT/CT) or FDG-PET/CT after a positive bone scan. Future research will be necessary. The results of this thesis demonstrated that validated uptake interpretation criteria are necessary, including the standardization of both the reconstruction parameters and the interpretation criteria. Validation in larger studies will be needed, but will not be easy...

Recommendations for future studies investigating PJI

This thesis demonstrated important shortcomings in studies investigated PJI. To advance knowledge and unify research for diagnosing PJI we recommend future studies to consider the following.

Design

We recommend future studies to investigate PJI in a prospective design. Because of the low incidence of low-grade PJI, larger (inter-)national trials and collaborations may be needed.

Subject

We strongly recommend future studies to investigate hip and knee joints as separate entities. Moreover, all important variables of the investigated subject should be reported. This includes:

- The implant characteristics:
 - cemented or uncemented implants.
 - type of implant (Hemiarthroplasty vs THA, metal-on-metal implants, hip resurfacing, Unicompartmental Knee Arthroplasty vs TKA).
- The surgical approach of the joint. For the hip: medial-, anterior-, anterolateral-, direct lateral- or posterior approach. For the knee: medial parapatellar-, midvastus, or subvastus approach.
- Prior surgery to the joint (DAIR, revision).
- The time interval after surgery (or implantation).
- The use of antibiotics.

Reference standard

All studies investigating PJI should use the international standard for diagnosing PJI. Because of the lack of a “golden standard” for diagnosing PJI, we recommend that future studies report the outcome of both the ICM and EBJIS criteria. We also recommend to explicitly report:

- The type of infection (acute, acute-on-chronic, hematogenous, chronic / low-grade PJI) and separately analyze these specific groups of patients.
- The outcome of all used diagnostic test separately (serum testing, synovial testing and nuclear imaging), including the documentation of “dry taps”.

The use of nuclear imaging in the diagnostic algorithm of knee and hip PJI.

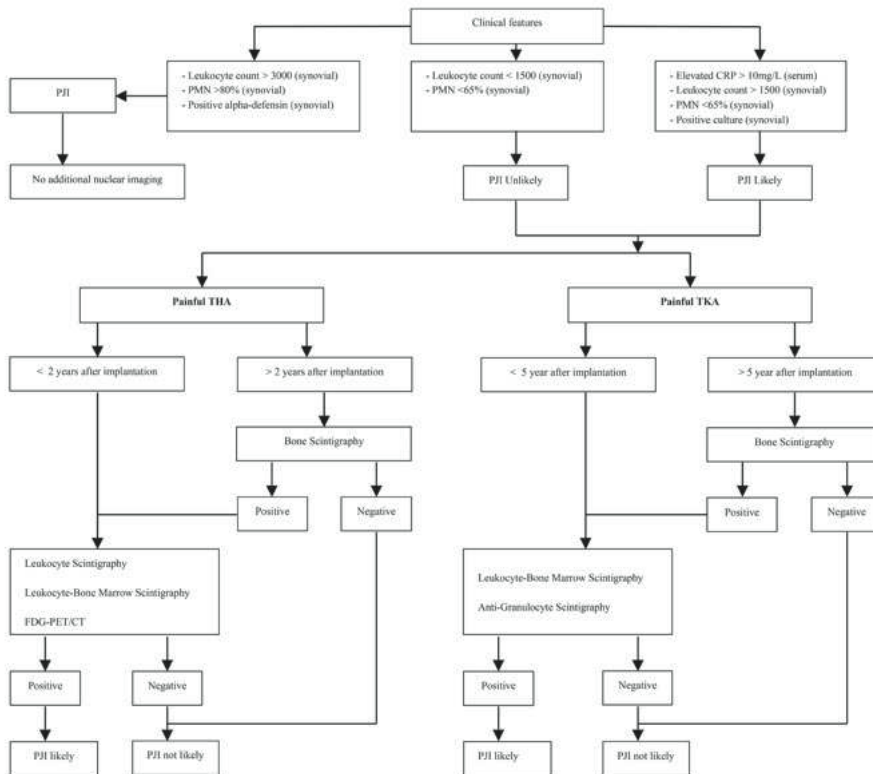
Nuclear imaging is a supportive diagnostic tool which is used before surgical exploration of the prosthesis. Therefore, nuclear imaging can be incorporated in the pre-operative phase of the diagnostic algorithms of the current international standards (EBJIS and ICM) for diagnosing PJI. This thesis emphasized a separate algorithm for painful hip- and knee prosthesis, in contrary to the current international standards.

The role of bone scintigraphy has been established in literature as a screening tool to exclude infection and should be used in the early phase of the diagnostic algorithm (in line with the EBJIS criteria). When the diagnosis of PJI is clear after clinical examination, serum testing, synovial testing and bone scintigraphy, there is no need for additional specific nuclear imaging. However, in this thesis we defined a specific, challenging patient group in which the diagnosing of PJI was not clear. In the EBJIS criteria: the “infection likely” group, and in the ICM criteria: the “possibly infected” group. Based on our findings, we suggest

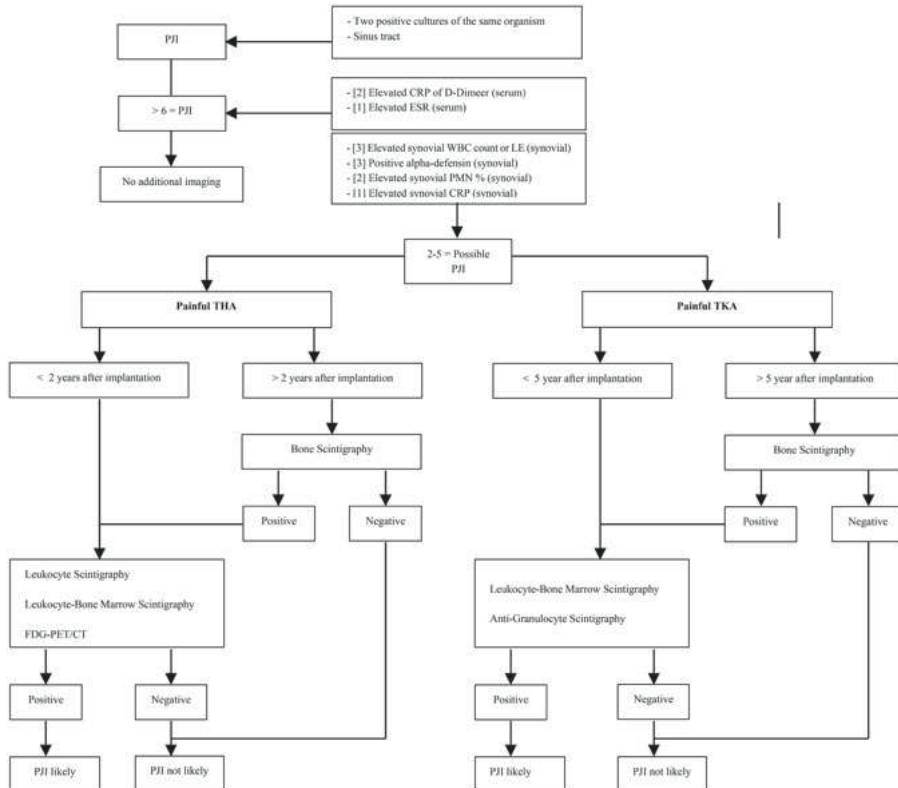
that the use of nuclear imaging (with high specificity) can contribute to possibly confirm (or exclude) PJI in this specific group of patients.

We recommend future studies to incorporate the use of nuclear imaging, supplemental (not as an isolated diagnostic test) to the international workup for diagnosing PJI. A flowchart, with the incorporation of nuclear imaging, in the pre-operative diagnostic phase of the EJBIS and ICM criteria (for knee -and hip arthroplasties separately) is presented below.

Flowchart with the incorporation of nuclear imaging, for knee- and hip arthroplasty, in the EJBIS (pre-operative) criteria for PJI.



Flowchart with the incorporation of nuclear imaging, for knee- and hip arthroplasty, in the ICM (pre-operative) criteria for PJI.



In case of a clinical suspicion of a possible low-grade or chronic PJI, we recommend the use of bone scintigraphy in the early phase of the diagnostic algorithm to exclude any type of prosthesis related pathological conditions. However, in the early phase after implantation (2 years after THA or 5 years after TKA), we recommend the use of a more specific imaging modality (LS, AGS, LS-BMS or FDG-PET/CT).

In case a more specific imaging test is required, we cannot make strict recommendations for the most specific imaging modality (which is also dependent on the local availability, time, costs and expertise). However, based on this thesis, we emphasize that future investigations should consider the differences between hip- and knee arthroplasties:

- For confirming hip PJI, we recommend the use of LS, LS-BMS or FDG-PET/CT.
- For confirming knee PJI, we recommend the use of AGS or LS-BMS.

For the interpretation criteria for diagnosing PJI, and the acquisition protocol, we recommend the use of the evidence-based guideline of the European Association of Nuclear Medicine (EANM)^{6,28,29}.

We also recommend to analyze the scans by multiple nuclear physicians and report the variables of the reproducibility. This includes:

- The experience of the observers.
- The intra- and interobserver agreement of the interpretations.

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11

Summary

The diagnosis of low-grade (chronic) periprosthetic infection (PJI) of the hip and/or knee can present a clinical challenge. Following a thorough medical history, the implementation of multiple diagnostic tests is often necessary. These supportive tests include serum analyses (such as CRP, leukocyte count, and erythrocyte sedimentation rate), synovial analyses (including microbiological cultures, leukocyte counts, CRP, calprotectin, D-dimer, and alpha-defensin), and potentially the use of (nuclear) imaging techniques. The aim of this thesis was to gain further insight into two supportive diagnostics: nuclear imaging and the alpha-defensin test (also known as the Synovasure test). Part 1 (Chapters 2-7) focuses on nuclear imaging. Chapter 2 details, based on the literature, the supportive (nuclear) imaging modalities used for the diagnosis or exclusion of PJI. Chapters 3 and 4 objectively assess, through a review and meta-analysis, the diagnostic accuracy of nuclear imaging in differentiating mechanical loosening from (low-grade) PJI of the hip and knee, respectively. The reproducibility and reliability of interpretations of the scans are discussed in a review presented in Chapter 5. In Chapters 6 and 7, we investigate the diagnostic accuracy of FDG-PET/CT scans in diagnosing hip PJI and the role of this modality in patients following the resection of total hip prostheses (THP) in the management of PJI. In part 2 (Chapters 8 and 9) we investigated the use of the synovial biomarker alpha-defensin (AD) for diagnosing PJI. Through a literature review and a meta-analysis of high-quality (prospective) studies (Chapter 8), we analyze the diagnostic accuracy of this test. Chapter 9 subsequently examines the sensitivity and specificity of the AD test in patients presenting with chronic pain following THP. The chapters are briefly described below.

Part 1: *The Contribution of Nuclear Imaging in Diagnosing Periprosthetic Joint Infection (PJI)*

Chapter 2 presents a review describing all imaging techniques employed in the literature for the diagnosis of PJI. Timely and accurate identification of PJI is crucial for effective treatment, which can significantly vary depending on the etiology of joint problems, such as infection or mechanical loosening of the prosthesis. Traditional imaging techniques, such as X-rays, computed tomography (CT), and ultrasound, have substantial limitations in reliably identifying PJI. Nuclear imaging techniques, particularly bone scintigraphy, leukocyte scintigraphy, and FDG-PET/CT, demonstrate higher diagnostic accuracy in either excluding or confirming PJI. Hybrid imaging techniques, such as PET/CT and SPECT/CT, can enhance diagnostic accuracy through the integration of anatomical and functional insights. The findings of this review reveal considerable variability within the literature. There is diversity in both the diagnostic criteria employed by the imaging techniques for a positive or negative scan (the index criteria) and in the reference standards used to establish a diagnosis of PJI. To date, there is no established “gold standard” for the diagnosis of PJI. Nuclear imaging contributes in the multimodal approach of the evaluation

of suspected PJIs, which also necessitates clinical evaluations, laboratory tests, and synovial analyses.

In **Chapter 3**, a literature review was conducted to assess the diagnostic accuracy of imaging in the diagnosis of hip periprosthetic joint infection (PJI). Through a systematic review, published studies were identified. A meta-analysis was performed to investigate the sensitivity and specificity of various imaging techniques, including bone scintigraphy, leukocyte scintigraphy (including anti-granulocyte scintigraphy), and FDG-PET/CT. We examined 31 clinical studies involving over 1,700 hip prostheses to determine which imaging methods are most effective. The analysis demonstrated that bone scintigraphy was highly sensitive but lacked specificity. Leukocyte scintigraphy proved to be a reliable technique with a higher specificity (sensitivity of 88% and specificity of 92%). This imaging technique involves labeling the patient's white blood cells to localize infections, but requires careful interpretation. FDG-PET/CT showed comparable diagnostic accuracy, with a sensitivity of 86% and specificity of 93%. Bone scintigraphy is useful for excluding a PJI. However, for the detection and diagnosis of hip PJI, leukocyte scintigraphy and FDG-PET/CT demonstrate similar results.

In **Chapter 4**, a literature review was also conducted to evaluate the diagnostic accuracy of imaging in the diagnosis of knee periprosthetic joint infection (PJI). Through a systematic review, 23 published studies were identified, and a meta-analysis was performed to investigate the sensitivity and specificity of 1,027 diagnostic images. We compared the diagnostic accuracy of various imaging techniques, such as bone scintigraphy, leukocyte scintigraphy (including anti-granulocyte scintigraphy), and FDG-PET/CT. The analysis revealed that while bone scintigraphy showed high sensitivity, with a sensitivity rate of 93%, it lacked specificity (56%). In contrast, anti-granulocyte scintigraphy and combined leukocyte-bone marrow scintigraphy demonstrated high specificity (95% and 93% respectively), indicating they are more reliable in confirming infections. FDG-PET/CT exhibited limited sensitivity of 70% for knee PJI. Chapters 3 and 4 emphasize that no single imaging method is perfect and that combining imaging with other diagnostic tests (such as serum tests and synovial analyses) is crucial for a more accurate diagnosis. A multidisciplinary meeting (MDM), can contribute to determining the eventual management strategy. New multicenter studies will be necessary to investigate the effectiveness of imaging and laboratory tests in clinical decision-making for complications related to hip and knee prostheses.

In **Chapter 5**, we conducted a literature review and performed a systematic review to analyze the reliability and reproducibility of the interpretation of nuclear scans in diagnosing periprosthetic joint infection (PJI). We analyzed over 3,000 studies and included 16 studies

that described the intra- and interobserver agreement of the scans. The study revealed considerable variability in the reproducibility of different nuclear imaging techniques, with bone scintigraphy displaying a particularly wide variation of intra- and interobserver agreement. Leukocyte scintigraphy and combined methods (such as leukocyte-bone marrow scintigraphy) demonstrated improved intra- and interobserver agreement, especially in diagnosing PJI. However, 40% of the studies demonstrated significant bias and the methodological quality of many studies was found to be moderate to poor. Moreover, factors such as the type of implant, the timing of imaging relative to surgery, and the level of expertise of observers were often inadequately reported, which could have influenced the outcomes. Although there is a suggestion that hybrid imaging techniques such as SPECT/CT or FDG-PET/CT may improve the accuracy of these assessments, this has not yet been well established in the literature. The review emphasizes the need for more precise and detailed research in the future.

In **Chapter 6**, we investigate the accuracy of FDG-PET/CT for diagnosing hip periprosthetic joint infection (PJI). The study analyzed FDG-PET scans of 33 painful hip prostheses, of which 16 were confirmed as infected and 17 as non-infected. Five different diagnostic criteria were tested to evaluate the effectiveness of FDG-PET. The results indicated that any increased periprosthetic FDG uptake yielded a sensitivity of 100%, but it lacked specificity (0%). However, an increase in specificity to 94% was observed with FDG uptake along the femoral bone-prosthesis interface, achieving a sensitivity of 81%. We concluded that while FDG-PET represents a valuable and supported diagnostic tool for identifying PJI, its accuracy is highly dependent on the used diagnostic criteria, and further research could further clarify its role in clinical practice.

The use of FDG-PET/CT was also examined in **Chapter 7**, focusing on the assessment of infection after resection of a total hip prosthesis (THP) in patients with hip periprosthetic joint infection (PJI). The study aimed to determine whether FDG-PET/CT could effectively identify which patients require additional treatment or may benefit from delayed re-implantation. By reviewing scans of patients with (persistent) elevated CRP and ESR following resection, we included 16 patients with 17 hip procedures. All patients exhibited increased FDG uptake in the resection area; however, no specific pattern was found that was indicative for infection in this area. However, additional infectious sites were identified in 59% of cases, which directly influenced the treatment. Overall, the findings suggested that FDG-PET/CT may be useful for detecting complicating infections in patients with persistently elevated infection parameters, but it was not effective in the assessment of the local (hip) infection site.

Part 2: *The Contribution of Alpha-Defensin in Diagnosing Periprosthetic Joint Infection (PJI)*

In **Chapter 8**, we investigated the effectiveness of two tests for diagnosing periprosthetic joint infection (PJI): the Alpha-Defensin ELISA test and the Alpha-Defensin lateral flow (LF) test. We conducted a systematic review and meta-analysis of prospective studies to examine the differences between these tests concerning their sensitivity and specificity in diagnosing PJI. We analyzed 15 studies involving 1,592 procedures, comparing these two tests in total hip and knee arthroplasties. Both tests demonstrated high sensitivity (90% for ELISA and 86% for LF) and high specificity (97% for ELISA and 96% for LF), with no significant differences in the pooled cohorts. However, the ELISA test exhibited lower sensitivity for hip PJI compared to knee PJI. This underscores the necessity for careful interpretation when utilizing the ELISA test for hip infections. In conclusion, neither test was superior, but both are valuable diagnostic tools for PJI. Although both tests can be useful in clinical practice, we emphasized the need to investigate the differences between the two tests separately for knee and hip PJI.

In **Chapter 9**, we investigated the effectiveness of the Alpha-Defensin lateral flow (AD-LF) test in patients with chronic pain following total hip arthroplasty (THA). Patients with acute infections were excluded from this study. Among the 57 analyzed patients, the AD-LF test produced positive results in nine cases, six of which were ultimately diagnosed with PJI. The test exhibited a sensitivity of 83% and a specificity of 92%, with a positive predictive value of 56% and a negative predictive value of 98%. We described the “Schrödinger’s hips,” referring to patients whose infection status cannot be definitively confirmed or excluded in the absence of operative confirmation of the diagnosis. The study highlights the need for a standardized approach to achieve more accurate diagnostics, enabling both definitive and follow-up evaluations of patients undergoing revision surgeries or not. We also emphasized the potential inaccuracies introduced by factors such as the presence of metallosis, which can lead to false-positive results. In conclusion, the AD-LF test is useful for diagnosing PJI; however, we recommend further studies to consider hip and knee infections as separate entities.



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Dutch Summary

Het diagnosticeren van een laaggradige (chronische) periprotetische infectie (PJI) van de heup en/of knie kan een klinische uitdaging zijn. Na een nauwkeurige anamnese, is de inzet van meerdere diagnostische testen vaak vereist. Deze ondersteunde testen omvatten onder andere serumtesten (zoals CRP, Leukocyten en de Bezinking), synoviale analyses (zoals microbiologische kweken, Leukocytentelling, CRP, Calprotectine, D-Dimeer en Alpha-Defensine) en eventueel de inzet van (nucleaire) beeldvorming. Het doel van dit proefschrift was om meer inzicht te krijgen in twee belangrijke ondersteunende diagnostica te weten nucleaire beeldvorming en de Alpha-Defensine test (ook wel synovasure test).

Deel 1 (hoofdstuk 2-7) is gericht op nucleaire beeldvorming. In hoofdstuk 2 beschrijven wij de details, op basis van de beschikbare literatuur, van de ondersteunende (nucleaire) beeldvorming voor het diagnosticeren of uitsluiten van PJI. In hoofdstukken 3 en 4 objectiveren wij, middels een review en meta-analyse, de diagnostische nauwkeurigheid van nucleaire beeldvorming in het onderscheiden van mechanische loslating versus (laaggradige) PJI van de heup en knie, respectievelijk. De reproduceerbaarheid en betrouwbaarheid van de interpretaties van de scans worden in een review beschreven in hoofdstuk 5. In hoofdstuk 6 en 7 onderzoeken wij de diagnostische nauwkeurigheid van FDG-PET/CT-scans in het diagnosticeren van heup PJI en de rol van deze modaliteit bij patiënten na resectie van de Totale Heupprothese (THP) in de behandeling van PJI.

Deel 2 (hoofdstuk 8 en 9) is gericht op de synoviale biomarker Alpa-Defensine (AD). Middels een review van de literatuur en een meta-analyse van hoogwaardige (prospectieve) studies (hoofdstuk 8) hebben wij de diagnostische nauwkeurigheid van deze test geanalyseerd. In hoofdstuk 9 onderzoeken wij vervolgens de sensitiviteit en specificiteit van de AD-test in patiënten met chronische pijnklachten na een THP. De hoofdstukken worden hieronder in het kort beschreven.

Deel 1: Het gebruik van Nucleaire Beeldvorming in het diagnosticeren van PJI

Hoofdstuk 2 omvat een review met als doel om alle beeldvormende technieken die worden gebruikt om PJI te diagnosticeren in de literatuur te beschrijven. Tijdige en nauwkeurige identificatie van PJI is cruciaal voor effectieve behandeling, die aanzienlijk kan verschillen afhankelijk van de oorzaak van de gewrichtsproblemen zoals infectie of mechanische loslating van de prothese. Traditionele beeldvormingstechnieken zoals röntgen, CT en echografie hebben aanzienlijke beperkingen in het betrouwbaar identificeren van PJI. Nucleaire beeldvormingstechnieken, met name bot scintigrafie, leukocyten scintigrafie en FDG-PET/CT, hebben een hogere diagnostische nauwkeurigheid om een PJI uit te sluiten, dan wel aan te tonen. Hybride beeldvormingstechnieken, zoals PET/CT en SPECT/CT, kunnen door de gecombineerde anatomische en functionele

inzichten de diagnostische nauwkeurigheid verbeteren. De bevindingen van dit review laten zien dat er een grote diversiteit bestaat in de literatuur. Er blijkt een diversiteit in zowel de gebruikte diagnostische criteria van de beeldvormende technieken voor een positieve dan wel negatieve scan (de index criteria), alsmede een diversiteit in de gebruikte referentiestandaard voor het vaststellen van een PJI. Tot op heden is er nog geen "gouden standaard" voor de diagnose van PJI. De nucleaire beeldvorming is een (bijdragend) onderdeel van de multimodale benadering bij het beoordelen van vermoedde PJI's die ook klinische evaluaties, laboratoriumtests en synoviale analyses vereist.

In **Hoofdstuk 3** werd een literatuurstudie uitgevoerd naar de diagnostische nauwkeurigheid van beeldvorming bij het diagnosticeren van heup PJI. Met behulp van een systematisch review werden gepubliceerde studies geïdentificeerd. Middels een meta-analysis werd de sensitiviteit en specificiteit van onder andere bot scintigrafie, leukocyten scintigrafie (inclusief antigranulocyten scintigrafie) en FDG-PET/CT onderzocht. Wij onderzochten 31 klinische studies met meer dan 1.700 heupprothesen om te bepalen welke beeldvormingsmethoden het meest effectief zijn. De analyse toonde aan dat bot scintigrafie zeer gevoelig was, maar het aan specificiteit ontbrak. Leukocyten scintigrafie bleek een betrouwbare techniek te zijn met een hogere specificiteit (gevoeligheid van 88% en specificiteit van 92%). Deze methode omvat het labelen van de witte bloedcellen van de patiënt om infecties te lokaliseren, maar vereist zorgvuldige interpretatie. FDG-PET/CT toonde een vergelijkbare diagnostische nauwkeurigheid, met een sensitiviteit van 86% en specificiteit van 93%. Bot scintigrafie is bruikbaar voor het uitsluiten van een PJI. Voor het aantonen, dan wel diagnosticeren van heup PJI, blijken leukocyten scintigrafie en FDG-PET/CT vergelijkbare resultaten te demonstreren.

In **Hoofdstuk 4** werd ook een literatuurstudie uitgevoerd naar de diagnostische accuratesse van beeldvorming bij het diagnosticeren van knie PJI. Met behulp van een systematisch review werden 23 gepubliceerde studies geïdentificeerd en met een meta-analysis werd de sensitiviteit en specificiteit van 1.027 diagnostische beelden onderzocht. Wij vergeleken de diagnostische nauwkeurigheid van de verschillende beeldvormende technieken zoals de bot scintigrafie, leukocyten scintigrafie (inclusief antigranulocyten scintigrafie) en FDG-PET/CT. De analyse toonde aan dat terwijl bot scintigrafie zeer gevoelig was, met een gevoeligheidspercentage van 93%, het aan specificiteit ontbrak en slechts 56% bereikte. In tegenstelling, antigranulocyten scintigrafie en de gecombineerde leukocyten-beenmerg scintigrafie toonden een hoge specificiteit, respectievelijk 95% en 93%, en blijken meer betrouwbaar in het bevestigen van infecties. FDG-PET/CT liet daarbij wel een beperkte sensitiviteit van 70% zien voor knie PJI. Over het geheel genomen benadrukken hoofdstuk 3 en 4 dat geen enkele beeldvormingsmethode perfect is en dat het combineren van beeldvorming met andere diagnostische tests (zoals

laboratoriumtesten en synoviale analyses) cruciaal is voor een nauwkeurigere diagnose. Daarbij is het tevens van belang dat klinische symptomen worden meegenomen in de uiteindelijke diagnose vorming. Overleg over de verschillende diagnostische uitkomsten in bijvoorbeeld een multidisciplinair overleg (MDO) kunnen bijdragen aan bepalen van het uiteindelijk beleid. Nieuwe multicenter studies zullen nodig zijn om de effectiviteit te onderzoeken van beeldvorming en laboratorium tests bij de klinische besluitvorming bij complicaties van heup en knieprotheses.

In **hoofdstuk 5** hebben wij een literatuurstudie uitgevoerd en met een systematisch review de betrouwbaarheid en reproduceerbaarheid van de interpretatie van nucleaire scan in het diagnosticeren van PJI geanalyseerd. We analyseerden meer dan 3.000 studies en includeerden 16 studies die de overeenstemming ("intra- en interobserver agreement") tussen de beoordelaars van de scans beschreven. De studie liet een grote variabiliteit in de reproduceerbaarheid van verschillende nucleaire beeldvormingstechnieken zien, waarbij met name bot scintigrafie een ruime variatie tussen beoordelaars vertoonde. Leukocyten scintigrafie en gecombineerde methoden (zoals leukocyten-beenmerg scintigrafie) toonden verbeterde overeenstemming tussen de beoordelaars, vooral bij het diagnosticeren van PJI. De methodologische kwaliteit van veel studies bleek matig tot slecht, waarbij ongeveer 40% significante bias vertoonden. Hierdoor bleken de bevindingen minder betrouwbaar. Bovendien waren factoren zoals het type implantaat, het moment van beeldvorming ten opzichte van de operatie, en het niveau van expertise van observatoren vaak onvoldoende gedocumenteerd, wat de uitkomsten kon beïnvloeden. Hoewel de suggestie bestaat dat hybride beeldvormingstechnieken zoals SPECT/CT of FDG-PET/CT de nauwkeurigheid van de beoordeling kan verbeteren, is dit nog niet goed bevestigd in de literatuur. Het review benadrukt de noodzaak voor meer nauwkeurig en gedetailleerd onderzoek in de toekomst.

In **Hoofdstuk 6** onderzoeken wij de nauwkeurigheid van FDG-PET/CT voor het diagnosticeren van heup PJI. De studie analyseerde FDG-PET-scans van 33 pijnlijke heupprotheses, waarvan 16 bevestigd als geïnfecteerd en 17 als niet-geïnfecteerd. Vijf verschillende diagnostische criteria werden getest om de effectiviteit van FDG-PET te evalueren. De resultaten toonden aan dat elke verhoogde peri-prothetische FDG-opname een gevoeligheid van 100% aangaf, maar het aan specificiteit (0%) ontbrak. Echter, een toename van de specificiteit naar 94 % werd aangetoond bij een FDG-uptake langs de femur-bot-prothese interface (met een sensitiviteit van 81%). De studie benadrukt het belang van het gebruik van precieze diagnostische criteria voor een nauwkeurige interpretatie van FDG-PET/CT-beelden. We concludeerden dat hoewel FDG-PET een waardevol en ondersteund diagnosticum is voor het aantonen van PJI, de nauwkeurigheid

ervan sterk afhankelijk is van de gebruikte diagnostische criteria, en verder onderzoek kan helpen om de rol in de klinische praktijk te verduidelijken.

Het gebruik van FDG-PET/CT werd ook onderzocht in **Hoofdstuk 7** met de beoordeling van infectie na resectie van een THP bij patiënten met PJI van de heup. De studie was gericht op het bepalen of FDG-PET/CT effectief kan identificeren welke patiënten aanvullende behandeling nodig hebben of gebaat kunnen zijn bij een uitgestelde re-implantatie. Door scans te herzien van patiënten met (persisterend) verhoogd CRP en BSE na resectie, includeerden wij 16 patiënten met 17 heupprocedures. Alle patiënten toonden verhoogde FDG-opname in het resectiegebied, maar er werden geen specifieke patronen aangetoond die bewijzend waren voor infectie. Er werden wel aanvullende infectieuze locaties in 59% van de gevallen geïdentificeerd, wat veranderingen in behandelplannen noodzakelijk maakte. Over het geheel genomen suggereerden de bevindingen dat FDG-PET/CT nuttig kan zijn voor het detecteren van complicerende infecties bij patiënten met persisterend verhoogde infectieparameters, maar niet effectief was voor het identificeren het lokale (heup) infectiegebied.

Deel 2: Het gebruik van Alpha-Defensine in het diagnosticeren van PJI

In **Hoofdstuk 8** onderzochten we de effectiviteit van twee tests voor het diagnosticeren van PJI: de AD ELISA-test en de AD lateral flow (LF) test. We voerden een systematische review en meta-analyse uit van prospectieve studies om het verschil te onderzoeken tussen deze testen ten aanzien van de gevoeligheid en specificiteit bij het diagnosticeren van PJI. We analyseerde 15 studies met 1.592 procedures, waarbij we deze twee tests vergeleken bij totale heup- en knieprothesen. Er werd een hoge sensitiviteit aangetoond voor beide testen (90% voor ELISA en 86% voor LF) en een hoge specificiteit (97% voor ELISA en 96% voor LF), zonder noemenswaardige verschillen in gepoolde cohorten. Echter, de ELISA-test toonde lagere sensitiviteit ten aanzien van heup PJI, in vergelijking met knie PJI. Dit benadrukt de noodzaak voor zorgvuldige interpretatie bij het gebruik van de ELISA-test voor de heup. Concluderend werd vastgesteld dat geen van de tests superieur was, maar dat beide bruikbare diagnostische hulpmiddelen voor PJI zijn. Hoewel beide tests nuttig kunnen zijn in de klinische praktijk, benadrukte wij de verschillen tussen beide testen separaat te onderzoeken voor knie en heup PJI.

In **Hoofdstuk 9** onderzochten wij de effectiviteit van de AD-LF test bij het diagnosticeren van PJI bij patiënten met chronische pijn na de implantatie van een THP. De patiënten met acute infecties werden uitgesloten van dit onderzoek. Van de 57 geanalyseerde patiënten produceerde de AD-LF-test positieve resultaten in negen gevallen, waarbij zes uiteindelijk werden gediagnosticeerd met PJI. De test toonde een gevoeligheid van 83% en

specificiteit van 92%, met een positieve voorspellende waarde van 56% en een negatieve voorspellende waarde van 98%. Wij beschreven de “Schrödinger’s heupen,” verwijzend naar patiënten waarvan de infectiestatus niet definitief kan worden bevestigd of uitgesloten bij het uitblijven van een operatieve bevestiging van de diagnose. De studie benadrukt de noodzaak van een standaardbenadering voor nauwkeurigere diagnostiek, die zowel definitieve als follow-up-evaluaties van patiënten mogelijk maakt die al dan niet revisie-operaties ondergaan. Wij benadrukte daarbij ook de potentiële onnauwkeurigheden die worden geïntroduceerd door factoren zoals de aanwezigheid van metallosis, hetgeen kan leiden tot vals-positieve resultaten. Concluderend is dat de AD-LF-test nuttig is voor het diagnosticeren van PJI, maar wij bevelen verdere studies aan om de nauwkeurigheid in verschillende patiëntgroepen te verbeteren, alsmede om de heup en knie als afzonderlijke entiteiten te beschouwen.



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mij te ondersteunen en begeleiden. Jouw rol is zeer waardevol geweest en zal ik nooit vergeten. Dank vriend! Hoog tijd voor een nieuwe nipnight...

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Chirurgie, Diaconessenhuis Utrecht/Zeist

Een Utrechtsche enclave waar ik met veel plezier mijn eerste klinische stappen heb gezet als ANIOS. Het is inmiddels een tijd geleden, maar ik heb nog steeds mooie herinneringen aan die periode. Dank aan iedereen voor deze kans en het plezier destijds. In het bijzonder te noemen dr. E.J.M.M. Verliesdonk, beste Egbert Jan, dr. R.M. Houwert, beste Marijn (ook al werkte jij daar destijds niet), dank voor jullie vertrouwen tijdens deze groentijd.

Chirurgie, Noordwest Ziekenhuisgroep (NWZ)

Een intensieve, maar buitengewoon leerzame vooropleiding in Alkmaar. Met iedereen met wie ik in deze tijd heb samengewerkt, veel dank! Een hechte assistentengroep met o.a. Leonie, Joris, Luc, Noëlle, Jort...het was een fantastische periode. Aan de gehele staf: dank voor het opleiden en de fijne samenwerking! In het bijzonder nog te noemen diegene met wie ik het meest heb samengewerkt; drs. Oñorbe Genovesi, beste Igande, drs. B. Mirck, beste Boj, dr. K.J. Ponsen, beste Kees Jan, beste J.S.K. Reinders, beste Jan Siert, dr. M.N. van Sterkenburg, beste Maayke, veel dank voor het vertrouwen tijdens eerste vliegreizen bij de traumachirurgie!

Orthopedie, Noordwest Ziekgroep (NWZ)

Dank voor het warme bad waarin ik mijn eerste stappen als AIOS Orthopedie kon zetten. Aan iedereen veel dank, inclusief de ondersteunende collegae en de verpleegafdeling. In het bijzonder de personen met wie ik veel samengewerkt heb. Drs. C.J. Vos, beste Stan, drs. D.J. Hofstee, beste Dirk-Jan, dr. P.C. Geervliet, beste Pieter, K. Slot, beste Karin; jullie waren top in de samenwerking en ik denk met veel plezier terug aan deze periode! Jullie zijn nu gelukkig verlost van vreemde tekeningen op de papieren rol van de onderzoeksbanken...

Orthopedie, Amsterdam UMC (AUMC)

Mijn academische stage was een bijzonder leerzame periode. Dr. M.U. Schafröth, beste Matthias, dr. A.J. Kievit, beste Arthur, drs. R. Saouti, beste Rachid; jullie waren mijn directe koppeling en ik heb van ieder van jullie veel mogen leren. Naast jullie, ook dank aan de gehele vakgroep en iedereen van de afdeling en poli Orthopedie!

Orthopedie, Spaarne Gasthuis (SG)

Het laatste deel van de AIOS-periode was een uitdagende periode. In het bijzonder nog te noemen (naast de eerdergenoemde personen) dr. R.E.A.M. Zwartelé, beste Rob en dr. W.G. Horstmann, beste Wieger. Onze koppelingen zijn voor mij erg waardevol geweest richting het einde van mijn opleiding, dank daarvoor! Ook drs. K.D. Ottink, beste Karsten, dr. M.V. Rademakers, beste Maarten en dr. B.G. Schutte, beste Bernard; dank voor de fijne samenwerking. Uiteraard ook de rest van de staf en gehele afdeling Orthopedie; veel dank voor de eindfase van mijn opleiding tot orthopedisch chirurg. Ook alle AIOS en ANIOS in deze periode, het was een genot om samen (hard) te werken. In het bijzonder nog te noemen Franske Hagemans: de middagpils houden we in stand...

Orthopedie, Groen Hart Ziekenhuis (GHZ)

Als jonge klare (lees: groen als gras), heb ik bij jullie de kans gekregen om te starten als orthopedisch chirurg. Er is geen vakgroep in Nederland die kan overtreffen wat jullie hebben neergezet. De sfeer, de samenwerking, jullie beleving en invulling van het vak zijn mijns inziens uitzonderlijk. Dank dat ik onderdeel mag uitmaken van dit prachtige team. Peer, Ron, Rene, Vincent, Pieter Stijn, Laurens en Rik...dank dat ik altijd bij jullie heb kunnen aankloppen bij vragen en uitdagende momenten (gelukkig steeds minder). Uiteraard ook veel dank voor de polidames (en Henro die gelukkig nog steeds langskomt), Iris, Adri en Anneke; in het hele team en de drukte van de dag zijn jullie onmisbaar! Uiteraard ook veel dank aan iedereen met wie ik op OK met veel plezier samenwerk. Ook nog te noemen; Henk Beekman. In het begin was jij er bij om mij de MRK (en later de SAIPH) eigen te maken. Naast de humor en het vele lachen, is jouw bijdrage belangrijk geweest voor de goede resultaten. Dank!

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Wijdbeens, Stevie en Huls, wat een eer en genot dat ik met jullie onze medische wereld heb kunnen delen! Ongekend veel gelachen, met Basingstoke als een van de hoogtepunten. Complimentendag is helaas te lang geleden, tijd voor nieuwe herinneringen. Berlijn?!

't Begijnhof

Heeren van het 't Hof. Wat een enorm genot om terug te denken aan onze prachtige jaren op 't Hof. Was de tijd daar maar stil blijven staan. Op de buurt!

Senatus Veteranorum 2007/2008

Met 9 mannen aan de ovale tafel. Een groep van 9 schreeuwende corpsballen is uitgegroeid tot een hechte vriendengroep. Een ongekend waardevol jaar en inmiddels vrienden voor het leven. Nu vaders en ploeterend door de tropenjaren. Ik kijk elke keer weer uit naar ons samenzijn!

Vrienden

Helaas kan ik niet alle vrienden afzonderlijk bedanken. Toch wil ik een aantal van jullie in het bijzonder bedanken. Skneepios en Amber, LoekieDennis, Lodemans, Slooootema, Kees van Damme, Koos en Ties, Jullie hebben mij bijgestaan in een bijzonder lastige tijd. Het gevoel van die steun, zal ik voor altijd bij me dragen. Omgekeerd zal ik er ook altijd voor jullie zijn.

Schoonfamilie

Lieve Joep en Iek, dank voor de bijzonder lieve zorgen en steun voor mij en ons gezin. De kinderen zijn dol op jullie! Ook de ooms en tantes (Sabine, Niels, Nicole en Died), neefjes en nichtjes (Beau, Lilly, Liv en James); het is steeds een genot om met z'n allen samen te zijn.

Mama

Lieve Mama, het is niet altijd makkelijk geweest, maar ik ben je dankbaar voor de lieve zorgen die je voor mij hebt gehad! Gelukkig heb je nu de rust gevonden om van het leven te genieten.

Zussen

Lieve Relinde, mijn grote zus. We hebben een echte broer-zus relatie. Nu beiden druk met het hectische gezinsleven. Alle geluk met Krijn, Laurien en Boaz. Hopelijk in de toekomst weer meer tijd samen met alle neefjes en nichtje!

Lieve Bodine, mijn kleine zusje, voor wie ik mij zo verantwoordelijk voel(de). Je bent zo enorm intelligent en zorgzaam. Hopelijk vind je weer het juiste spoor om van het leven te genieten.

Lieve kinderen

Een apart woordje voor jullie afzonderlijk. En ja, “ongekend trots” x 5.

Lieve Reinier, de tijd gaat zo snel. Je bent al 6 jaar oud en begint nu met lezen en dingen echt begrijpen... Je hebt geen idee hoe ongekend trots papa op jou is. Ik zie mijzelf volledig in jou terug. Hoe jij omgaat met alles wat er om je heen gebeurt is heel bijzonder en ongelooflijk knap. Je bent zo’n mooi, sterk en lief ventje. Jouw grappen (van hetzelfde niveau als papa), intelligentie, sportiviteit (nu al zo goed met tennis!), het klieren met Tom en Jack, maar ook jouw zorgzaamheid voor iedereen om jou heen (waaronder je kleine broertje Jules en zusje Liz) maken papa trots. Ook op school doe jij het nu al zo ontzettend goed! Lieve Rein, papa geniet van elk moment dat wij samen zijn en kan niet wachten op alle jaren die nog volgen.

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Lieve Jules, je bent zo’n ontzettend lief, vrolijk en knap mannetje. Ook jij kunt dit (nog) niet lezen, want je bent nog maar 2 jaar oud. Ooit ga je dit gelukkig wel lezen. Je bent zo enorm bezig met alles om je heen en papa en mama genieten elke dag van jou. Elke dag leer je weer nieuwe dingen en begin je steeds meer een echt mannetje te worden. Het is zo mooi om te zien dat je alles kopieert van Liz, Reinier, Jack en Tom... Maar je krijgt ook steeds meer besef van wat er om je heen gebeurt. Ook jij bent nu al zo sportief (vooral met balsporten), lief en zorgzaam... maar gelukkig kun jij ook al net zo goed klieren als je broers en zusje. Papa geniet steeds van de start van de dag samen met jou. Elke (vroeg) ochtend, als jij je aan mij vastklampt, vergeet ik alles om me heen. Papa zou het liefst willen dat je zo blijft, maar ook jij groeit (te snel). Juultje, papa en mama zijn ongekend trots op jou!

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en enorm knap. Je begint steeds meer vertrouwen in jezelf te krijgen en dat is prachtig om te zien. Ook jij bent enorm sociaal en lief voor iedereen om je heen... als oudste van het stel geef je steeds meer het goede voorbeeld. Mama en ik zijn ongekend trots op jou!

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Papa

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Renske

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Cheers.

"For the good and the bad"



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Curriculum Vitae



Steven Jeroen Verberne, born in Amersfoort, the Netherlands, was a professional soccer player at VVV-Venlo during his high school years.

After graduating from high school, he began his academic career in Utrecht. He obtained Bachelor's degrees in Economics (BSc), Law (BSc), and Medicine (BSc).

Subsequently, he completed Master's degrees in Law (LL.M.) and Medicine (MSc).

In 2016, he gained his first research experience in collaboration with Dr. Olivier Temmerman. This eventually resulted in a PhD project, together with Dr. Pieter Raijmakers.

His first clinical experience was in 2016 at the general surgery department of Diaconessenhuis Utrecht. In January 2017, he started his orthopaedic surgery residency training. Between 2017 and 2022, he worked as a resident at the Noordwest Ziekenhuisgroep (Dr. W.H. Schreurs and Dr. B.J. Burger), Amsterdam University Medical Centers (Prof. Dr. G.M.M.J. Kerkhoffs), and Spaarne Gasthuis (Dr. A. van Noort).

In 2023, he started his career as an orthopaedic surgeon at the Groene Hart Ziekenhuis (GHZ) in Gouda.

In July 2024, he became engaged to the love of his life, Renske. He is the proud father of Reinier (2019), Liz (2021), and Jules (2023). Together with Tom (2015) and Jack (2018), the family currently lives in Reeuwijk.



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Steven Jeroen Verberne, born in Amersfoort, the Netherlands, was a professional soccer player at VVV-Venlo during his high school years.

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