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PET and SPECT in Osteomyelitis and Prosthetic Bone and Joint Infections: A Systematic Review

Wouter van der Bruggen, MD,* Chantal P. Bleeker-Rovers, MD, PhD,†,‡
Otto C. Boerman, PhD,*,‡ Martin Gotthardt, MD, PhD,* and Wim J.G. Oyen, MD, PhD*,‡

Objective To review the literature on diagnostic accuracy and clinical value of single-photon emission computed tomography (SPECT) and positron emission tomography (PET) for imaging of bone and joint infections.

Methods The PubMed/MEDLINE and Embase (OvidSP) literature databases were systematically searched for publications on SPECT and PET on osteomyelitis and prosthetic bone and joint infections using specific guidelines with MeSH-terms, truncations, and completion using cross-references.

Results In 44 original articles (15 for SPECT and 29 for ^{18}F-fluorodeoxyglucose [FDG]-PET) on osteomyelitis and prosthetic bone and joint infection, 1634 patients were included (580 patients SPECT, 1054 patients FDG-PET). Level of evidence (Oxford criteria) was *2-3b*. For SPECT, the highest diagnostic accuracy of 95% for diagnosis of bone and joint infections is achieved with combined ^{111}In-WBC and ^{99m}Tc-sulfur colloid. Acceptable diagnostic accuracy was also obtained with ^{99m}Tc-WBC or ^{111}In-WBC combined with ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP). FDG-PET is useful for diagnosis of osteomyelitis with a sensitivity and specificity generally over 95%. In patients with orthopedic implant infections, sensitivity varies widely from 28% to 91% and specificity from 9% to 97%. This variation in FDG-PET performance in orthopedic implant infections depends largely on the (use of different) criteria to diagnose infection. Determination of the best criteria is still a matter of debate.

Conclusions SPECT/computed tomography (CT) with ^{111}In-WBC combined with ^{99m}Tc-MDP or ^{99m}Tc-sulfur colloid seems to be the best imaging technique for diagnosis of bone and joint infections. FDG-PET is also useful for diagnosis of osteomyelitis with improved spatial resolution over SPECT imaging, allowing more accurate localization. Localization can be further improved by adding CT. Diagnosis of orthopedic implant infections with FDG-PET depends strongly on the localization of the implant and the criteria used to diagnose infection. Confirmation of well defined criteria to diagnose infection on FDG-PET in patients with metallic implants is thus of paramount importance for optimal diagnosis.

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Acute and chronic osteomyelitis, spondylodiscitis, and orthopedic implant infections are a heterogeneous group of infectious disease entities. A common denominator is the complex diagnostic and therapeutic challenge that is regularly encountered by clinicians, radiologists, and nuclear medicine physicians. Although these disease entities share some common features, they present different problems in both diagnostic procedures as in therapy. Therefore, the different infectious diseases and the respective performance of single-photon emission computed tomography (SPECT) and positron emission tomography (PET) will be discussed separately.

The patient's history, subjective symptoms, and biochemical and physical findings are often inconclusive, particularly in the early stages. First abnormalities because of osteomyelitis may not become visible on a plain x-ray until 10-21 days after onset of osteomyelitis, as 30%-50% loss of bone density must occur before radiographs can detect the disease.[1] De-

*Department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
†Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
‡Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
Address reprint requests to Wouter van der Bruggen, MD, Department of Nuclear Medicine (internal postal code 444), Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB, Nijmegen, The Netherlands. E-mail: W.vanderBruggen@nucmed.umcn.nl

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tailed anatomical imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is often unable to detect osteomyelitis at an early stage of the disease as well. Early detection is crucial in this disease for adequate treatment.[1] To detect osteomyelitis before anatomical changes are present, functional imaging could have some advantages over anatomical imaging. Diagnosis of infection in patients with joint prostheses or metallic implants is difficult for more than one reason. On CT and MRI, metallic implants cause troublesome artifacts. On functional imaging, however, the mere presence of metallic implants can result in increased focal accumulation of the radiopharmaceutical uptake, not necessarily indicating infection or clinically relevant inflammation.

A variety of nuclear medicine techniques have been developed for evaluation of infection of the locomotor system. ^{67}Ga-citrate has been used for imaging of infection and inflammation ever because of its discovery in the early seventies.[2] Multiphase skeletal scintigraphy with ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) and radiolabeled white blood cells (WBC) have become the most widespread clinically used agents for the imaging of bone and joint infections. Radiolabeled leukocytes have been the "gold standard" imaging technique for infection for a long time. Nowadays, a variety of new radiopharmaceuticals is also used in infection imaging. A wide variety of other radiolabeled probes, based on antibodies, cytokines, and other receptor-binding ligands, are under (preclinical) investigation. Each tracer and technique has its own inherent strongholds and shortcomings.

After years in which planar scintigraphy used to be the standard, the need for improved localization was met by SPECT. This allows more detailed 3D localization, compared with planar imaging, which can provide crucial information, particularly in patients with osteomyelitis, but also in patients suspected of infected joint prostheses. Recently integrated SPECT/CT was developed. Furthermore, the utility of positron emitting radiopharmaceuticals for PET and PET/CT was explored, allowing acquisition of high-resolution images with good anatomic localization. Therefore, these 3D imaging techniques (with or without CT for accurate localization) are more widely used. For PET, nearly all interest has focused on ^{18}F-fluorodeoxyglucose (^{18}F-FDG). This review aims to provide a concise, structured overview of SPECT and PET imaging in patients suspected of osteomyelitis, spondylodiscitis, and orthopedic implant infections.

Overview of Radiopharmaceuticals Used in Bone and Joint Infections

Many radiopharmaceuticals have been studied and have been used for imaging of bone and joint infections in patients. Here, a concise overview of the performance of most important tracers for SPECT and PET imaging of bone and joint disease is described.

^{99m}Tc-Bisphosphonates

^{99m}Tc-labeled bisphosphonates (such as MDP and hydroxymethylene diphosphonate [HDP]) are the most commonly used radiopharmaceuticals to image osteoblastic activity. In patients with osteomyelitis and infected orthopedic prostheses, increased osteoblastic activity occurs. Detection of osteomyelitis with ^{99m}Tc-MDP is highly sensitive (>90%). When the bone has not been violated by other pathologic conditions, specificity is high as well (around 90%). In post-traumatic patients and after surgery, specificity is dramatically lower (circa 35%).[1]

^{67}Ga-Citrate

^{67}Ga-citrate has been used for imaging of infection and inflammation ever since the early seventies.[2] Although ^{67}Ga-citrate scintigraphy has a high sensitivity for both acute and chronic infection and noninfectious inflammation, there are several shortcomings: the need for delayed imaging (>48 h), low specificity, limited spatial resolution, physiological bowel excretion, and the high radiation dose of the procedure. The physiological bowel uptake of ^{67}Ga-citrate can be overcome by delayed imaging.[3] ^{67}Ga-citrate has been used routinely, mainly to diagnose or to exclude osteomyelitis,[2] with reasonable sensitivity (73%) and relatively low specificity (61%).[4] ^{67}Ga-citrate is now less frequently used, because of these drawbacks and because compounds and techniques with more favorable characteristics have been developed.

Radiolabeled Leukocytes

Scintigraphy with ^{111}In-labeled leukocytes has an excellent performance in diagnostic accuracy; a sensitivity of more than 95% has been reported.[5] After successful labeling of leukocytes with ^{99m}Tc using hexamethylpropylene amine oxime, ^{99m}Tc-labeled white blood cells (^{99m}Tc-WBC) have replaced ^{111}In-labeled leukocytes for most indications, because of more favorable imaging characteristics.[1] Scintigraphy with ^{99m}Tc-WBC shows high sensitivity and specificity for imaging of infection. Uptake in acute osteomyelitis (supposedly due to the enhanced influx of leukocytes in acute osteomyelitis) is generally higher, compared with chronic osteomyelitis. The main drawbacks of ^{111}In-WBC and ^{99m}Tc-WBC are their laborious preparation, requirement of specialized equipment, and the handling of potentially infectious blood.[2] Therefore, a radiopharmaceutical with at least as good clinical performance as radiolabeled leukocytes that can be prepared off-the-shelf is warranted.[1] Unlike ^{111}In-WBC, ^{99m}Tc-WBC is reliably unstable, and ^{99m}Tc-hexamethylpropylene amine oxime can elute from the WBC, and can subsequently be excreted through the kidneys, the gallbladder, and the intestine.[6] Low sensitivity for osteomyelitis of the spine has been reported in studies using ^{111}In-WBC and ^{99m}Tc-WBC, resulting in nonspecific "cold spots."[7]

Radiolabeled Specific Antigranulocyte Monoclonal Antibodies and Nonspecific IgG

Radiolabeled antigranulocyte antibodies have been developed for in vivo labeling of white blood cells. Antibodies accumulate in infectious and inflammatory foci mainly by nonspecific extravasations, because of the enhanced vascular permeability in combination with specific targeting of infiltrated granulocytes. Intact antibodies (whole IgG) show rel-

ative slow blood clearance, while antibody fragments [Fab' or $F(ab')_2$] and IgM antibodies clear much faster. Uptake of intact IgG antibodies is higher in the liver compared with radiolabeled leukocytes and lower in the spleen. Overall sensitivity for infection detection with radiolabeled antibodies is approximately 80%-90%. Peripheral bone infections are adequately visualized, but sensitivity decreases when the infection is located closer to the spine.[8] This is mainly a result of physiological uptake in normal bone marrow and limited infiltration of leukocytes, comparable to diagnostic difficulties for ^{111}In-WBC and ^{99m}Tc-WBC to diagnose spondylitis. ^{99m}Tc-anti-CD15 IgM and ^{99m}Tc-anti-NCA-95 IgG are among the most effective antibodies to diagnose bone and joint infections.[9,10]

Radiolabeled nonspecific human IgG accumulates in infectious and inflammatory foci by nonspecific extravasation facilitated by enhanced vascular permeability.[7,11] ^{111}In-IgG has shown excellent performance in the localization of musculoskeletal infection and inflammation.[7] ^{99m}Tc-HYNIC-lgG scintigraphy is equally effective as^{111} ln-lgG scintigraphy, for the detection of infection and inflammation. The apparent physical and logistic advantages of ^{99m}Tc over^{111}In make ^{99m}Tc-HYNIC-IgG in this respect a more attractive radiopharmaceutical for imaging infection and inflammation.[12]

^{18}F-fluorodeoxyglucose (FDG)

FDG is transported into cells by glucose transporters (glut-1, glut-3) and phosphorylated by hexokinase inside the cell to form fluorodeoxyglucose-6-phosphate. The phosphorylated deoxyglucose cannot be further metabolized, and therefore FDG accumulates in activated lymphocytes, neutrophils, and macrophages with minimal decrease over time.[13,14] FDG therefore accumulates in sites of infection, although it is a nonspecific tracer that also accumulates in regions of aseptic inflammation, as well as in malignant lesions.[15] These characteristics make FDG-PET suitable for imaging of various inflammatory and infectious diseases, mostly nonosseous infections but also osteomyelitis.[16,17] Several groups have studied the role of FDG-PET in the diagnosis of chronic osteomyelitis. Acute osteomyelitis and spondylitis can also be successfully diagnosed with FDG-PET.[18]

Methods

Search Strategy

The PubMed/MEDLINE and EMBASE (through OvidSP) literature databases were systematically searched for publications from January 1980 up to December 2008 on conventional scintigraphy, SPECT, and PET in bone and joint infections according to the guidelines provided in "Update of the FDG-PET search strategy" by Mijnhout et al[19] The search strategy is summarized in Table 1.

Article Selection

Original articles in English were included. Case reports, reports from meetings, editorial comments, or letters to the editor were excluded. Articles not concerning human bone infections, preclinical animal experiments, and articles discussing results of less than 5 patients with bone or joint infections were excluded. The remaining 39 full text articles from PubMed/MEDLINE and the 38 full text articles from EMBASE (through OvidSP) were further evaluated. After correction for duplicates from both databases, this resulted in 43 unique original articles. In addition to these original articles, review articles were included for cross-referencing. Identification of 18 cross-references resulted in 61 articles, which were analyzed and included in this review.

Table 1 Systematic Query in PubMed/MEDLINE and EMBASE* (Through OvidSP)

Bone and Joint Infections	Imaging Techniques
Bone diseases, infectious (MeSH)	PET (MeSH)
	PET
Osteomyelitis (Mesh)	PET/†
Osteitis (Mesh)	Petscan†
Periostitis (Mesh)	PET/CT†
Spondylitis (Mesh)	PET-CT†
Spondylodisc†	CT/PET†
Prosthesis	CT-PET†
Prosthetic	(Positron† AND emission,† AND tomograph†)
	Tomography, emission-computed, single-photon (MeSH)‡
	SPECT†
	SPECT/CT†
	SPECT-CT†
	CT/SPECT†
	CT-SPECT†

*In EMBASE terms were used with "include all subheadings".
†Truncation.
‡In EMBASE (OvidSP) the corresponding term was "Single Photon Emission Computer Tomography".

Data Interpretation and Analysis

Test performance was derived from the various studies and put into perspective. The following criteria and outcome measures were regarded as the major topics of interest for this review:

- level of evidence of the study (Oxford Centre for evidence-based medicine levels of evidence)
- number of patients with bone or joint infection
- radiopharmaceutical of choice
- patient selection: acute osteomyelitis, chronic osteomyelitis, spondylodiscitis, and orthopedic implant infection
- sensitivity, specificity, and accuracy of conventional radionuclide imaging, SPECT, and PET for the different entities of bone and joint infections
- prognostic value of these techniques in patients with (prosthetic) bone and joint infections
- change in management of patients with bone and joint infections due to FDG-PET and SPECT

Conventional, SPECT, and SPECT/CT Imaging in the Diagnosis of Bone and Joint Infections

The role of SPECT in bone and joint infections has been investigated using a series of radiopharmaceuticals. The qualified studies for this review include ^{67}Ga-citrate, ^{99m}Tc-MDP, ^{99m}Tc-HDP, ^{99m}Tc-MDP, ^{111}In-WBC and ^{99m}Tc-WBC, ^{99m}Tc-labeled antigranulocyte antibodies, and ^{99m}Tc-sulfur colloid. The level of evidence of the studies (Oxford Centre for evidence-based medicine Levels of Evidence) *ranges from 2 to 3 b*. The included studies regarding SPECT imaging are summarized in Table 2.

Osteomyelitis

^{99m}Tc-MDP

In 11 patients, Palestro et al[9] present excellent sensitivity for planar bone scintigraphy with ^{99m}Tc-MDP, with a limited specificity (11 true positives in 11 patients with proven osteomyelitis and 5 true negatives in 13 patients without osteomyelitis). This high sensitivity and poor specificity for ^{99m}Tc-MDP in patients with osteomyelitis was confirmed by studies by Hakim et al[20] with 34 cases of osteomyelitis and Horger et al with 9 relevant cases.[21] Therefore, more specific radiopharmaceuticals are warranted in patients suspected of osteomyelitis. SPECT imaging of ^{99m}Tc-MDP alone[20] or ^{99m}Tc-HDP alone[21] resulted in acceptable sensitivity (78%-84%), but specificity remained inadequate (33%-50%).[20,21] In hybrid ^{99m}Tc-HDP-SPECT/CT, however, specificity was appreciably higher, when compared with SPECT alone, ie, 86% compared with 50% due to better anatomical localization by adding CT.[21]

Radiolabeled WBC

Palestro et al[9] reported that planar scintigraphy with ^{111}In-WBC resulted in good sensitivity and reasonable specificity (10 true positives in 11 patients with proven osteomyelitis and 8 true negatives in 13 patients without osteomyelitis), being accurate in 18 out of 24 patients. Rini et al[15] reported an insufficient result for diagnosing osteomyelitis with ^{111}In-labeled leukocytes, with 4 true positives in 7 patients with proven osteomyelitis and 2 true negatives in 6 patients without osteomyelitis, using ^{111}In-WBC SPECT imaging.

Theoretically, specificity of imaging with ^{111}In-WBC is hampered, because of uptake in normal bone marrow, which varies between patients and is not specific for disease.[29] Palestro et al[9] showed that combination of planar ^{111}In-WBC and ^{99m}Tc-MDP resulted in good sensitivity and specificity (11 true positives in 11 patients with proven osteomyelitis and 10 true negatives in 13 patients without osteomyelitis) with an accuracy of 87%. Besette et al[23] also investigated the test parameters of combined ^{111}In-WBC SPECT and ^{99m}Tc-MDP in diagnosing 25 patients with proven postsurgery sternal osteomyelitis.[23] In this study they found a good sensitivity (84%) and excellent specificity (100%). In 26 patients, Seabold et al[24] showed that combined ^{111}In-WBC and ^{99m}Tc-MDP SPECT seems to be the best technique for follow-up of postoperative patients with osteomyelitis in the mastoid region, when compared with CT or MRI. This combination resulted in a sensitivity of 95% and a specificity of 93%.[24] In a study by Weber et al,[25] including 20 patients suspected of temporal and facial osteomyelitis, 30 combined ^{111}In-WBC and ^{99m}Tc-MDP scans were performed. Performance of combined ^{111}In-WBC and ^{99m}Tc-MDP was adequate with 15 true positives in 16 scans with proven osteomyelitis and 13 true negatives in 14 scans without osteomyelitis. Palestro et al[29] proposed the use of combined ^{111}In-WBC and bone marrow imaging performed with ^{99m}Tc-sulfur colloid. ^{111}In–WBC and ^{99m}Tc-sulfur colloid accumulate in the bone marrow, where ^{111}In-WBC also accumulate in sites of infection and ^{99m}Tc-sulfur colloid does not.[29] Activity on the ^{111}In-WBC image without corresponding activity on the ^{99m}Tc-sulfur colloid image was therefore considered positive for infection. Any other pattern was considered a negative study for infection.[29] This combined ^{111}In-WBC and bone marrow imaging with ^{99m}Tc-sulfur colloid showed a 100% sensitivity and 98% specificity in 50 patients with suspected infected total-hip arthroplasty.[30]

Antibodies

Palestro et al[9] reported that scanning with ^{99m}Tc-labeled murine anti-CD15 IgM antigranulocyte antibodies in patients with suspected osteomyelitis showed 10 true positives in 11 patients with proven osteomyelitis and 9 true negatives in 13 patients without osteomyelitis, when imaging 2 hours after injection. With an accuracy of 91%, this combination of ^{99m}Tc-anti-CD15 IgM and ^{99m}Tc-MDP, seems to approach the diagnostic accuracy of radiolabeled leukocytes. Unfortunately, this radiopharmaceutical is no longer commercially available. With ^{99m}Tc-anti-NCA-95 IgG, Horger et al[10] showed in 27 patients that sensitivity for detection of relapsing posttraumatic osteomyelitis was excellent and identical for SPECT and hybrid SPECT/CT (100%), whereas specificity improved from 78% with SPECT to 89% when using hybrid SPECT/CT. Analysis of interobserver agreement with regard to localization of infectious foci resulted in kappa = 0.68 for immunoscintigraphy alone and kappa = 1.0 for SPECT/CT, demonstrating the high reliability of this method.[10] In addition, they concluded that in 27.5% of the cases SPECT/CT imaging led to a change in diagnosis when compared with SPECT, which also resulted in a change of management in these patients.[10] Wuest et al[31] also showed a change in clinical diagnosis in 7 out of 11 patients with peripheral orthopedic disorders (4 patients with osteomyelitis) because of adding CT to SPECT.

An interesting feature of nuclear medicine techniques is the ability to monitor therapy response. Weber et al[28] investigated the response after treatment of facial and temporal osteomyelitis. They found that ^{111}In-WBC in combination with ^{99m}Tc-MDP bone SPECT imaging revealed normalization after successful treatment of osteomyelitis much more rapidly than ^{67}Ga-citrate or CT scans, and concluded that ^{111}In-WBC/^{99m}Tc-MDP bone SPECT is most useful during follow-up.[28] However, Hakim et al[20] reported that FDG-PET possibly performs even better than ^{99m}Tc-MDP-SPECT, showing normalization 1 month after onset of therapy (albeit

Table 2 Studies Regarding SPECT Imaging

	Author	Number of Patients*	Pathology	Radiopharmaceutical	Gold Standard	Study Design and Level of Evidence†
^{99m}Tc-MDP and ^{99m}Tc-HDP	Hakim et al (2006)[20]	42 (34)	Suspected chronic osteomyelitis of the mandible	^{99m}Tc-MDP	Histology, radiographs, clinical, and laboratory parameters	Prospective cohort design, 2b
	Horger et al (2007)[21]	31 (9)	Suspected osteomyelitis (no prosthesis)	^{99m}Tc-DPD (comparison with hybrid CT)	Surgery, biopsy, or follow-up, including microbiology and radiology	Prospective cohort design, 2b
^{67}Ga-citrate	Gratz et al (2002)[4]	16 (11)	Suspected spondylitis (no prosthesis)	^{67}Ga-citrate	Culture, surgery, and histopathology	Prospective cohort design, 2b
	Bar-Shalom et al (2006)[3]	82 (32)	Suspected osteomyelitis (no prosthesis)	^{67}Ga-citrate or ^{111}In-WBC SPECT, both with CT	Culture, surgery, clinical follow-up (24 mo), and correlative imaging	Retrospective case control design, 3b
	Palestro, et al (1990)[30]	92 (23)	Suspected infected total hip arthroplasty	^{111}In-WBC/^{99m}Tc-sulfur colloid	Surgery	Retrospective case control design, 3b
	Palestro et al (1991)[22]	71 (28)	Suspected vertebral osteomyelitis	^{111}In-WBC	Culture and biopsy	Retrospective case control design, 3b
	Besette et al (1993)[23]	32 (32)	Suspected sternal osteomyelitis postsurgery	Combined ^{111}In-WBC with ^{99m}Tc-MDP (compared with CT)	Surgically and "clinically proven" osteomyelitis	Retrospective case control design, 3b
WBC ^{99m}Tc-WBC ^{111}In-WBC	Seabold et al (1995)[24]	26 (24)	Suspected cranial osteomyelitis (no prosthesis)	^{111}In-WBC and ^{99m}Tc-MDP	Culture and clinical follow-up	Retrospective case control design, 3b
	Weber et al (1995)[25]	20 (20)	Suspected temporal and facial osteomyelitis (no prosthesis)	^{111}In-WBC/^{99m}Tc-MDP	Biopsy/culture results in 18 patients and by endoscopic and clinical evaluation	Retrospective case control design, 3b
	Van Acker et al (2001)[26]	21 (6)	Suspected infected total knee arthroplasty	^{99m}Tc-HMPAO-labeled leukocytes	Operative findings, culture, and clinical outcome	Prospective cohort design, 2b
	Vanquickenborne et al (2003)[27]	17 (17)	Suspected infected hip prostheses	^{111}In-WBC	Culture or clinical follow-up	Prospective cohort design, 2
	Filippi et al (2006)[28]	28 (28)	Suspected osteomyelitis (15) and metallic implants (13)	^{99m}Tc-HMPAO leukocytes (hybrid with CT)	Surgery or cultures	Prospective cohort design, 2b
	Rini et al (2006)[15]	51 (47)	Suspected osteomyelitis, (17) prosthesis (21), and various infections (5)	^{111}In-WBC	Histopathology, microbiology, surgery, or clinical follow-up	Prospective cohort design, 2b
Antigranulocyte antibodies	Palestro et al (2002)[9]	24 (24)	Suspected osteomyelitis (12) and metallic implants (12)	^{99m}Tc-labeled murine IgM monoclonal antigranulocyte antibody and ^{111}In-WBC	Pathology and clinical outcome	Prospective cohort design, 2b
	Horger et al (2003)[10]	27 (27)	Suspected relapsing posttraumatic osteomyelitis	^{99m}Tc-labeled antigranulocyte antibodies (with CT)	Surgery, biopsy, cultures, or follow-up >6 mo	Prospective cohort design, 2b

*Number of patients with suspected osteomyelitis or suspected infected prosthetic bone and joint disease, with number of proven infection in parentheses.
†Level of evidence and design of the study (Oxford Centre for evidence-based medicine Levels of Evidence).

in only 2 cases), where the first normalization was seen after 2 months on SPECT.[20]

The additional role of SPECT/CT vs planar imaging was investigated for ^{67}Ga-citrate and ^{111}In-WBC by Bar-Shalom et al[3] in 32 patients with osteomyelitis. The main diagnostic difficulty for both ^{67}Ga-citrate and ^{111}In-WBC-SPECT was the inability to localize an infectious focus within a specific organ. Contribution of SPECT/CT to diagnosis and localization was 39% for ^{67}Ga-citrate and 47% for ^{111}In-WBC in assessment of osteomyelitis.[3]

Spondylitis and Spondylodiscitis

Performance of scintigraphy with ^{111}In-WBC for spondylitis and spondylodiscitis is drastically lower compared with detection of osteomyelitis in peripheral bone, as reported in several studies.[5,22] On planar images acquired after injection of ^{111}In-WBC or ^{99m}Tc-WBC, up to 50% of all patients with spondylodiscitis show photopenic lesions because of encapsulation of the infection[4] and hence relatively hampered migration of leukocytes. These photopenic lesions are not specific for infection.[32] Another disadvantage is physiological uptake of ^{111}In-WBC and ^{99m}Tc-WBC in normal bone marrow.[4] Both mechanisms result in low sensitivity for ^{111}In-WBC and ^{99m}Tc-WBC for infection detection in the spine. Palestro et al[22] showed 15 patients with decreased focal activity of ^{111}In-WBC, 11 patients with increased uptake, and 2 cases with normal uptake in 28 confirmed patients with spondylitis, exemplifying the diagnostic difficulty of spondylitis.

Infection of Metallic Implants

Scintigraphy with ^{111}In-WBC was able to reliably differentiate between infected and sterile orthopedic metallic implants.[18] Although the number of patients with suspected infected metallic implants scanned with ^{111}In-WBC SPECT was limited (17 patients) in the study of Rini et al,[15] they reported 3 true positives in 3 patients with proven orthopedic implant infection and 14 true negatives in 14 patients without orthopedic implant infection. Palestro et al[30] confirmed good performance of ^{111}In-WBC in 92 patients with total hip arthroplasties (23 infected), with 87% sensitivity and 94% specificity.

Love et al[33] concluded that planar imaging with ^{111}In-WBC/^{99m}Tc-sulfur colloid in case of prosthetic joint infection results in excellent diagnostic value: sensitivity 100%, specificity 91%, and diagnostic accuracy 95%. This was significantly better than FDG-PET in the same group of patients ($<$0.001). FDG-PET showed good sensitivity (95%), but inadequate specificity (35%), resulting in a worse accuracy (61%) compared with ^{111}In-WBC/^{99m}Tc-sulfur colloid.[33]

The study by Van Acker et al,[26] including 19 patients with suspected orthopedic implant infection, reported sensitivity for ^{99m}Tc-WBC-SPECT of 100% with a specificity of 53% for diagnosis of infection.[26] They managed to improve specificity to 93% when only lesions that were identified on a bone scan with ^{99m}Tc-MDP were taken into account. This did not affect the sensitivity, which remained at 100%. The study by Filippi and Schillaci[28] including 15 patients with suspected orthopedic implant infection investigated SPECT/CT imaging with ^{99m}Tc-WBC for diagnosis of metallic implant-associated infection. Sensitivity and specificity were 100%. This exemplifies 2 different methods (ie, combining 2 different radiopharmaceuticals or adding CT) being able to reach high specificity in diagnosing infection in patients with suspected orthopedic implant infection.[26,28] Vanquickenborne et al[27] showed that the SPECT ^{99m}Tc-WBC provided better lesion contrast than FDG-PET in these patients, resulting in an 88% sensitivity and a 100% specificity on 4 hours images, while 24 hours planar images were of no additional value. The analysis of ^{18}F-FDG-PET alone resulted in 88% sensitivity and 78% specificity.[27] Therefore, they concluded that scanning with ^{99m}Tc-WBC leukocytes is sensitive and more specific than ^{18}F-FDG-PET for detecting infection in patients with metallic implants.[27] Test performance of combined ^{99m}Tc-MDP and ^{111}In-WBC SPECT in suspected bone or joint infection was reported by 2 studies.[24,25] This resulted in a sensitivity ranging from 95% to 97% and specificity ranging from 93% to 100% in 44 patients.[27,28]

Regardless of the radiopharmaceutical used or the disease entity (osteomyelitis or orthopedic implant infection), specificity of scintigraphic imaging increases when CT is added.[10,21,31] This was most strikingly demonstrated in the study of Horger et al[21] where specificity of ^{99m}Tc-HDP improved from 50% to 86% in 31 patients with suspected osteomyelitis by the addition of CT. A second important improvement by the addition of (low dose) CT is the enhanced interobserver agreement.[21]

FDG-PET and FDG-PET/CT Imaging in Diagnosing Bone and Joint Infections

In most studies investigating the performance of PET in bone and joint infections, FDG was used. The level of evidence of the included studies (Oxford Centre for evidence-based medicine levels of evidence) ranges from 2b to 3b. Table 3 summarizes the studies with a gamma camera in coincidence setting, the studies with full ring dedicated PET and combined FDG-PET/CT.

Osteomyelitis

The detection of osteomyelitis with FDG-PET is generally excellent, with sensitivities ranging from 94% to 100%.[16,18,34-36,53] FDG dual head gamma camera coincidence imaging in patients with chronic osteomyelitis of the mandible, yielded considerably lower sensitivity of 64%, recognizing only 16 patients out of 25 with chronic osteomyelitis, well below the sensitivity of 3-phase bone scintigraphy.[20] Although there is a study with coincidence camera that performs well in detecting osteomyelitis,[34] using a gamma coincidence camera instead of a full-ring PET camera apparently reduces the sensitivity of the method from 95% to less than 70% for patients with osteomyelitis of the mandible.

Specificity of FDG-PET for osteomyelitis ranges from 87% to 100%[16,18,34-36,53] when using a full ring PET scanner. When using a coincidence camera specificity was lower (78%) in the study, including patients suspected of osteomyelitis of the mandible.[20] Specificity can be adversely affected by lack of adequate clinical information, as was demonstrated in the study of Zhuang et al[16]: 2 false positives in 16 patients could have been avoided when critical information at the time of interpretation of the images had been available.[16] The lack of intrinsic high specificity of FDG-PET therefore demands a complete relevant medical history for the interpreter. Sensitivity and specificity for FDG-PET in patients with osteomyelitis in the included studies is summarized in Figure 1.

Rini et al[15] showed good sensitivity of FDG-labeled human autologous leukocytes, where specificity, however, was disappointing (6 true positives out of 7 patients having confirmed osteomyelitis and 3 true negatives and 3 false positives among 6 patients without osteomyelitis).

Sahlmann et al[44] investigated the relationship between the change in the standard uptake value (SUV) over time and the ability to discriminate between malignant and benign osseous lesions.

The hypothesis was that in osteomyelitis, lesions exhibit relatively stable SUVs during dynamic imaging, where malignant bone lesions generally show an increase in SUV over time. The authors hypothesized that when choosing the right cut-off values for the SUV these characteristics may be used to improve the specificity of FDG-PET for the differentiation between malignant and benign bone lesions.[44] In osteomyelitis, the SUV_{max} and SUV_{mean} remained stable or decreased in 16 out of 17 patients between 30 and 90 minute postinjection. In these patients, a median decrease of 6% for SUV_{max} (range 1%-31%) and a median decrease of 8.5% for SUV_{mean}

(range 0%-24%) were observed. In 1 patient, SUV_{max} and SUV_{mean} increased over the time. The histology of this patient revealed multiple foreign body granulomas in addition to a mononuclear infiltrate. In malignant lesions the SUV_{max} and SUV_{mean} between 30 and 90 minute postinjection increased.[44]

Osteomyelitis in Patients with Diabetes

Basu et al[49] described a perfect accuracy in 6 patients with proven osteomyelitis or neuropathic osteoarthropathy with FDG-PET in diabetic patients. FDG-PET was predominantly helpful in patients with a concomitant foot ulcer with a high negative predictive value in ruling out osteomyelitis in 5 patients (pathology confirmed absence of osteomyelitis, where MRI resulted in 2 false-positives).[49] Keidar et al[51] found excellent performance of FDG-PET/CT for diagnosing osteomyelitis in 9 patients with diabetic feet, all true positives and no false negatives.[51] In 7 patients with known diabetic ulcers, but without clinical suspicion of osteomyelitis, Schwegler et al[50] found very low sensitivity of FDG-PET for detection of osteomyelitis (2 true positives in 7 patients with proven osteomyelitis). MRI (which detected 6 out of 7 cases of unsuspected osteomyelitis) seems to be superior to FDG-PET in detecting foot ulcer-associated osteomyelitis, and might be the preferred imaging modality in patients with nonhealing diabetic foot ulcers without signs of osteomyelitis.[50] There is no satisfactory explanation for the discrepancy between the results in these studies, thus the determining factor of success for FDG-PET in detecting osteomyelitis in patients with diabetic foot ulcers remains unclear.

Spondylitis and Spondylodiscitis

Three studies[4,18,32] specifically investigated the value of FDG-PET in patients with spondylitis and spondylodiscitis. Gratz et al[4] used a double-headed gamma camera operated in coincidence detection mode in 16 patients with suspected spondylitis (with 12 confirmed cases) and reported good performance with 12 true positives out of 12 patients with infection and 14 true negatives out of 16 patients without spondylodiscitis. The performance of FDG-coincidence imaging was superior to MRI, ^{67}Ga-citrate, and ^{99m}Tc-MDP, especially in patients with low-grade spondylitis.[4] Kalicke et al[18] showed that spondylitis was detected by FDG-PET in 100% of the patients (n = 7). Schmitz et al[32] reported a sensitivity of 100% and specificity of 75% in 16 patients with suspected spondylodiscitis. Figure 2 shows an example of a patient with biopsy proven *Brucella* spondylodiscitis on FDG-PET/CT. Guhlmann, et al. found good performance of FDG-PET for detection of infection in 28 patients with suspected central skeleton infections, with an accuracy of 96% (5 patients had proven spondylodiscitis). The study by de Winter et al[37] confirmed the performance of FDG-PET in 17 patients with suspected central skeleton infections, with a sensitivity of 100% and a specificity of 90%, resulting in 94% accuracy for central skeleton infections.

Diagnostic accuracy of FDG-PET was compared with performance of SPECT/CT with ^{67}Ga-citrate and MRI in spondylitis in 16 patients by Gratz et al[4] They reported a diagnostic accuracy of 96% for FDG-PET vs 80% for ^{67}Ga-citrate SPECT and 81% diagnostic accuracy for MRI.[4] Especially in infected bone regions with diminished vascularity, FDG-PET proved to be superior to anatomical imaging with MRI and ^{67}Ga-citrate SPECT or ^{99m}Tc-MDP SPECT.[4]

Orthopedic Implant Infections

In a group of 53 patients with hip prostheses, studied by Chacko et al[42] with 12 confirmed infections, FDG-PET correctly diagnosed 11 out of 12 infections. In 41 noninfected cases, FDG-PET was correct in all cases except one.[42] For patients with knee prostheses the same sensitivity was found, but in only 18 cases out of 24 an infection could be correctly excluded, indicating lower specificity for FDG-PET to exclude infection in knee prostheses, compared with hip prostheses.[42] According to Mumme et al,[46] diagnostic performance of FDG-PET is adequate for differentiation between septic and aseptic hip arthroplasty with 91% sensitivity, 92% specificity, resulting in 91% accuracy in 50 patients. It is superior to three-phase bone scintigraphy with ^{99m}Tc-HDP, with a 78% sensitivity, a 70% specificity, and a 74% accuracy.[46] Of critical importance is their conclusion that calculation of SUV is unsuitable as a sole criterion for image interpretation. FDG-PET results in high focal uptake in patients with polyethylene and metal wear-induced chronic inflammation followed by periprosthetic osteolysis,[46] lowering specificity for detection of infection of metallic implants.

Stumpe et al[45] showed that FDG-PET was significantly more specific ($P = .035$), but less sensitive ($P = .016$) than conventional radiography for the diagnosis of infected total hip prostheses. In a study population of 21 patients with suspected infected total hip implants, sensitivity of FDG-PET was below 30% with approximately 80% specificity, where three-phase bone scintigraphy with ^{99m}Tc-MDP resulted in a sensitivity of approximately 50% with a 90% specificity for detecting infected hip implants.[45] Two years later, the same group[52] concluded that for painful knee arthroplasty, diffuse synovial and focal extrasynovial FDG uptake is commonly found in patients with malrotation of the femoral component and is not related to pain location. The information provided by FDG-PET does not contribute to diagnosis and management of individual patients with persistent pain after total knee replacement. The overall performance of FDG-PET in total knee replacement was worse than in total hip replacement.[52] Sensitivity and specificity for FDG-PET in patients with orthopedic implants infections are summarized in Figure 3.

In the study by Delank et al[48] no false negatives were seen with FDG-PET in 5 patients with proven infected joint prostheses. In patients with inflammation due to periprosthetic aseptic foreign-body reactions (ie, polyethylene abrasion), 9 out of 20 scans were false positive for infection.[48] In patients with not much abrasion, 2 out of 11 patients were false-positive for infection.[48] This illustrates 1 cause for the limited specificity in detection of infected joint prostheses with FDG-PET. Van Acker et al[26] concluded that FDG-PET is highly sensitive for detection of metallic implant infection with insufficient specificity (73%-80%). However, when only

Table 3 Studies Regarding ^{18}F-FDG imaging

	Author	Bone* (n)	Pathology	PET-Tracer†	Gold Standard	Study Design and Level of Evidence‡
^{18}F-FDG with hybrid PET using coincidence camera	Gratz et al (2002)[4]	16 (12)	Suspected spondylitis	FDG	Surgery, histopathology, and fine needle biopsy	Prospective cohort design, 2b
	Meller et al (2002)[34]	30 (7)	Suspected chronic osteomyelitis	FDG	Histology, culture	Prospective cohort design, 2b
	Love et al (2004)[33]	49 (25)	Suspected infection of knee and hip prostheses	FDG	Microbiology	Retrospective case control design, 3b
	Hakim et al (2006)[20]	42 (32)	Chronic osteomyelitis of the mandible	FDG	Histology and radiographs, clinical and laboratory parameters	Prospective cohort design, 2b
	Rini et al (2006)[15]	47 (12)	Skeletal infection, including prosthesis	FDG-labeled human autologous leukocytes	Histopathology, microbiology, surgery, or clinical follow-up	Prospective cohort design, 2b
^{18}F-FDG-PET with full ring PET-scanner (no CT)	Guhlmann et al (1988) rad[35]	31 (18)	Suspected chronic osteomyelitis	FDG (no CT) Att. Corr. +	Culture of surgical specimens, histopathology	Prospective cohort design, 2b
	Guhlmann et al (1988) JNM[36]	51 (28)	Suspected chronic osteomyelitis	FDG (no CT) Att. Corr. +	Culture of surgery, histopathology, and clinical follow-up >2 yr	Prospective cohort design, 2b
	De Winter et al (2001)[37]	60 (25)	Suspected chronic musculoskeletal infection	FDG (no CT) Att. Corr?	Histopathology, culture, clinical follow-up >6 mo	Prospective cohort design, 2b
	Zhuang et al (2000)[16]	22 (6)	Chronic osteomyelitis	FDG (no CT) Att. Corr. + and Att. Corr. −	Surgery, clinical follow-up >1 yr	Retrospective case control design, 3b
	Kalicke et al (2000)[18]	15 (15)	Suspected acute or chronic osteomyelitis or inflammatory spondylitis	FDG (no CT) Att. Corr. +	Histopathology	Prospective cohort design, 2b
	Schmitz et al (2001)[32]	16 (12)	Spondylodiscitis	FDG (no CT) Att. Corr. +	Histopathology	Prospective cohort design, 2b
	Van Acker et al (2001)[26]	21 (6)	Suspected total knee arthroplasty	FDG (no CT) Att. Corr. + and Att. Corr. −	Operative findings and culture, clinical outcome	Prospective cohort design, 2b
	Zhuang et al (2001)[38]	62 (11)	Infected hip arthroplasty	FDG (no CT) Att. Corr. + and Att. Corr. −	Surgery, clinical follow-up >1 yr	Prospective cohort design, 2b
	Chacko et al (2002)[39]	32 (12)	Suspected hip arthroplasty infection	FDG (no CT) Att. Corr ?	Microbiology, histopathology, surgical findings, and clinical follow-up >9 mo	Retrospective case control design, 3b
	Manthey et al (2002)[40]	23 (4)	Suspected infection or loosening of prosthesis	FDG (no CT) Att. Corr. −	Operative findings or clinical outcome	Retrospective case control design, 3b
	Zhuang et al (2002)[41]	27 (27)	Infected hip arthroplasty	FDG (no CT) Att. Corr. + and Att. Corr. −	NA	Partially prospective and retrospective case control design, 3b
	Chacko et al (2003)[42]	56 (34) 104 (28)	Chronic osteomyelitis Orthopedic implants	FDG (no CT) Att. Corr. +	Surgical pathology, clinical follow-up >6 mo	Retrospective case control design, 3b
	Schiesser et al (2003)[43]	29 (14)	Suspected metallic implant−associated infections after trauma	FDG (no CT)§ Att. Corr. + and Att. Corr. −	Microbiology of surgical specimens and intraoperative findings	Prospective cohort design, 2b
	Vanquickenborne et al (2003)[27]	17 (8)	Suspected infected hip prostheses	FDG (no CT)	Culture or clinical follow-up for up to 6 mo	Prospective cohort design, 2b
	Sahlmann et al (2004)[44]	17 (17)	Histology proven osteomyelitis	FDG (no CT) Att. Corr. +	Histology	Prospective cohort design, 2b
	Stumpe et al (2004)[45]	21 (9)	Suspected infection related loosening of prosthesis	FDG (no CT) Att. Corr. + and Att. Corr. −	Microbiology of surgical specimens, joint aspiration + clinical follow-up >6 mo	Prospective cohort design, 2b
	Mumme et al (2005)[46]	50 (42)	Suspected infection or loosening of prosthesis	FDG (no CT) Att. Corr. +	Operative findings, microbiology and histology, clinical follow up >9 mo	Prospective cohort design, 2b
	Pill et al (2006)[47]	92 (21)	Suspected infected hip prostheses	FDG (no CT) Att. Corr. +	Intraoperative histology and cultures	Prospective cohort design, 2b

Table 3 Continued

	Delank et al (2006)[48]	27 (5)	Septic joint arthroplasty infection	FDG (no CT) Att. Corr. +	Surgery, histopathology, cultures	Prospective cohort design, 2b
	Basu et al (2007)[49]	6 (6)	Proven osteomyelitis secondary to complicated diabetic foot	FDG (no CT) Att. Corr. + and Att. Corr. –	Histopathology and clinical follow-up	Retrospective case control design, 3b
	Schwegler et al (2008)[50]	20 (7)	Suspected osteomyelitis in diabetic foot ulcers	FDG (no CT)	Biopsy	Prospective cohort design, 2b
^{18}F-FDG-PET/CT	Keidar et al (2005)[51]	10 (4)	Suspected osteomyelitis in diabetic feet	FDG-PET/CT	Histopathology, culture of surgical sample, biopsy, and clinical and imaging follow-up	Prospective cohort design, 2b
	Stumpe et al (2006)[52]	28 (9)	Suspected knee arthroplasty infection	18 FDG-PET/CT 10 FDG (no CT)	Microbiology of surgical specimens, clinical follow-up >6 mo	Prospective cohort design, 2b
	Hartmann et al (2007)[53]	33 (18)	Suspected osteomyelitis after trauma	FDG-PET/CT	Histopathology or bacteriologic culture	Retrospective case control design, 3b

*Number of patients with suspected osteomyelitis or joint prosthesis infection, with number of proven infection in parentheses.
†Level of evidence of the study (Oxford Centre for evidence-based medicine levels of evidence).
‡Att. Corr. = Attenuation correction.
§Two patients were scanned with FDG-PET/CT.

lesions also seen on bone scan were taken into account, specificity increased to 93% without loss of sensitivity. Combined reading of these 2 studies could therefore be advantageous in patients with suspected infection of hip and knee prostheses. In Figure 4, an FDG-PET scan of a patient with extensive infection of a megaprosthesis of the left knee is shown.

Rini et al[18] reported 3 true positives in 3 patients with proven orthopedic implant infection with 14 true negatives in 14 patients without orthopedic implant infection using PET with[18] FDG-labeled human autologous leukocytes.[18] Performance of this radiopharmaceutical needs further investigation to determine its value in patients with suspected infected orthopedic implants.

Criteria to Conclude Infection on FDG-PET in Case of Metallic Implants

It is known that the mere presence of metallic implants can result in increased focal uptake of FDG, not necessarily indicating infection or clinically relevant inflammation.[33,39,41,46,54] This phenomenon of false-positive FDG-uptake in patients with metallic implants might be explained by high glucose metabolism in the joint capsule and around the prosthesis neck, caused by inflammation because of granulomatous foreign body reaction against polyethylene debris particles.[55] Because of this lack of specificity, in 4 studies[33,38,39,41] the criteria to conclude infection on FDG-PET for hip and knee prostheses were specifically investigated. Love et al[33] investigated criteria in both knee and hip prostheses. Not surprisingly, when considering any periprosthetic FDG activity, regardless of location or intensity as positive for infection, this resulted in a sensitivity of 100% with a poor specificity of 9% (accuracy 47%). None of their constructed criteria (including solitary bone–prosthesis interface activity) led to satisfactory results, and they concluded that FDG-PET cannot replace conventional radiolabeled leukocyte/marrow imaging for diagnosing infection of failed prosthetic joints.[33]

Chacko and coworkers[44] confirmed that specificity is poor when using increased FDG-uptake as the sole criterion for diagnosing infection for hip prostheses, even when using a SUV_{max} threshold of 7. Therefore, they evaluated 2 criteria for the assessment of hip prostheses. Their first criterion in which only uptake at the bone—prosthesis interface was considered positive for infection, resulted in good performance with sensitivity of 92% and specificity of 97% in 41 prostheses, of which 12 were proven to be infected. Their second criterion defined that periprosthetic infection was diagnosed if there was any increased FDG uptake (mild, moderate, or severe) adjacent to the prosthesis (regardless whether it was localized at the bone or prosthesis interface, the tip of the femoral component or in the soft tissues surrounding the prosthesis). This second constructed criterion lead to excellent sensitivity (100%), but poor specificity (45%).[39]

Zhuang et al[38] also formulated criteria for hip arthroplasties, in which FDG uptake around the femoral head and neck and around the tip of the prostheses were considered as nonspecific. They hypothesized that the interface between bone

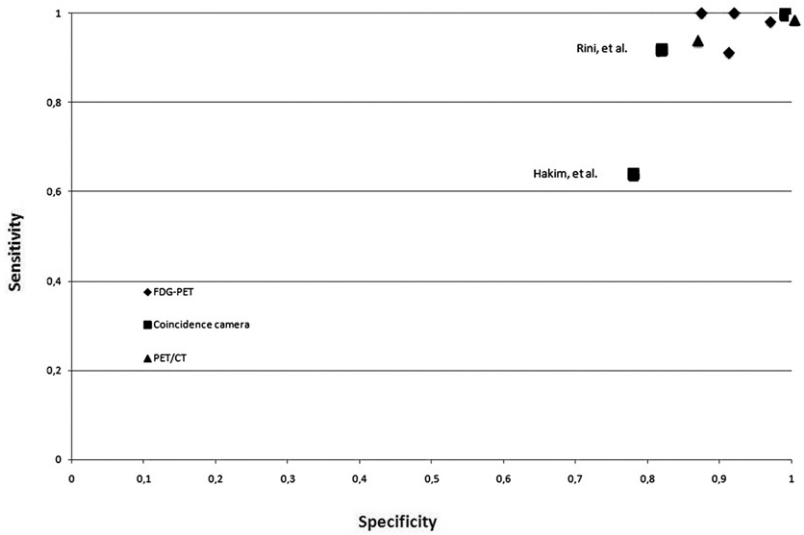

Figure 1 Test characteristics of FDG-PET for osteomyelitis in terms of sensitivity and specificity.

and prosthesis does not display high FDG-uptake in asymptomatic patients or in those with aseptic loosening and FDG-positivity in that area was therefore highly suggestive of infection.[41] Furthermore, Zhuang et al[56] demonstrated that FDG uptake normalizes within 3 months unless the process is complicated by infection or malignancy. This phenomenon of false-positive FDG-uptake in patients with metallic implants might be explained by high glucose metabolism in the joint capsule and around the prosthesis neck, caused by inflammation due to granulomatous foreign body reaction against polyethylene debris particles.[55]

The best criterion to conclude infection in patients with suspected orthopedic implant infection on a FDG-PET scan altogether seems to be considering uptake at the bone—prosthesis interface (with exclusion of the head and the tip) as positive for infection.[38,41,55] It is still a matter of debate whether satisfactory diagnostic accuracy for diagnosing infection can be obtained with FDG-PET in patients with metallic implants. Therefore, this last criterion and other suggested criteria need further validation, to assess its value in daily clinical practice.

Current Status and Future Perspectives in Pet Imaging of Bone and Joint Infections

Differentiation between osteomyelitis and infection of the adjacent soft tissues may be better obtained with FDG-PET than with CT or MRI, because of better lesion-to-background contrast and because of prominent artifacts arising from metallic implants in CT and MRI.[57] Strobel et al[58] observed that combined PET/CT was significantly more accurate (86%) in the differentiation of benign and malignant lesions than PET alone with an accuracy of 68% ($P = .039$). There might be a role for FDG-PET in differentiation of uneventful bone heal-

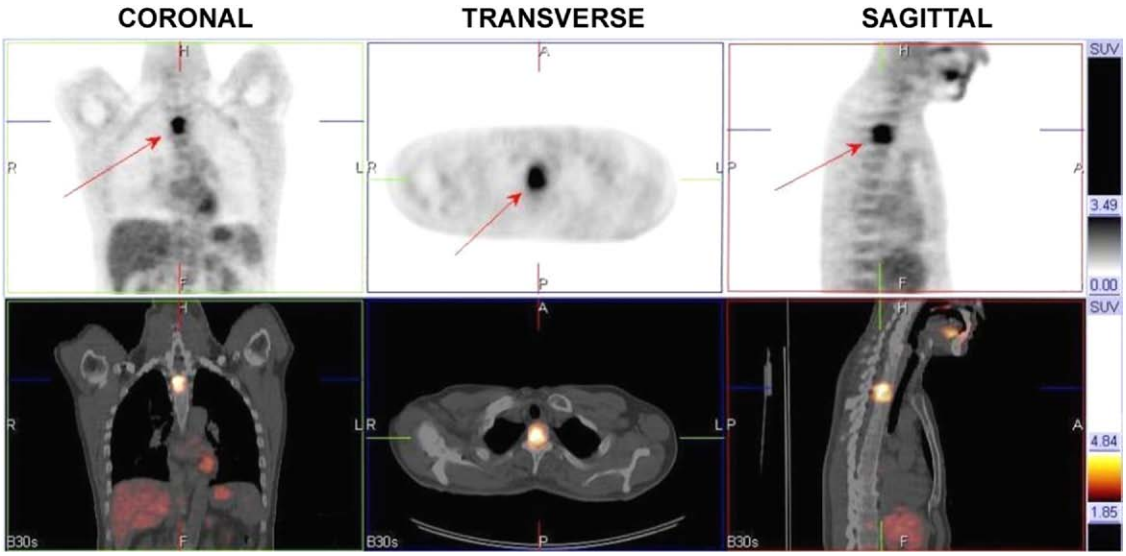

Figure 2 Patient with biopsy proven *Brucella* spondylodiscitis of the thoracic spine (Th2-Th3).

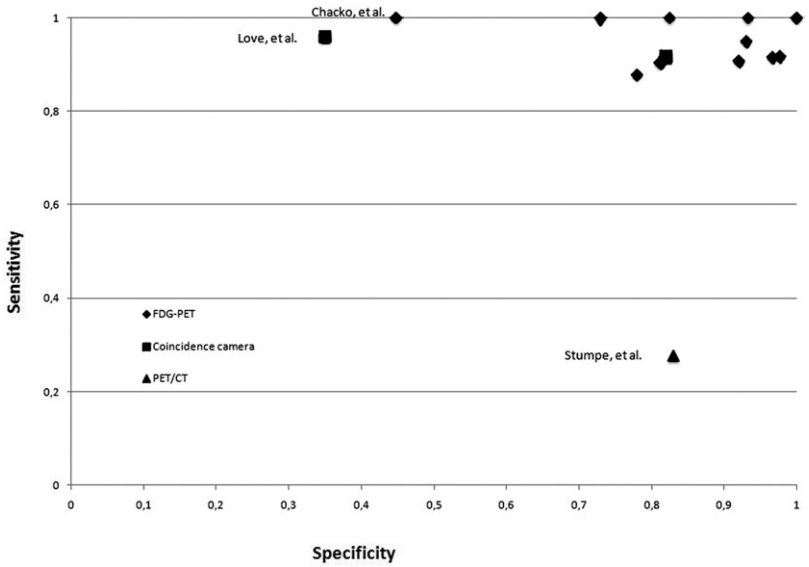

Figure 3 Test characteristics of FDG-PET for suspected orthopedic implant infections in terms of sensitivity and specificity.

ing from bone healing complicated by localized osteomyelitis, as was demonstrated in preclinical research by Koort et al[59] and later confirmed in patients by Zhuang et al.[41]

Discussion and Conclusions

Because of considerable heterogeneity in inclusion criteria, methodology and outcome measures, meaningful calculation of pooled sensitivity and specificity for detection of infection with SPECT and PET in patients with osteomyelitis and prosthetic bone and joint infections is not possible.

When relying on conventional scintigraphy, best results for detecting osteomyelitis were observed when using combined ^{111}In-WBC and ^{99m}Tc-MDP SPECT with SPECT/CT with sensitivity in the range of 84%-97% and specificity 98%-100%.[24,25] ^{99m}Tc-labeled antigranulocyte antibodies (^{99m}Tc-anti-NCA-95 IgG) also showed excellent sensitivity for detection of relapsing posttraumatic osteomyelitis (100%) with good specificity (89%) using hybrid SPECT/CT, with 100% interobserver agreement.[10] The detection of (chronic) osteomyelitis with FDG-PET is feasible and adequate, with high sensitivity and specificity.[16,19,34-36,53] Several studies concerning FDG-PET imaging in diabetic patients with osteomyelitis provide conflicting results. These differences can be explained by small numbers of included patients and heterogeneity in inclusion criteria.

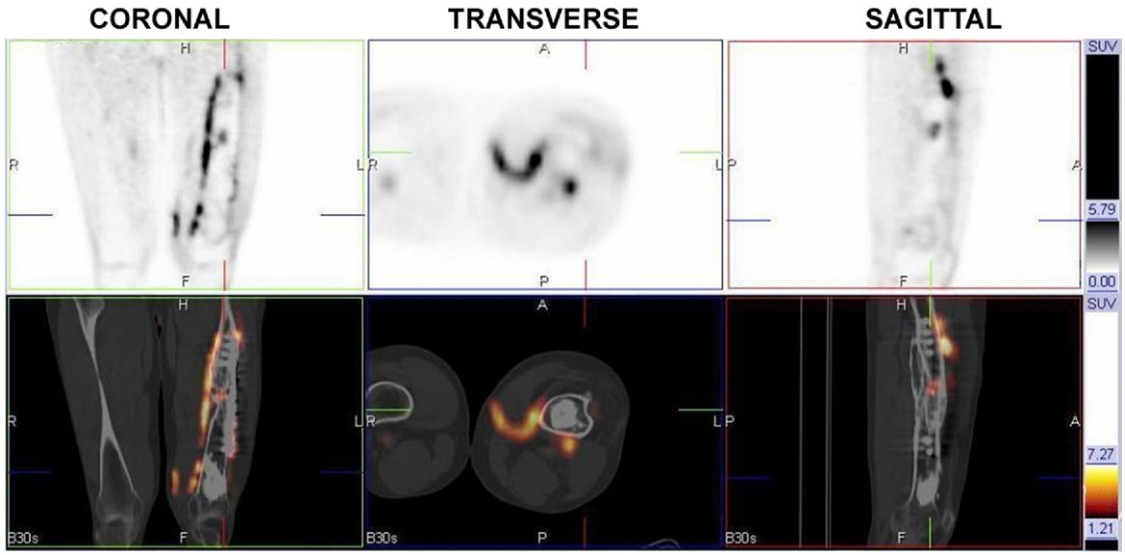

Figure 4 Patient with an extensively infected mega prosthesis of the knee and osteomyelitis (cultures confirmed *Citrobacter freundii* infection with pathology results showing active infection and necrosis). Note the fistula on the medial side of the left knee.

Spondylitis and spondylodiscitis are well diagnosed with FDG-PET.[4,18,32]

Combined ^{111}In-WBC and ^{99m}Tc-sulfur colloid SPECT/CT are adequate tools to diagnose (prosthetic) bone and joint infections. With a sensitivity of 100%, specificity of 91% and accuracy of 95%, it seems to be significantly better than FDG-PET.[33] ^{99m}Tc-WBC is a very sensitive tool (>95%) for imaging of infection in patients with metallic implants. Specificity is also high (93%-100%) in ^{99m}Tc-WBC SPECT/CT,[26,28] but it seems dramatically lower (53%) in case of ^{99m}Tc-WBC SPECT alone.[26] The improvement of specificity by addition of CT to SPECT is of substantial importance, as has been shown in multiple studies.[10,15,21,26,29,31] For patients with metallic implants, FDG-PET has a good sensitivity (91%-100%) for diagnosis of infection.[26,27,38,39,43,46,47] Specificity of FDG-PET in patients with metallic implants, however, is strongly dependent on the used criteria to report infection based on both localization and intensity of FDG-uptake, ranging from 9% to 97%.[33,38,39,41] Specificity is generally higher in hip prostheses, compared with knee prostheses.[42] An adequate criterion seems to be to consider uptake at the bone—prosthesis interface (with exclusion of the head and the tip) as positive for infection, with 92% sensitivity and 97% specificity.[41] This criterion remains to be validated in a prospective study design as another study failed to reproduce this observation.[33]

For both SPECT and PET, specificity improves considerably when the scintigraphic images are fused with CT.[10,15,21,26-28,31,58] For SPECT, this holds true for combining ^{111}In-WBC or ^{99m}Tc-WBC with ^{99m}Tc-MDP or ^{99m}Tc-sulfur colloid.[26,30] Adding CT also enhances interobserver agreement.[31]

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