Skeletal Radiology (2019) 48:1565–1572
https://doi.org/10.1007/s00256-019-03215-y

SCIENTIFIC ARTICLE

Detection of aseptic loosening in total knee replacements: a systematic review and meta-analysis

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Received: 4 January 2019 / Revised: 26 February 2019 / Accepted: 25 March 2019 / Published online: 12 April 2019

Abstract

Objective The aim of this study was to compare the diagnostic accuracy of nuclear imaging modalities in the detection of aseptic loosening of total knee arthroplasty (TKA).

Materials and methods MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched from database inception to December 2018 in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Included studies compared the results of a single imaging modality against an appropriate reference standard of prosthetic TKA loosening, with sufficient information to determine either sensitivity and/or specificity. The methodological quality of the studies was assessed using the QUADAS-2 tool.

Results The search strategy identified 572 abstracts. Of these, 12 studies comprising 401 patients across four modalities (bone scintigraphy, 18F-FDG-PET, SPECT/CT arthrogram, radionuclide arthrogram) met the inclusion criteria. All included studies used operative findings, a period of clinical or radiographic observation or both as a reference standard for aseptic loosening. Sixteen comparisons with the reference standards were extracted. All studies were at risk of bias across patient selection, the index test, reference standard, and flow and timing of patients. The most accurate test for diagnosis of aseptic loosening in TKA was SPECT/CT arthrography demonstrated by the summary receiver operating characteristic curve.

Conclusions The best available evidence suggests the most accurate modality for the detection of aseptic loosening in TKA is SPECT/CT arthrography. However, the available evidence has a high risk of bias, and total number of patients studied for each modality is small so further studies are warranted.

Keywords Meta-analysis · Total knee arthroplasty · Nuclear medicine · Prosthesis loosening · Sensitivity · Specificity

Introduction

Total knee arthroplasty (TKA) is an effective surgery for osteoarthritis [1]. Last year, over 55,000 operations were performed in Australia [2]. Aseptic loosening is the most common reason for revision of primary total knee replacements in Australia and remains the major factor limiting the survival of joint replacements. Aseptic loosening is described as the failure of the integration between a prosthesis and bone in the absence of infection. Loosening reported in the first few years of implantation of a prosthesis is most likely due to failure of the implant to gain fixation, however, loosening in later years likely reflects loss of fixation due to bone resorption [2].

Insidious progression of tissue damage around the implant due to particulate deposition poses a major challenge, as signs and symptoms of failure may not become clinically detectable

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00256-019-03215-y) contains supplementary material, which is available to authorized users.

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until its late stages [3]. The basis of this periprosthetic tissue destruction is complex and multifactorial. Particle accumulation can be a result of articular wear of the prosthesis, oxidative reactions, and micromotion occurring in response to corrosion [4]. The particle debris, typically polyethylene, is phagocytosed by macrophages, which results in osteoclast upregulation and osteoblast downregulation. This activation culminates in enhanced osteoclast recruitment and activity adjacent to bone–implant interfaces, leading to osteolysis. If osteolysis is left untreated, it can lead to periprosthetic fracture at areas of bone erosion or joint instability due to destruction of the soft tissues. These pathologies can be difficult to manage and hence early identification of loosening is critical.

Pre-operative evaluation and diagnosis is vital for selecting appropriate patients for revision arthroplasty, as it is major surgery with inherent complications. Sequential radiography is typically used to monitor aseptic loosening over time, particularly in higher-risk stratification patient groups as recommended by the Australian Arthroplasty Society [3]. Radiographs are less sensitive in detecting abnormalities such as the earliest stages of loosening (undetectable by radiographs) or minor implant malposition and are better at detection of gross prosthetic malposition, radiolucency, and fractures [5–7].

For the assessment of loosening at a single time point, nuclear medicine techniques have been advocated [8–10]. Their principal advantage is the elimination of metal artefact that compromises computed tomography (CT) imaging and magnetic resonance imaging (MRI). Using a sensitive search strategy, we were unable to find studies of CT imaging using metal artefact suppression techniques for the detection of TKR loosening. MRI has been considered as an effective way to assess periprosthetic structures with metal artefact suppression techniques [11], however, there are no original papers that assess this with a criterion standard. The only study considering the sensitivity and specificity of MRI was in cadavers and would be considered exploratory rather than clinically applicable [12]. Consequently, any perceived advantage of more contemporary metal artefact suppression techniques remains unproven. In light of these considerations, this review aimed to ascertain the optimal nuclear medicine imaging modality for the diagnosis of periprosthetic loosening.

The aim of this study was to compare the diagnostic accuracy of available nuclear medical imaging modalities in the detection of aseptic loosening of knee prostheses. Imaging modalities considered were bone scintigraphy; single-photon emission computed tomography (SPECT/CT), SPECT/CT arthrography, radionuclide arthrography, and photon emission tomography fludeoxyglucose scanning (18F-PET-FDG).

Methods

Search strategy

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. This approach is advocated as an effective and efficient means to retrieving studies on diagnostic accuracy [14]. The search strategy was deliberately broad, and was constructed utilizing empirical evidence to optimize the retrieval of relevant articles [15]. The Boolean operators, MeSH, and keyword search terms were adapted for each electronic database and are presented in Appendix 1. All types of indexed publications written in English were considered and no date restriction was applied. The last search was completed on Friday the December 28, 2018.

Study selection

Included studies compared the results of a single imaging modality against an appropriate criterion standard of prosthetic total knee arthroplasty loosening. There is no single accepted criterion standard for aseptic loosening. We decided a priori to accept operative findings as a criterion standard, but were prepared to accept other compelling evidence of aseptic loosening. In practice this was an appropriate clinical or radiological course and exclusion of competing differential diagnoses. Other inclusion and exclusion criteria are listed in Table 1.

Where a range of sensitivities and specificities were provided due to different diagnostic imaging criteria, the values utilized were those that achieved the “nearest to top left corner” in receiver operating curve (ROC) analysis [16, 17].

Data were extracted separately by each of the two authors using a standardized data extraction tool. This sought information on population, setting, modality tested, data acquisition, reference standard used, number studied, and raw numbers of true positives, false positives, false negatives, and true negatives. Differences were resolved by consensus.

Study quality and analysis

Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [18]. Following review of the relevant signaling questions to be included in the tool, both reviewers assessed each included study and differences were resolved by consensus. Risk of bias was judged as low, high, or unclear. If all signaling questions for a domain are answered yes, then the risk of bias was judged to be low. If any signaling question was answered no, this indicated the potential for bias. In line with published recommendations [18], we sought to avoid utilizing the

Table 1 Inclusion and exclusion criteria for studies

Inclusion criteria	Exclusion criteria
Study population included patients with suspected aseptic loosening of a total knee arthroplasty	Imaging modality applied after a diagnostic decision had been made
Application of an imaging modality	Inability to separate results of knee from other prostheses (e.g., hip)
Subsequent comparison of imaging findings against a criterion standard of operative findings or comparable standard	Inability to separate results for different pathologies (e.g., septic from aseptic loosening)
Results reported or extractable as true positives, true negatives, false positives, and false negatives	

unclear category other than in situations of genuine uncertainty over key signals.

In line with recommendations of the Cochrane collaboration, we did not calculate pooled estimates of sensitivity and specificity [17] but generated a summary receiver operating characteristic curve (SROC) to compare the diagnostic accuracy of the competing modalities [16]. Each point on the SROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold [19]. A test with perfect discrimination, with no overlap in the two distributions, has an SROC curve that passes through the upper left corner. The upper left corner represents 100% sensitivity and 100% specificity. Therefore, the closer the SROC curve is to the upper left corner, the higher the overall accuracy of the test [19].

Results

Five hundred seventy-two studies were retrieved by the search strategy. The full text of 46 studies were retrieved and read. Of these, 12 met inclusion criteria [20–31]. The reasons for exclusion of the 34 retrieved papers are documented in Fig. 1. Included studies are listed in Table 2.

Computerized tomographic radiography was included in the search strategy to capture the hybrid nuclear medicine imaging technique of SPECT/CT. This also provided an opportunity to confirm whether any studies had considered this radiographic modality alone. Only one such study, using cone CT, was retrieved. It used each of four studies per patient as the unit of study, precluding extraction of patient-level data [32].

Fig. 1 PRISMA flow diagram

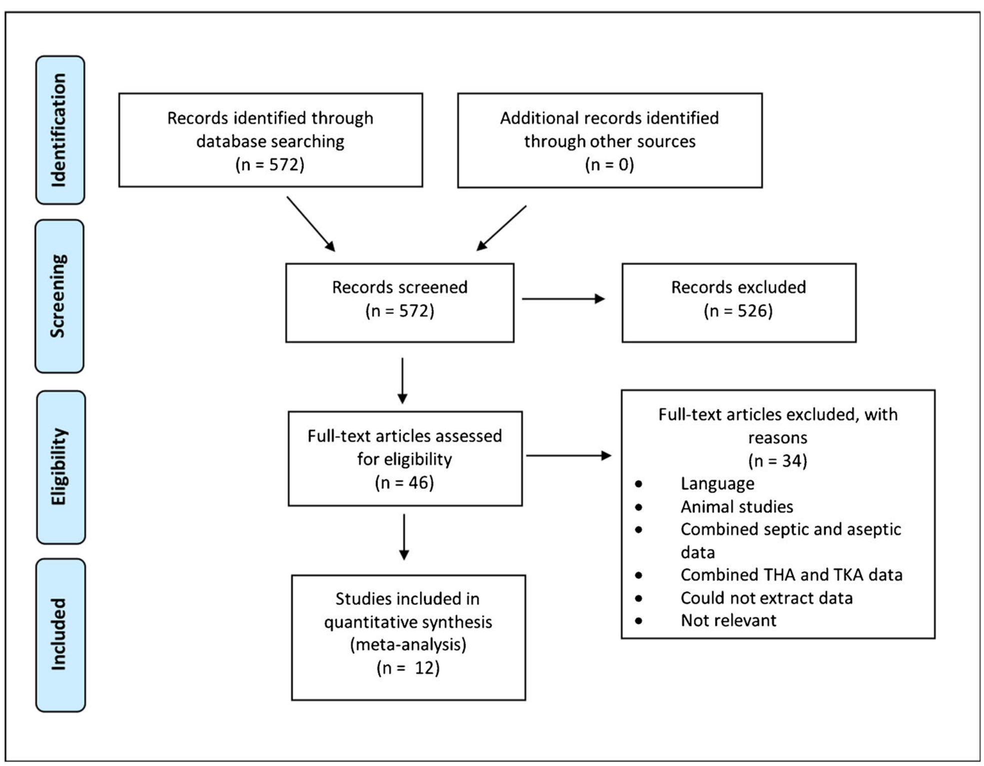

Table 2 Characteristics of the included studies

Modality	Study	Country	Population	Data acquisition	Number of patients	Age (years mean)	Sex (F/M)	Criterion standard
Bone scintigraphy	Claassen et al. 2014	Germany	Symptomatic knee arthroplasty	Retrospective	46	68.6	36/11	Operative findings
	Mandegaran et al. 2018	United Kingdom	Symptomatic knee arthroplasty	Retrospective	9	N/A*	N/A*	Operative findings and clinical follow-up evaluation
	Saccheti et al. 1996	Italy	Symptomatic knee arthroplasty	Retrospective	13	N/A*	N/A*	Operative, clinical, and radiologic findings of loosening
	Smith et al. 2001	United Kingdom	Symptomatic knee arthroplasty	Retrospective	71	66.2	42/33**	Operative findings
	Verlooy et al. 1993	Belgium	Symptomatic TKR < 1 year post TKR	Retrospective	8	NR	NR	Clinical and radiologic findings of loosening
18F-FDG-PET	Manthey et al. 2002	Germany	Symptomatic knee arthroplasty	Prospective	4	N/A*	N/A*	Operative findings and clinical follow-up evaluation
	Mayer-Wagner et al. 2010	Germany	Symptomatic knee arthroplasty	Prospective	44	N/A*	N/A*	Operative findings
	Sterner et al. 2006	Germany	Symptomatic knee arthroplasty	Prospective	14	70.5	6/9**	Operative findings and clinical follow-up evaluation
SPECT/CT arthrogram	Abele et al. 2015	Canada	Symptomatic knee arthroplasty	Retrospective	17	N/A*	N/A*	Operative findings and clinical follow-up evaluation
	Chew et al. 2010	Australia	Patients referred for investigation of implant loosening TKA and UKA	Retrospective	44	NR	NR	Operative findings and clinical follow-up evaluation
Radionuclide arthrogram	Chew et al. 2010	Australia	Patients referred for investigation of implant loosening TKA and UKA	Retrospective	42	NR	NR	Operative findings and clinical follow-up evaluation
	Kitchener et al. 2006	Australia	Symptomatic knee arthroplasty with or without concern of radiology findings TKA and UKA	Retrospective	66	62	19/24	Operative findings (revision or arthroscopy)
	Marx et al.	Germany	Symptomatic knee arthroplasty	Prospective	23	67	14/9	Operative findings

NR Not reported

*N/A** not available as unable to extract data as combined with other data

**Data did not match number of patients due to drop outs

All included studies used operative findings, a period of clinical or radiographic observation or both as a criterion standard for aseptic loosening. We considered these to be appropriate and equivalent for the purposes of this review.

The majority of studies (8 of 12) were retrospective, based on chart reviews of those patients who had been referred for nuclear medicine studies and who had subsequently undergone either surgical revision, arthroscopy, or an appropriate period of observation (Table 2).

Five studies of planar bone scintigraphy were included, two of SPECT/CT arthrography, three of radionuclide arthrography, and three of 18F-FDG-PET. There was only

Bone scintigraphy

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Claassen et al	26	2	8	10	0.76 [0.59, 0.89]	0.83 [0.52, 0.98]
Mandegaran et al	8	0	1	0	0.89 [0.52, 1.00]	Not estimable
Saccheti et al	7	0	1	5	0.88 [0.47, 1.00]	1.00 [0.48, 1.00]
Smith et al	15	13	2	41	0.88 [0.64, 0.99]	0.76 [0.62, 0.87]
Verlooy et al	5	2	0	1	1.00 [0.48, 1.00]	0.33 [0.01, 0.91]

18F-FDG-PET

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Manthey et al	2	0	1	1	0.67 [0.09, 0.99]	1.00 [0.03, 1.00]
Mayer-Wagner et al	9	5	7	23	0.56 [0.30, 0.80]	0.82 [0.63, 0.94]
Sterner et al	5	4	0	5	1.00 [0.48, 1.00]	0.56 [0.21, 0.86]

SPECT/CT arthrogram

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abele et al	2	1	0	14	1.00 [0.16, 1.00]	0.93 [0.68, 1.00]
Chew et al (SPECT FEMUR)	9	12	3	20	0.75 [0.43, 0.95]	0.63 [0.44, 0.79]
Chew et al (SPECT TIBIA)	6	5	1	32	0.86 [0.42, 1.00]	0.86 [0.71, 0.95]

Radionuclide arthrogram

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chew et al (RN FEMUR)	2	1	10	29	0.17 [0.02, 0.48]	0.97 [0.83, 1.00]
Chew et al (RN TIBIA)	5	8	3	26	0.63 [0.24, 0.91]	0.76 [0.59, 0.89]
Kitchener et al	23	5	3	35	0.88 [0.70, 0.98]	0.88 [0.73, 0.96]
Marx et al (FEMUR)	4	3	9	7	0.31 [0.09, 0.61]	0.70 [0.35, 0.93]
Marx et al (TIBIA)	1	2	11	9	0.08 [0.00, 0.38]	0.82 [0.48, 0.98]

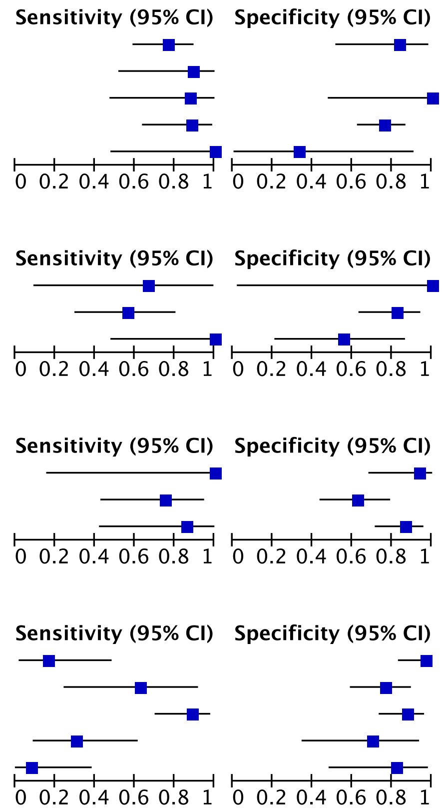

Fig. 2 Forest plot of included studies

one study relating to SPECT/CT precluding comparison to any other studies [24]. One study [21] included considerations of two modalities, and two studies reported separately on tibial and femoral components [21, 31]. Of the 12 eligible studies, we were able to perform 16 comparisons with the criterion standard.

The sensitivities and specificities from each study for each modality are displayed in Fig. 2. Most studies were small, so the confidence intervals around the point estimates of sensitivity and specificity are wide. In line with current recommendations, we have consciously not calculated pooled estimates for sensitivity or specificity [17].

The diagnostic accuracy of the assessed modalities is displayed in the SROC (Fig. 3). The individual curves are derived by combining the results from different studies of the same test. The curve that passes closest to the upper left corner of the graph has the greatest area under the curve, and represents the most accurate test [16], in this case, SPECT/CT arthrography.

Discussion

Before accepting these findings, it is important to consider the strengths and limitations of this study. The reliability and utility of a systematic review are determined by the rigor of the techniques used in the performance of the review and the quality of the available studies. We have sought to perform this review in line with expert recommendations. Database selection and search strategies were informed by the Cochrane Collaboration [14] and supported by empirical evidence [15]. Data were extracted from available studies by both authors, and analyzed according to current recommendations, most notably the use of summary operating receiver curves [16, 17, 19].

The main weakness of this review and meta-analysis is the poor quality of the included studies. An ideal trial for inclusion would involve a prospectively applied test in a diverse and representative range of patients, the results of which are appraised blindly and compared to a definitive reference standard. For the diagnosis of aseptic arthroplasty loosening, there is no single reference standard. Most of the included studies have small numbers and were retrospective in nature. On formal assessment, all papers had a high risk of bias in at least one domain (Table 3). The key issue in considering our results of this study is whether the small numbers and high risk of bias preclude any firm conclusions from being reached. This is made more difficult since the outcome measure of the summary ROC curves are close for the two most accurate techniques, SPECT/CT arthrogram and bone scintigraphy. We

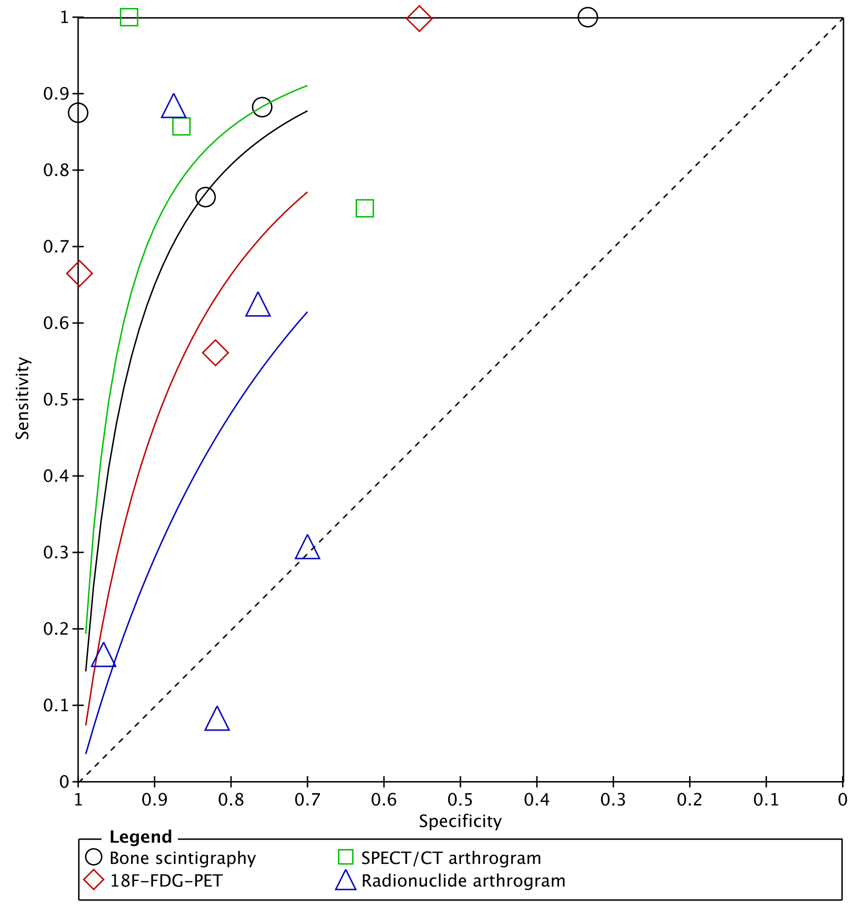

Fig. 3 Summary receiver operating characteristic curve (SROC) of included studies

Table 3 Quality assessment of the studies included using the QUADAS-2 tool

Study	Risk of bias				Concerns regarding applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Claassen et al. 2014	High	Low	High	Low	Low	Low	Low
Mandegaran et al. 2018	High	Low	High	High	Low	Low	Low
Saccheti et al. 1996	High	High	High	High	Low	Low	Low
Smith et al. 2001	High	High	High	Low	Low	Low	Low
Verlooy et al. 1993	High	High	High	High	Low	Low	Low
Manthey et al. 2002	Low	Low	High	High	Low	Low	Low
Mayer-Wagner et al. 2010	Low	Low	High	Low	Low	Low	Low
Sterner et al. 2006	Low	Low	High	High	Low	Low	Low
Abele et al. 2015	High	High	High	High	Low	Low	Low
Chew et al. 2010	High	Low	High	High	Low	Low	Low
Kitchener et al. 2006	High	Low	High	High	Low	Low	Low
Marx et al	Low	Low	High	Low	Low	Low	Low

consider that our findings are likely to be fragile to change from larger and better conducted studies. At the same time, they represent the best available evidence concerning this clinical question.

We have not considered the utility or accuracy of serial investigations, or whether some investigations would have additional utility in considering other competing diagnoses (such as FDG-PET for malignancy or infection). Explicitly, this study sought to determine the accuracy of different techniques for the detection of aseptic loosening. It does not consider the ability of a test to differentiate between other diagnoses, which is a different clinical question. The detection of periprosthetic infection has been considered in other formal reviews [33]. This information could be combined with the findings of the present study in formal decision analysis for individual patients.

Several studies were excluded from the current analysis on the basis that the sensitivity and specificity for individual diagnoses or joints was not able to be extracted from the data. This risks losing important data. We would recommend that future studies report findings for each combination of diagnosis, joint, and modality or provide raw data that enable this information to be calculated in a two-by-two table.

Very few papers commented on the time between primary arthroplasty and the radiology investigation, or the time between the radiology investigation and the reference standard. Lengthy time periods between the index investigation and reference standard in diagnostic accuracy papers will increase the risk of bias. Furthermore, the information gathered from these specific time points would be critical to both radiologists and orthopedic surgeons in recommending appropriate timing and potential yield of these scans.

Mindful of the potential limitations of this study, nuclear arthrography with SPECT/CT appears to be the most accurate means of identifying aseptic prosthetic joint loosening. This observation has face value in that the pathological processes are at the implant/bone interface, and accessing this area with a bone-avid agent directly, rather than through systemic dissemination, would seem likely to be more reliable. Moreover, the detailed spatial localization provided by hybrid imaging enables typical diagnostic patterns and sites of pathological uptake to be identified. This technique has other potential advantages over non-arthrographic techniques. Septic loosening is an important differential diagnosis in this clinical setting, and as part of an arthrography study, a diagnostic arthrocentesis can be performed. The disadvantage and risks of arthrography are primarily the introduction of infection, a potentially catastrophic complication, so it is axiomatic that strict aseptic technique is applied in combination with orthopaedic consultation.

In conclusion, this meta-analysis suggests that the most diagnostically accurate modality for the detection of aseptic loosening in TKA is SPECT/CT arthrography. However, the included studies are compromised by a high chance of bias, small numbers, and are likely to be fragile to change in the face of larger studies with less risk of bias. Further, carefully conducted studies are indicated, and should include CT and MRI assessments using contemporary metal artefact reduction techniques as potential investigations. The clinical consequences of a wrong diagnosis, including revision arthroplasty, place a premium on accuracy for this clinical question.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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