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Hybrid imaging systems in the diagnosis of osteomyelitis and prosthetic joint infection

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Early diagnosis of osteomyelitis and prosthetic bone infection is essential for successful therapy and prevention of complications. Nuclear medicine offers a variety of modalities for this aim, including both single photon emission tomography (SPET) and positron emission tomography (PET) radiopharmaceuticals. The main limitation of these functional images is the fact that they are lacking the structural delineation of the pathologic processes; this important drawback can sometimes render interpretation difficult and diminish the diagnostic capability. The recent availability of hybrid SPET/computed tomography (CT) and PET/CT devices that acquire both functional and anatomical data can solve these problems. In fact, the combination of SPET or PET with CT provides exact anatomical registration with bone and joint lesions and improves the accuracy of the nuclear medicine images. This article reviews the currently available literature and addresses the use of hybrid systems in the diagnosis of osteomyelitis and prosthetic bone infection. The first reports indicate that hybrid imaging is very useful in these indications, because it is able to provide further information of clinical value in several cases. The advantage of accurately localizing the areas of increased radiotracer uptake allows a precise differentiation between soft tissue and bone infection, that is crucial for the choice of therapy and patients' management. However, data are still very limited and further studies are needed to verify if hybrid imaging may really become clinically relevant in the near future for early diagnosis of osteomyelitis and prosthetic bone infection.

Key words: **Infections - Osteomyelitis - Joint prostheses.**

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Nuclear medicine techniques play an important role in evaluating infection and inflammation, particularly in the musculoskeletal system, using both single photon emission tomography (SPET) and positron emission tomography (PET) radiopharmaceuticals.[1, 2] It is well known that nuclear medicine images demonstrate function, rather than anatomy: they are very useful in diagnosing various disorders, because they are able to demonstrate disease before anatomical changes and clinical manifestations.[3] However, although gross anatomic detail can be inferred from nuclear medicine imaging, the information of fine anatomic details can ameliorate diagnostic accuracy and can aid in the decision making process by facilitating the discrimination of physiologic from pathologic radiotracer uptake, and by enabling better localization and definition of lesions and organs.[4, 5] Due to the increasing use of medical images in healthcare, it is common that patients suffering from infection and inflammation are imaged several times, with the same modality or with different modalities. Therefore, due to the great number of imaging studies performed, it is essential to correlate one image to another to help the observer in obtaining the pertinent information. Traditionally, images from several modalities are compared side-by-side and mentally integrated by the physician to draw clinical con-

clusions, but this process is often difficult and requires mental compensation for changes in subject position.[6] Computer-aided techniques can be very helpful for this aim, especially imaging registration which aligns the images in a manner that corresponding features can easily be related, making more exact comparison possible.[7, 8] The process of image registration and fusion has been extremely facilitated and improved by the recent development of hybrid systems (SPET/computed tomography [CT] and PET/CT devices), capable of performing functional and morphological images by exploiting the features of both techniques without moving the patient from the acquisition bed.[9, 10] As will be discussed further, these systems, able to integrate functional and anatomic information, add significantly to diagnostic confidence.

The following review deals with the applications of hybrid SPET/CT and PET/CT devices in patients with osteomyelitis and in patients with orthopedic joint prostheses.

Hybrid devices

The hybrid imaging systems are able to acquire functional and structural data in the same scanning session, and, therefore, to limit the problems often observed with software approaches for image registration and fusion.[9] The SPET/CT and PET/CT devices now commercially available provide structural data from the CT scan that can be used for attenuation and scatter correction of the emission data, for facilitating anatomical localization of radiopharmaceutical uptake and, of course, for fusion.[11] The fusion with anatomical images is not only a valuable adjunct for the interpretation of functional data, but offers the possibility to overcome some intrinsic limitations of nuclear medicine images, like poor spatial resolution, limited signal to noise ratio, and often poor tracer uptake in the diseased condition.[10] Fusion is of the utmost importance in accurately localizing radiopharmaceuticals' accumulations, in detecting occult pathological sites, in characterizing the functionally active area of a known lesion, in precisely drawing regions of interest to perform quantitative studies.[12]

The first commercial SPET/CT system was developed in 1999: it combines a dual-head, variable angle γ camera with a low-dose X-ray tube, that is attached to the same rotating gantry to which the γ camera heads are mounted.[13] This device is able to provide, together with SPET data, cross-sectional X-ray transmission images. SPET is acquired according to the radiopharmaceutical used and the type of clinical study performed.[14] For transmission data, the X-ray tube and the linear detector array rotate together around the patient in a fixed geometry at 2.6 revolutions per minute, with a single slice being imaged in 14 s. Multiple transmission slices are obtained by moving the table by a slice step before acquiring the next slice; the full field of view consists of 40 slices with the slice thickness fixed at 1 cm. At the completion of the first type of acquisition (transmission or emission), the patient is automatically repositioned so that the 40-cm axial field that was just scanned matches the 40-cm axial field of view of the second imaging modality. X-ray images are reconstructed in the nuclear medicine workstation, and transmission data are integrated in the nuclear medicine database. The alignment of slices is automatically performed; then matching pairs of X-ray and scintigraphic images are fused generating new images overlying SPET and CT data.[15]

Now, a new version of this system has been introduced: it uses the same gantry as the original one, but it acquires 4×5 mm thick slices with each rotation, instead of one 1-cm slice, and the CT scan time is 5 min for a 40 cm field of view. It delivers a low radiation dose to the patient and requires minimal room shielding; the design has the same very compact configuration as the first device.[16]

SPET/CT devices with high-power CT capabilities were introduced in 2004: they typically match a dual-head SPET system with a multi-slice CT scanner having performance similar to conventional diagnostic CT. The multi-slice capability (2- to 16-slice) of these higher-power CT subsystems offers detailed anatomical information with improved spatial resolution and fast scan speed sufficient for performing studies with intravenous iodine contrast enhancement. In fact, with these systems, CT slice thickness is variable and can be adjusted from 0.6 mm up to 10 mm, and the scan speed for a 40-cm axial field of view is <30 s. However, because of the addition of a separate CT gantry, these hybrid devices are rather larger than conventional SPET systems and so they need very different siting and shielding requirements when compared to the first developed SPET/CT apparatus.[17]

PET/CT scanners incorporating clinical CT and clinical PET performance became commercially available in 2001. Different types of dedicated PET/CT systems are now on the market: they incorporate top perfor-

mance PET components combined with diagnostic multi-slice CT up to 64 slices. A complete review on this topic has been recently published.[18]

SPET/CT

Radiopharmaceuticals for the detection and localization of infectious and inflammatory processes have been introduced since the 1950s.[19, 20] The SPET radiopharmaceuticals used to diagnose bone infection can be divided into infection/inflammation-seeking agents (^{67}Ga, radiolabelled leucocytes and radiolabelled anti-granulocyte antibodies are the most common today) and other agents that reflect metabolic changes associated with infection/inflammation, like radiolabelled diphosphonates for bone scan.[4]

The first paper on the value of hybrid imaging with a SPET/CT system in patients with bone infections was published by Horger *et al.* in 2003.[21] They evaluated 27 patients with 29 sites of suspected post-traumatic osteomyelitis by means of immunoscintigraphy with ^{99m}Tc-labelled anti-granulocyte antibodies. Planar scans were acquired immediately, 4 h and 24 h after injection, with SPET/CT performed subsequently. Accumulation of antibodies in inflammatory lesions was quantified, comparing the uptakes at 4 and 24 h after injection. The final diagnosis was based on culture data derived from surgical or biopsy samples (20 lesions) or clinical follow-up without further therapy (9 lesions). Nine suspected lesions were negative for infection. The accuracy for immunoscintigraphy for correct diagnosis of different types of disease was 58.6% (17/29), whereas the accuracy for SPET/CT was 96.4% (28/29). The only incorrect finding of hybrid imaging was a false positive result in a patient with acute inflammation due to rheumatic arthritis; the false positive results of conventional immunoscintigraphy were found in the same patient and in an artifact due to accidental skin contamination. In all of the 20 infected lesions, SPET/CT provided a correct diagnosis: 4 soft tissue infections with active bone infections requiring surgery, one low-grade osteomyelitis, 4 soft tissue infections without bone involvement, 4 soft tissue infections with cortical reaction, 5 joint empyemas, one septic prosthetic loosening, and one multilevel spondylodiscitis. Using 50% isocontours, hybrid imaging was able to obtain exact delineation of infectious foci in all patients, whereas conventional immunoscintigraphy yielded a correct result in only 12 out of 20 lesions (60%).

In particular, soft tissue infection without bone involvement was hard to diagnose by immunoscintigraphy alone, that falsely diagnosed osteomyelitis in 5 out of 8 lesions (62.5%).

The results of this study demonstrate that hybrid SPET/CT imaging improves the accuracy of anti-granulocyte immunoscintigraphy in diagnosing chronic post-traumatic osteomyelitis and/or accompanying joint and soft tissue infection, allowing accurate localization of infectious foci, in particular the correct differentiation between soft tissue infection and bone involvement of the appendicular skeleton. Moreover, because the management of these two clinical situations is different, SPET/CT may gain relevance in selecting patients for surgical therapy.

The same group have subsequently evaluated the added value of SPET/CT as an adjunct to combined three-phase bone scan (with planar and SPET acquisitions after [^{99m}Tc]DPD injection) for the diagnosis and localization of bone infection.[22] This prospective study included 31 consecutive patients with the clinical suspicion of acute or chronic osteomyelitis. Scintigraphic images were interpreted with regard to the presence of hyperperfusion and increased bone uptake in suspected sites of infection (extremities: N.=13; spine: N.=7; skull: N.=6; pelvis: N.=5), and classified as positive, negative, or equivocal for the presence of osteomyelitis; then they were compared to SPET/CT findings. Final diagnosis was based on surgery or biopsy in 15 patients, and derived from clinical, radiological or microbiological follow-up in 16 cases: osteomyelitis was diagnosed in 9 patients, whereas bone infection was excluded in the remaining 22 cases. Bone scintigraphy correctly classified 7 lesions as positive and 11 ones as negative for osteomyelitis, 6 scans were falsely positive, 2 falsely negative and 5 were classified as equivocal. Rating the latter as positive for bone infection, sensitivity of bone scan was 77.8%, and specificity 50%. SPET/CT resulted true positive in 7 patients, and true negative in 19: sensitivity was the same (77.8%) as for bone scintigraphy (planar and SPET), but specificity was significantly higher (86.4%). It is worth noting that hybrid imaging correctly classified 4 out of 5 lesions (80%), which were equivocal in bone scintigraphy, and allowed an easier definition of anatomical localization of inflammatory foci due to better depiction of underlying structural details. Moreover, SPET/CT data gave an added value with respect to conventional bone scan in 15 out of 31 patients (48.4%), not only

by furnishing a correct diagnosis due to anatomical correlation, but also providing a precise localization for preoperative planning or a correct extension of inflammation in true positive studies. The results of this study clearly indicate that SPET/CT improves the diagnostic performance of three-phase bone scintigraphy with radiolabelled diphosphonates for osteomyelitis, in particular by reducing false positive or equivocal findings.

The role of SPET/CT as an adjunct to ^{67}Ga or ^{111}In-labelled white blood cells (WBC) scintigraphy for diagnosis or localization of infection has been assessed by Bar-Shalom *et al.*[23] in a series of 82 patients with known or suspected infectious processes, who underwent 88 SPET/CT examinations. Thirty-two of these patients were evaluated for suspected osteomyelitis (21 by ^{67}Ga and 11 by ^{111}In WBC). Additional information obtained by hybrid imaging for diagnosis or localization of infection, as compared with planar scan and SPET, was assessed; moreover, the contribution of SPET/CT was recorded both on a patient and site basis. For the patient-based analysis, hybrid imaging was considered contributory if it provided incremental data for at least one suggestive site; for the site-based analysis, SPET/CT was considered contributory when it provided data that could not be obtained from planar and SPET images concerning the presence of infection or its precise location. Final diagnosis was obtained by culture or surgery, and by correlative imaging data or clinical follow-up: 12 patients had osteomyelitis. Overall, SPET/CT provided more accurate data than did planar and SPET scintigraphies for the diagnosis and localization of bone infection in 16/32 patients (50%): in particular, in 10/21 (47.6%) studied by ^{67}Ga scan and in 6/11 (54.6%) submitted to ^{111}In WBC imaging. On site-based analysis, SPET/CT was more accurate than scintigraphy for the diagnosis and localization of osteomyelitis in 19 of 46 suggestive foci (41.3%): in 12 out of 31 (38.7%) with ^{67}Ga and in 7 out of 15 (46.7%) with ^{111}In WBC. In fact, conventional scintigraphy and SPET/CT results were discordant for the diagnosis and localization of bone infection in these 19 sites. In particular, in the 12 sites evaluated by ^{67}Ga scan, hybrid imaging enabled to exclude osteomyelitis in 6 cases, to correctly define the extent of osteomyelitis and soft tissue infection in 3, to localize the infection to bone in 2, and to exclude the infection in a hip prosthesis. In the 7 sites studied by ^{111}In WBC scan, SPET/CT contribution was the following: exclusion of osteomyelitis in 3, correct definition of extent of osteomyelitis and soft tissue infection in 2, diagnosis of osteomyelitis in 2 (one in a hip prosthesis). In this study, it is worth noting that SPET/CT contributed to better diagnosis of infection only in a few patients, whereas the main value of hybrid imaging, observed in a high percentage of cases, was related to the precise anatomic localization of an infectious process and to the delineation of its extent after its diagnosis on conventional ^{67}Ga or ^{111}In WBC scintigraphy. Therefore, SPET/CT could not be routinely performed on all patients referred for suspected bone infections: in the every-day nuclear medicine scenario, the decision to perform a hybrid imaging study should be directed by clinical or prior conventional imaging diagnostic dilemmas or by equivocal scintigraphic findings.

^{99m}Tc-HMPAO-labeled WBC scintigraphy has demonstrated highly accurate and clinically useful in the diagnosis and follow-up of patients with suspected osteomyelitis.[2]

However, in several cases, planar images alone may not be sufficiently accurate to precisely delineate the extent of disease; it has been reported that SPET is able to improve the sensitivity of planar images,[24] but SPET does not provide precise anatomic information.

Therefore, we have recently conducted a prospective study aimed to verify the usefulness of a hybrid SPET/CT camera in ^{99m}Tc-HMPAO WBC scintigraphy for imaging bone and joint infections.[25] A total of 28 consecutive patients were included and divided into 2 groups: 15 with suspected bone infection (group 1) and 13 with suspected orthopedic implant infection (group 2). Planar scans were acquired 30 min, 4 h, and 24 h after ^{99m}Tc WBC injection; SPET/CT was performed 6 h after radiotracer injection. In all patients, scintigraphic results were compared with the findings of surgery or cultures and of clinical follow-up. SPET/CT was considered contributory if it accurately localized the anatomic site of infection and, in particular, when it allowed the discrimination between bone and soft-tissue involvement. ^{99m}Tc-WBC scintigraphy was positive for infection in 18 of 28 patients (for a total 21 sites of uptake) and negative in 10 of 28 subjects. SPET/CT allowed an accurate anatomic localization of all positive foci of uptake; with regard to the final diagnosis, hybrid imaging gave a significant clinical contribution in 10 out of 28 patients (35.7%). In particular, in group 1 scintigraphy was positive for active infection in 10 of 15 patients, with a total of 12

sites of uptake, and true-negative in 5 patients. SPET/CT was able to precisely define the site of uptake, discriminating soft tissue from bone, excluding lower-limb osteomyelitis in 3 patients; in 5 subjects with structural bone alterations and focal tracer uptake on both planar and SPET images, SPET/CT precisely defined osteomyelitis; in 2 patients with bone infection, SPET/CT localized two additional soft tissue sites. In the group of 13 patients with suspected prosthesis joint infection (7 with a hip prosthesis and 6 with a knee prosthesis), scintigraphy was positive in 8 cases, with a total of 9 sites of infection, and negative in 5. SPET/CT provided an accurate discrimination between prosthesis and soft-tissue uptake in 5 patients with a hip prosthesis, excluding bone involvement in 2; in 2 patients with a knee implant, SPET/CT correctly localized leukocyte uptake in the synovium, thus excluding prosthesis involvement; in one patient with suspected hip prosthesis infection, hybrid imaging revealed leukocyte accumulation along the femoral stem of the prosthesis and another site of infection in the neighbouring soft tissue. Moreover, SPET/CT disclosed one area of tracer uptake in the abdomen due to an unknown intestinal inflammatory polyp, that was afterwards confirmed by biopsy during colonoscopy. In our series, the interpretation of conventional ^{99m}Tc WBC scintigraphy (planar and SPET) was radically changed by the acquisition of SPET/CT imaging in 5/15 patients (33.3%) of group 1 and in 5/13 patients (38.5%) of group 2; in particular, osteomyelitis was excluded in 7 patients and the extent of infection was more correctly delineated in 3 patients. Then, SPET/CT was found particularly useful for the diagnosis of relapsing osteomyelitis in patients with structural bone abnormalities after trauma, and able to improve specificity more than sensitivity of the scintigraphic studies, by providing accurate anatomic localization and precise definition of the extent of infection. Our findings in this study confirms that SPET/CT is very useful in patients with planar images positive for active infection but equivocal for localization (Figure 1); in fact, in such cases, a substantial diagnostic yield is reached with only a relatively low additional radiation burden (0.5 mSv) to the patients when using a low-dose CT subsystem.[26]

From a technical point of view, precise alignment of the body region of interest is of the utmost importance in hybrid imaging. Therefore, because involuntary movements particularly in the extremities can affect the precise anatomical localization of the foci of uptake, the whole procedure should be accurately explained to patients, and eventually patients' legs should be fixed when performing SPET/CT.

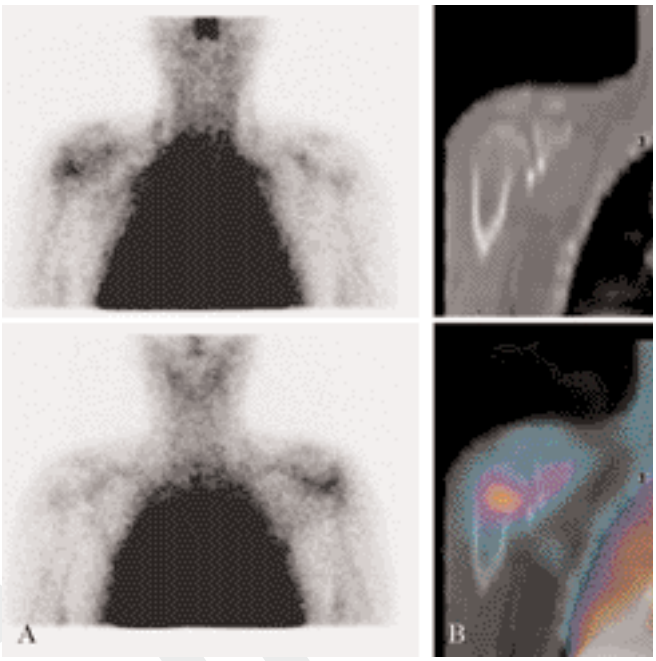

Figure 1.—^{99m}Tc-HMPAO-labeled WBC scintigraphy of a 45-year-old man in whom post-traumatic osteomyelitis of right scapulo-humeral bones was suspected. A) Twenty-four hours planar images (top: anterior view; bottom: posterior view) show diffusely increased tracer uptake in the right shoulder. B) SPET/CT (bottom, coronal view) accurately localizes this WBC uptake in the right caput humeri; the corresponding CT scan is on the top. WBC: white blood cells; SPET: single photon emission tomography; CT: computed tomography.

PET/CT

PET/CT imaging with F-18 fluorodeoxyglucose (FDG) is widely used for assessing a multitude of malignant tumours.[27] The degree of cellular FDG uptake is related to the cellular metabolic rate and the number of glucose transporters.[28] Increased FDG uptake in tumors is due, in part, to an increased number of glucose transporters in malignant cells;[29] however, FDG is not specific for malignancies: a similar situation exists in inflammation; activated inflammatory cells demonstrate increased expression of glucose transporters, and, in addition, in inflammatory processes, the affinity of glucose transporters for deoxyglucose is apparently increased by various cytokines and

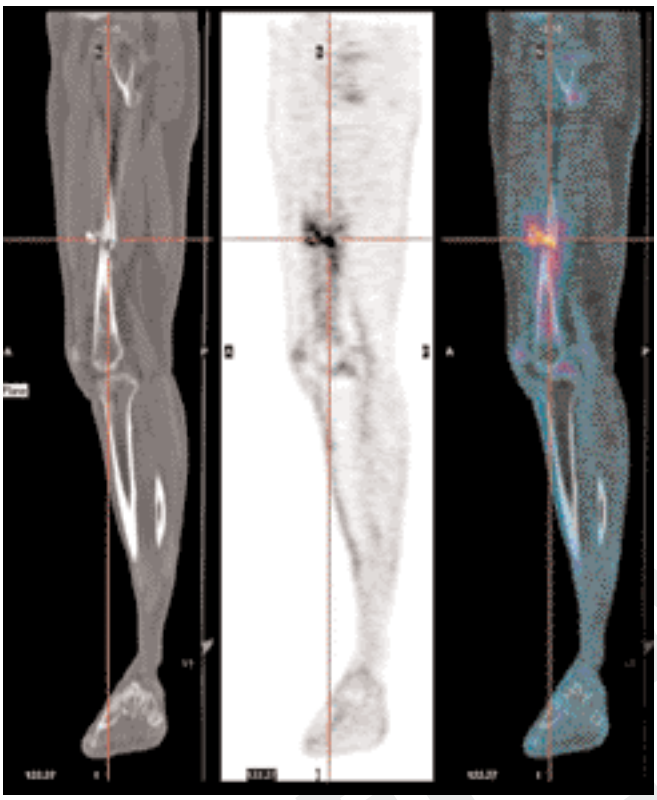

Figure 2.—FDG PET/CT of a 51-year-old man in whom post-traumatic osteomyelitis of left femur was suspected. Sagittal images: PET alone (center) shows increased FDG uptake in the mid left thigh, that PET/CT (right) precisely localizes in the femur and surrounding soft tissues; the corresponding CT scan is on the left. FDG: F-18 fluorodeoxyglucose; PET: positron emission tomography; CT: computed tomography.

growth factors.[30, 31] FDG uptake in infections is related to the granulocytes and mononuclear cells using large quantities of glucose by way of the hexose monophosphate shunt.[32] Moreover, FDG PET is able to furnish high resolution images in a short time, so it has emerged as a promising modality also for evaluating a variety of infectious and inflammatory conditions, including those of the bone.[33, 34] In particular, recent experimental data in an animal model suggest that FDG specifically accumulates in osteomyelitis rather than in the bone healing process.[35]

The diagnostic value of FDG PET/CT in trauma patients with suspected chronic osteomyelitis was evaluated in 33 patients (in 10 infection was suspected in the axial, and in 23 in appendicular skeleton, respectively) by Hartmann *et al.*[36] In 18 cases, PET/CT was performed in the presence of metallic implants. Final diagnosis was based on histopathology or bacteriological culture: 18 patients had chronic osteomyelitis and 15 had no osseous infection (7 soft tissue infection, 3 non-union fracture, one foreign body reaction against the metallic device and 4 without any infection). Sensitivity, specificity and accuracy of FDG PET/CT was 94.4%, 86.7% and 90.9% for the whole group, 88.9%, 100% and 88.9% for the axial skeleton and 100%, 85.7% and 91.7% for the appendicular skeleton, respectively. There was one false negative result in the axial skeleton in a patient with osseous infection of the mandible. There were two false positive findings in the appendicular skeleton: one in a foreign body reaction to the prosthetic device, the second one in a non-union fracture of the left distal femur. Moreover, surgeons retrospectively assessed the influence of FDG PET/CT on their treatment decisions and found that hybrid imaging influenced the clinical decision-making process in about 50% of patients. In particular, the addition of the CT scan to the PET examination furnished complementary information important to surgical planning, and enabled the surgeon to determine the precise extent of resection and so to anticipate the appropriate surgical approach. The findings of this retrospective study suggest that FDG PET/CT is accurate for the diagnosis of chronic osteomyelitis in trauma patients (Figure 2). Especially in the axial skeleton, FDG PET/CT appears as an important imaging technique, superior to other nuclear medicine modalities available in this specific clinical application. Moreover, it allows accurate differentiation between osteomyelitis and infection of the adjacent soft tissues because of the high lesion-to-background contrast and the less severe artefacts arising from metallic implants compared with CT.

In patients with diabetes mellitus, osteomyelitis occurs in about 20% of foot wounds and markedly increases the risk of amputation.[37] Therefore, early diagnosis of osteomyelitis in diabetic foot ulcers is very important because prompt antimicrobial treatment can be curative and it is able to decreases the amputation rate.[38] However, the detection of early osteomyelitis in the diabetic foot is often difficult because the clinical signs are absent in many cases.[39] The most accurate method of diagnosing osteomyelitis is histological or microbiological evaluation of a specimen obtained from bone, preferably before antibiotic therapy.[40]

The role of FDG PET/CT in the diagnosis of diabetic foot osteomyelitis has been prospectively evaluated in

14 patients by Keidar *et al.*[41] with suspected foot infection, based on the presence of necrotic ulcers, non-healing wounds, cellulitis, or severe foot pain. The 14 patients presented with 18 sites suggestive of infection, and they had undergone bone scintigraphy within a week before PET/CT. The final diagnosis of osteomyelitis, soft-tissue infection, or non-infected site was obtained by histopathologic findings and bacteriologic assays after surgery or by further imaging work-up or clinical follow-up. PET alone in 10 patients detected a total of 14 foci of increased FDG uptake that were considered positive for infection, but it could not precisely localize these sites to bone or soft tissue. In 4 patients PET/CT localized 8 bone foci, indicating a diagnosis of osteomyelitis; CT revealed bone changes consistent with osteomyelitis in 5 out of these 8 sites. PET/CT excluded osteomyelitis in 5 foci (5 patients) by precisely localizing the pathological FDG uptake in the soft tissues, whereas CT indicated bone changes of osteomyelitis only in 2 of these 5 sites.

Moreover, FDG PET/CT revealed that a focus of mild uptake was due to diabetic osteoarthropathy changes demonstrated on CT. Four patients showed no pathologic FDG uptake: on CT, one of these 4 patients had severe structural changes, so osteomyelitis could not be excluded. It is worth noting that bone scan resulted positive in all the cases of osteomyelitis, soft-tissue infection and osteoarthropathy, and in one of the 4 suspected sites that revealed no infection. These outcomes, although obtained in a limited series, suggest the potential value of FDG PET/CT in diabetic patients with suspected foot infections. In fact, hybrid imaging allowed an accurate differential diagnosis between osteomyelitis and soft-tissue infection, by means of the precise anatomic localization of abnormal radiopharmaceutical accumulation. Moreover, besides helping diagnosis, PET/CT can guide tissue-sampling procedures, and, therefore, improve treatment planning of patients with diabetes related foot infections.

Hyperglycemia (*i.e.* >200 mg/dL) was present in 7 patients at the time of FDG injection, including 2 patients with negative and 5 patients with positive PET findings, so elevated glucose serum levels did not lead to false-negative studies.[41] In this study, therefore, there was no relationship between the presence or absence of abnormal FDG uptake and the glycemic state, confirming previous data indicating that high glucose levels may not impair FDG uptake in infection.[42]

Differentiating infection from aseptic loosening, the most common cause of joint arthroplasty failure, is very important because the management of these two conditions is quite different.[43] A recent systematic review and meta-analysis, including 11 relevant studies and 635 prostheses, has reported for FDG PET a pooled sensitivity and specificity in detecting prosthetic hip or knee joint infection of 82.1% (range: 22-100%) and 86.6% (range: 61.5-100%), respectively.[44] Overall sensitivity of FDG PET in knee prostheses was higher than in hip prostheses (90.4% *versus* 82.6%), whereas overall specificity in hip prostheses was significantly higher than that in knee prostheses (89.8% *versus* 74.8%). The conclusion of this meta-analysis is that the overall diagnostic performance of FDG PET for diagnosing prosthetic joint infection is moderate to high, but caution is warranted because results of individual studies were heterogeneous and could not be fully explored.

It is worth noting that all evidence regarding the clinical capability of FDG PET in the management of patients with arthroplasty has been obtained with stand-alone PET scanners, which use a ^{137}Cs or ^{68}Ge source for attenuation correction; now hybrid PET/CT systems are replacing the stand-alone PET devices everywhere, but they may perform differently in this clinical application because they use CT-based attenuation correction. This is an important issue because attenuation correction induced artefacts can affect PET image interpretation in patients with arthroplasty.[5]

The influence of ^{68}Ge and CT-based transmission imaging on the introduction of artefacts in the final PET image in the presence of metallic prosthetic material has been studied by Goerres *et al.*,[45] who scanned hip prosthetic material and a steel rod in a water bath of FDG with PET and PET/CT devices to evaluate the generation of artefacts adjacent to the metal. Six prostheses were measured: 3 were made of titanium, and 3 were made of steel alloys. The findings of the experiments performed in this study clearly indicate that PET imaging of prosthetic material can generate artefacts, that manifest as artificial increases in activity adjacent to metal implants like hip prostheses. These artefacts are visible on images obtained with all types of PET scanners at the borders between normal tissue and prosthetic material, because of the inherent problem of partial volume mapping at the borders of metal and surrounding tissues.[45] Therefore, since artefacts are only generated when differences between high-den-

sity metal objects and surrounding tissues are present, both the prosthesis shape and the absorption properties of the surrounding tissues, are important. Moreover, the authors noted that movement of the prosthesis between emission and transmission scans leads to a clear increase in visibility of the artifact. This phenomenon is almost equally well evident with both ^{68}Ge and CT-based attenuation correction, but it is somewhat better visible with CT-based method, due to the better quality of the CT-based attenuation map.[11] Finally, when attenuation-weighted iterative reconstruction was used, the artefacts were less evident.

A recent phantom study suggests that high-density materials do not show false increased uptake without motion on PET/CT.[46] Therefore, although metallic implants such as arthroplasties can sometimes cause artefacts on CT, these are probably due more to patient movement between the PET and the CT acquisition than to the presence of prostheses themselves.[18] However, the non-attenuation corrected images are always available to solve the doubtful cases and to avoid false-positive results.[43]

The well-known avidity of FDG for metabolically active cells like inflammatory ones is the basis for the *ex vivo* labeling of leukocytes with this radiopharmaceutical.[47] Such an approach combines the properties of cell-bound radionuclide trafficking from the blood-pool compartment to the lesion with the high image quality of PET.

The feasibility of FDG labeling of autologous leukocytes was firstly reported by Osman *et al.* in 1992.[48] Then, in 2002, Forstrom *et al.*[49] reported biodistribution and dosimetry of FDG-WBC in 4 normal volunteers. More recently, the imaging properties of FDG and FDG-labelled leukocytes were compared in sterile and septic inflammation animal models.[50] Whole-body biodistribution demonstrated a significantly higher uptake ratio of FDG-WBC compared to FDG in all sterile and septic inflammation models. Moreover, a higher uptake of both radiotracers was reported in infected muscles in comparison to normal contralateral ones, and the average ratio FDG-WBC infected to non-infected muscle ratio were about twice as high as the corresponding FDG ratios. These data suggest that the increased accumulation of FDG-WBC at the site of inflammation is not simply due to accumulation of free FDG which might have been released from the radiolabeled leukocytes *in vivo* after their injection. Moreover, the better performance of FDG-WBC over FDG, due to sensitization and recruitment of radiolabelled cells by the chemo-attracting factors released into and around the inflammation areas, might have important clinical implications.

As a matter of fact, Dumarey *et al.*[51] have subsequently evaluated the feasibility and the potential role of PET/CT with FDG-labelled autologous WBC in 21 consecutive patients with suspected or documented infections. No adverse effects were observed after radiotracer injection. The results of FDG-WBC PET/CT were compared with histologic or bacterial diagnosis in 15 patients, in the other patients the final diagnosis was based on a review of all clinical, radiological, surgical, and biochemical data. Globally, 37 lesions were detected by FDG-WBC PET/CT: the minimum standardized uptake value (SUV) was 0.9 and the maximum SUV value was 37.4. Sensitivity, specificity and accuracy were each 85.7% on a patient-per-patient basis and 91.3%, 85.7%, and 89.5% on a lesion-per-lesion basis, respectively; furthermore, the absence of areas with increased WBC uptake on PET/CT scans had a 100% negative predictive value. In the group of patients in whom an infection involving bone structures was suspected, PET/CT correctly exclude osteomyelitis or septic joint in 8 of the 11 patients with clinical suspicion of osteomyelitis or septic joint and correctly diagnose osteomyelitis or septic joint in the other 3 cases; moreover, it enabled a precise mapping of infection extension in 3 diabetic foot patients. These findings demonstrate also for bone infection diagnosis the clinical feasibility of FDG-WBC PET/CT, which allows definitive results within 3 h of radiotracer injection. In this group of patients, it reached precise distinction of closely related lesions and discrimination between osseous and soft-tissue infection, that is of major clinical importance as treatment drastically differs when osteomyelitis is present, in particular for diabetic foot cases. Nevertheless, the potential clinical role of FDG-WBC PET/CT as a diagnostic modality in bone infection imaging deserves further investigation in larger series.

Conclusions

SPET and PET imaging with different radiopharmaceuticals is largely used for several years in patients with suspected osteomyelitis and prosthetic joint infections. The main drawback of these functional images is their lack of the structural delineation of the patho-

logic processes they detect, a fact that can render difficult interpretation. Although the more skilled nuclear medicine physicians might be able to reach a correct diagnosis of bone infection in several clinical situations, the recent availability of hybrid SPET/CT and PET/CT devices can significantly improve the diagnostic accuracy of nuclear medicine examinations, and help the less experienced observers, thus suggesting greater reliability for these imaging modalities. The first reports indicate that hybrid systems are very useful in imaging bone infections, because they are able to provide further information of clinical value in several cases. In particular, the main advantage of combined nuclear medicine and CT images is the capability of precisely localizing the areas of increased radiotracer uptake, and so to allow an accurate differentiation between soft tissue and bone infection. However, data are still very limited, especially for PET/CT in patients with arthroplasty, and further prospective studies are needed to fully verify the clinical role and the added value of SPET/CT and PET/CT in the diagnosis of osteomyelitis and prosthetic bone infections, and to compare in this group of patients the diagnostic performance of hybrid systems with that of conventional nuclear medicine studies and radiology modalities.

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