PET imaging in MSK infections

Glaudemans, Andor W.J.M.

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Andor WJM Glaudemans, Multimodality Imaging of Infections and Inflammatory Diseases, Medical Imaging Center, Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

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Introduction

Infections of the musculoskeletal system are common in clinical practice, highly feared and form a serious healthcare problem. The incidence is increasing due to an aging population, an increase in surgery with metallic implants (such as joint prostheses), a rising number of trauma leading to complicated fractures, and an increase in immunocompromised patients who are more vulnerable for infections. Furthermore, it often involves young people, leads to a huge impact on daily life since it requires a long-lasting treatment regimen with often multiple surgeries, has a high recurrent rate, may lead to limb amputation or—in case of infection dissemination and sepsis—can even be life threatening.

The diagnosis musculoskeletal infection is not always evident and often part of a differential diagnosis. In an acute phase, with clinical symptoms such as swelling, redness, visible metallic implant, fistula or pus, the diagnosis is clear and imaging is not necessary. However, often this is not the case, and especially in a chronic latent phase without clinical symptoms, settling the correct diagnosis can be very challenging and sometimes requires multiple diagnostic investigations. There is no single routine test available that can detect an infection with sufficiently high diagnostic accuracy. Mostly, a combination of clinical, laboratory, microbiological, and imaging tests is performed based on personal experience, available techniques, and expertise in the institute and financial aspects.

Diagnostic imaging techniques can be divided into radiological imaging techniques such as ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI), and nuclear medicine imaging techniques, such as the three phase bone scan with ^{99m}TC-labeled diphosphonates, white blood cell (WBC) scintigraphy with ^{99m}Tc-HMPAO or ^{111}In-labeled leukocytes, or ^{18}F-fluorodeoxyglose positron emission tomography (FDG-PET).

If we talk about musculoskeletal infections, we can divide this into (1) infections in the peripheral bone, (2) infections in the spine, including spondylodiscitis, (3) infections after placement of a joint prosthesis, (4) infections in the diabetic foot, and (5) infections in the sternal bone or surroundings. This chapter provides an overview of the use of FDG-PET in the above mentioned musculoskeletal infections.

FDG-PET/CT imaging

FDG-PET imaging is one of the most used imaging techniques in oncological diseases. The use of FDG-PET in infectious diseases increased significantly during the last decade. This technique has several advantages: no blood manipulation is required, high spatial resolution, one imaging time point which is already 1 h after infection, one-stop-shop possibility with contrast enhanced CT, etc. It is therefore considered an essential tool when looking for an infection or inflammation in a patient with fever of unknown origin. The main limitation however is that FDG is taken up both in inflammatory and infectious lesions and discrimination between both is difficult, especially when there is metallic hardware in situ or if there was a recent fracture and/or surgery, since reactive inflammation due to foreign body material also leads to FDG uptake in a certain extent.

The advent of hybrid imaging technologies combining molecular/functional and anatomical information has significantly increased the diagnostic accuracy of conventional nuclear exams by increasing sensitivity and specificity and reducing the number of equivocal lesions. This hybrid technology has redefined the work-up of our patients and has influenced patient management. The hybrid imaging techniques has improved image properties because of (1) advances in detector designs and collimator modeling, inherent to newer devices, (2) incorporation of CT data into PET reconstruction, and (3) fusion of anatomic and functional data, allowing more accurate localization and assessment of disease extent. PET/CT to combine (patho)physiology with anatomy is already considered the gold standard, the use of a PET only camera nowadays is considered obsolete.

FDG-PET/CT is considered highly sensitive and specific for diagnosing infections in the musculoskeletal system. However, there are still concerns whether the presence of fractures or metallic implants may induce false positive uptake of FDG that might reduce the diagnostic accuracy of the method. Currently, there are no clear interpretation criteria for declaring a FDG-PET as positive or negative for an infection in the musculoskeletal system, and mostly diagnosis is based on subjective criteria and personal experience.

In 2013, a joint guideline by delegates of the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) was published. In that guideline, major indications for the use of FDG-PET were peripheral bone osteomyelitis (non-postoperative, non-diabetic foot), and suspected spinal infection (spondylodiscitis or vertebral osteomyelitis, non-postoperative). White blood cell scintigraphy was thought to be the first imaging technique, so preferred above FDG-PET, in patients with suspected diabetic foot infection, and prosthetic joint infections (Jamar et al., 2013). However, we are now almost 10 years on, and it is clearly time to have a thorough look again to these indications and the preferred imaging technique, since many more evidence-based data are available.

Infections in the peripheral bone

Peripheral bone infection includes both osteitis (direct infection of the bone and surrounding soft tissue after a trauma and/or surgery) and osteomyelitis (endogenous infection of the bone marrow by hematogenous spread, with subsequent involvement of the cortical bone). The strategy regarding diagnosis of osteitis or osteomyelitis is similar, and both terms are often used interchangeably.

Both WBC scintigraphy and FDG-PET/CT can be used, both with several advantages but also some limitations as mentioned before. Many research regarding these imaging modalities took place in the last years. In 2017, a systematic review on the accuracy of diagnostic imaging modalities for peripheral post-traumatic osteomyelitis was published (Govaert et al., 2017). Some important items can be learned from this systematic review: (i) the number of studies that could be included was limited and used imaging techniques were heterogeneous, (ii) when using the correct protocols and hybrid imaging (SPECT/CT, PET/CT) the diagnostic accuracy was significantly higher, and (iii) based on this limited evidence, both WBC scintigraphy with SPECT/CT and FDG-PET combined with CT have the best diagnostic accuracy for diagnosing peripheral post-traumatic osteomyelitis.

Two studies including a large homogenous patient group with suspected peripheral post-traumatic osteomyelitis evaluated the value of WBC scintigraphy and FDG-PET/CT. In the first study, 192 consecutive patients in whom WBC was performed (Govaert et al., 2018). WBC scintigraphy was found to have a sensitivity of 79%, a specificity of 97%, a positive predictive value of 91%, a negative predictive value of 93% and a diagnostic accuracy of 92% for detecting FRI in the peripheral skeleton. Three other important messages were mentioned: (i) the duration of the interval between surgery and WBC scintigraphy did not influence its diagnostic accuracy, (ii) concomitant use of antibiotics and/or NSAIDs did not influence its diagnostic accuracy, and (iii) the majority of the patients with a false-negative scan suffered from an infected non-union.

In the second retrospective cohort study all patients undergoing FDG-PET/CT scans in two level-1 trauma centers were included (Lemans et al., 2019). Visual assessment of the scans showed a sensitivity of 89%, a specificity of 80%, a positive predictive value of 74%, a negative predictive value of 91%, and a diagnostic accuracy of 83%. Semi-quantitative analysis with calculation of standardized uptake values (SUVs) resulted in a lower diagnostic performance, but combining them with the visual assessment yielded a somewhat higher area under the curve than visual assessment alone. An important other finding was that an interval between surgery and FDG-PET/CT scan of less than 1 month was associated with a sharp increase in false positive scan results.

The above-mentioned two studies evaluated the use of imaging techniques for the local situation. In case of suspicion for spread of infection (fever, elevated infection parameters in the blood, positive blood cultures), FDG-PET/CT is the best option. Despite only a limited numbers of papers exist on this topic, it is obvious from daily clinical practice that a whole-body imaging technique is favorable to visualize all infectious lesions within a patient. It is possible to see not only other infectious foci in the musculoskeletal system, but also possible foci in liver, spleen, kidneys, lungs, heart etc. When having suspicion of hematogenous spread of infection, FDG-PET/CT is the imaging modality of choice.

Recently, four European Societies (EANM, European Society of Radiology—ESR, European Bone and Joint Infection Society—EBJIS, and the European Society of Clinical Microbiology and Infectious Diseases—ESCMID) shared their forces to develop a practical evidence-based guideline for diagnosing peripheral bone infections in adults (Glaudemans et al., 2019). The value of clinical parameters, laboratory parameters, bone biopsy, radiological imaging techniques, and nuclear imaging techniques, was assessed. Uniform statements were addressed for each topic with the aim of positioning all diagnostic procedures in a commonly agreed and evidence-based diagnostic flowchart. First, initial regular work-up should be undertaken in a patient with suspected peripheral bone infection. This consists of clinical examination, laboratory tests (CRP, ESR, leukocyte count), X-ray (or CT in complex anatomical areas) and probe-to-bone test if applicable. Laboratory tests should be performed over time since the trend to increase or decrease is more important than a single value. The probe-to-bone test can be helpful in some cases, e.g. when an ulcer is present.

When still having a suspicion after this initial work-up, (image-guided) bone biopsy should be performed to detect infection and the causative microorganism. Bone biopsy is really preferred, since sinus tract cultures may be false-positive due to contamination, and superficial swab cultures only have a low diagnostic value. Besides the bone biopsy, advanced diagnostic imaging tests should be done. There are no large studies in homogenous patient groups that compare radiological imaging tests directly to nuclear medicine imaging tests. Therefore, no choice can be made at this time-point between MRI on the one hand and nuclear imaging techniques on the other.

When choosing nuclear medicine techniques, the choice depends on having a patient with a low or a high probability for an infection. When having a low probability patient, you can start with a three-phase bone scan. When negative, an infection can be excluded. When positive, there is a need for other nuclear medicine techniques (WBC with SPECT/CT or FDG-PET/CT). When having a high probability patient, it is best to surpass the bone scan and immediately perform WBC scintigraphy or FDG-PET. When having a patient with recent surgery, recent fracture or metallic hardware in situ, then the best choice is WBC scintigraphy with SPECT/CT. When having a patient without recent surgery, without recent fracture, and without metallic hardware, then FDG-PET/CT is the first option. The exact time frame is unknown. The only thing we know is that performing FDG-PET/CT in the first month after surgery may lead to false positive results, and that WBC scintigraphy does not have that limitation, this technique can already be performed shortly after surgery. When having suspicion of dissemination of the infection, then FDG-PET/CT is the best choice. Two clinical examples are depicted below (Figs. 1 and 2).

Spine infections/spondylodiscitis

Spinal infections include vertebral osteitis (infection of the vertebral body), discitis (infection of the intervertebral disc), and spondylodiscitis (infection of the intervertebral disc and two adjacent vertebral bodies). This can be due to a direct infection (after trauma, surgery of interventional procedures), or due to hematogenous spread of infection via the bone marrow.

When there is suspicion for vertebral osteitis or spondylodiscitis, MRI is often the preferred imaging technique of choice, especially since MRI is able to detect involvement of the spinal canal and the prevertebral space. FDG-PET/CT is the nuclear imaging technique of choice, since other nuclear techniques, such as the WBC scintigraphy, is less sensitive due to high physiological accumulation in the bone marrow and since leukocytes are not able to enter the vertebral disc due a decrease in vascular blood flow. FDG-PET/CT was found to show a good diagnostic accuracy for this indication, and can also be used for evaluation of residual infection after treatment.

In a retrospective study of Smids et al. (2017) the diagnostic value of FDG-PET/CT and MRI in diagnosing spondylodiscitis and its complications was evaluated in a cohort of 68 patients. This study showed a significantly better overall sensitivity, negative predictive value, and accuracy of FDG-PET/CT when compared to MRI, especially when imaging was performed within the first 2 weeks after onset of symptoms. After 2 weeks of symptoms both modalities showed a similar yield. MRI showed highest sensitivity in diagnosing epidural and spinal abscesses while FDG-PET/CT was more sensitivity in diagnosing paravertebral and psoas abscesses (Smids et al., 2017).

When interpreting the FDG-PET/CT results in a patients with suspected discitis/spondylodiscitis, the scoring system by Hungenbach is mostly used. This is a scoring system based on uptake patterns: Score 0, normal findings and physiological FDG distribution, consistent with no infection; Score 1, slightly elevated uptake in the inter- or paravertebral region, consistent with no infection; Score 2, clearly elevated uptake of a linear or disciform pattern in the intervertebral space, consistent with discitis; Score 3, clearly elevated uptake of a linear or disciform pattern in the intervertebral space and involvement of ground or cover plate of both plates in the adjacent vertebrae, consistent with spondylodiscitis; and Score 4, clearly elevated uptake of a linear or disciform pattern in the intervertebral space and involvement of ground or cover plate of both plates of the adjacent vertebrae and surrounding soft tissue abscess, consistent with spondylodiscitis with spread to the surrounding soft tissue (Hungenbach et al., 2013).

Recently, a guideline for the diagnosis of spine infection (spondylodiscitis) in adults was written by delegates of three European societies, the EANM, the ESCMID, and the European Society of NeuroRadiology (ESNR) (Lazzeri et al., 2019). High level of evidence was found for three statements:

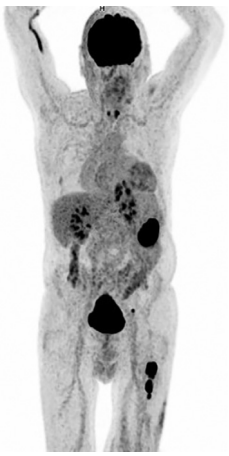

Fig. 1 Example of a FDG-PET scan (MIP image) of a patient with peripheral bone infection of the left femur with spread of infection to the spleen.

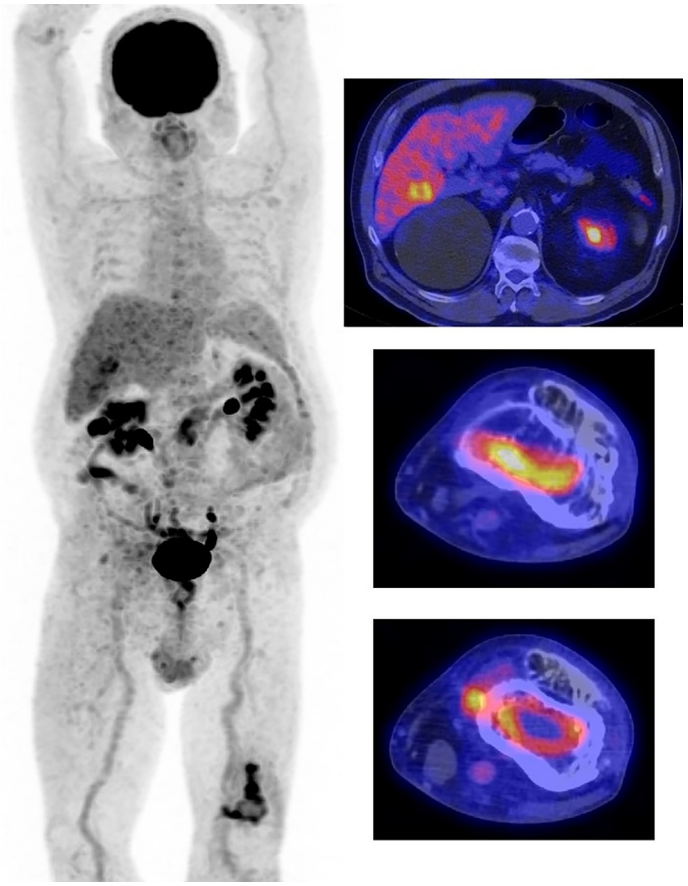

Fig. 2 Example of a FDG-PET scan (left: MIP image, right transversal fused FDG-PET/CT images) of a patient with an osteomyelitis of the distal left femur with spread of infection in the soft tissue around the bone, and spread of infection to the liver.

(i) In primary and postsurgical spondylodiscitis, if MRI is contraindicated, the imaging modality of choice is FDG-PET/CT.
(ii) In postsurgical spondylodiscitis, with or without spinal hardware, FDG-PET/CT can detect both spine infection and soft tissue infection.
(iii) In patients with suspected spine infection and elevated ESR and/or CRP and doubtful MRI, FDG-PET/CT should be performed.

The proposed diagnostic flowchart of the same guideline mentions the following criteria for clinical suspicion of spondylodiscitis: new or worsening spine pain and/or new myelo-radicular symptoms and (at least one) fever, elevated ESR, CRP or WBC, bloodstream infection or infective endocarditis, blood cultures for both aerobic and anaerobic bacteria, serology suspected for Brucella infection, and/or a PPD test and an interferon-γ release in patients suspected for TBC infection. In case of suspicion of a hematogenous cause of spondylodiscitis, MRI is the first choice imaging technique, but FDG-PET/CT can be used in patients with contra-indications for MRI or in patients with an inconclusive MRI. When there is suspicion of a post-surgical or percutaneous cause of spondylodiscitis, FDG-PET/CT can be used as first imaging technique; when inconclusive followed by a CT guided bone biopsy. Two examples of the use of FDG-PET/CT in patients with spondylodiscitis are shown below (Figs. 3–5).

Prosthetic joint infections

The number of prosthetic joint replacements and, as a consequence, prosthetic joint infections (PJI) has increased significantly over the last decades due to the increased life expectancy. According to the time of onset, PJI can be divided into early (within the first 3 months after surgery), delayed (between 3 months and 2 years after surgery), and late (more than 2 years after surgery) (Zimmerli et al., 2004). In the early phase, clinical symptoms are often clear and imaging is not required. In the delayed and late phase, however, symptoms can be vague and non-specific. In case of suspected PJI, WBC scintigraphy is the first choice nuclear imaging technique. It is well known that the uptake of FDG around the metallic implants is non-specific, heterogeneous and can vary in time, therefore caution must be taken when interpreting a FDG-PET/CT scan in a patient with suspected PJI. Several authors tried to define interpretation criteria, with the one from Reinartz et al. (2005) most often used (Reinartz et al., 2005), but they all failed in daily

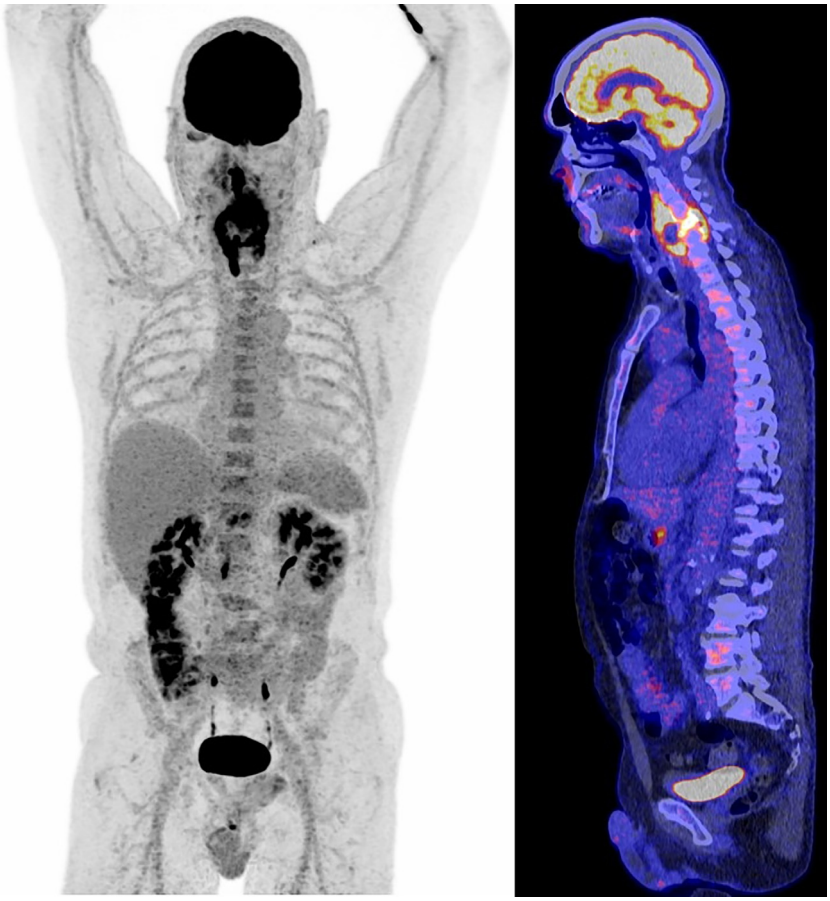

Fig. 3 FDG-PET/CT (left MIP image, right sagittal FDG-PET/CT fusion image) of a patient with cervical spondylodiscitis with epidural and prevertebral abscesses.

clinical practice and an unanimous consensus still does not exist (Glaudemans et al., 2013). However, FDG-PET/CT can be used to exclude an infection, when there is no FDG uptake around the prosthesis implant. Also when there is suspicion of hematogenous spread of infection, FDG-PET/CT can be used. Direct comparisons between WBC scintigraphy and FDG-PET/CT in patients with suspected PJI are lacking, and the results are discordant mainly due to different acquisition protocols and interpretation criteria used.

Recently, delegates of four European Societies (EANM, ESR, EEBJIS, and ESCMID) developed a practical evidence-based guideline for diagnosing peripheral bone infections in adults (Signore et al., 2019). First, initial regular work-up should be undertaken consisting of clinical examination, laboratory tests (CRP, ESR, leukocyte count), X-ray and blood cultures. If suspicion persists, then bone or soft tissue biopsy or joint fluid aspiration should be performed, followed by advanced imaging tests. There are no large studies in homogenous patient groups that compare radiological imaging tests directly to nuclear medicine imaging tests. Therefore, no choice can be made at this time-point between MRI on the one hand and nuclear imaging techniques on the other.

When choosing nuclear medicine examinations, within the first 2 years after prosthesis implantation, WBC scintigraphy is the first choice imaging method. When the prosthesis implantation was more than 2 years ago, and the clinical probability is low, it is possible to start with FDG-PET/CT to rule out an infection. However, when FDG-PET/CT is positive, this should be followed by a WBC scan for a definitive diagnosis.

Diabetic foot infections

A diabetic foot (ulcers, Charcot osteoarthropathy, osteitis, osteomyelitis) occurs in patients with long-standing, not well-controlled, diabetes mellitus complicated by peripheral neuropathic and/or vascular diseases. The diabetic foot represents a major health burden, and may lead to severe complications such as amputation, or even mortality in case of dissemination of infection.

For the use of FDG-PET/CT in the suspected infected diabetic foot, the same holds true as for other infections in the musculoskeletal system: FDG is a non-specific radiopharmaceutical, and will taken up both in severe degeneration (which exists in the Charcot osteoarthropathy) and infection. A meta-analysis, published in 2013, on the use of FDG-PET/CT in patients with

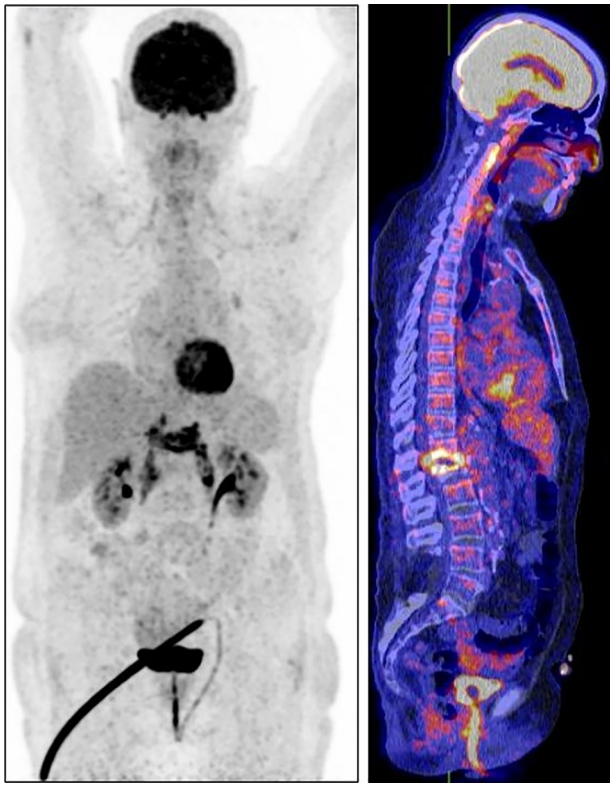

Fig. 4 FDG-PET/CT (left MIP image, right sagittal FDG-PET/CT fusion image) of a patient with lumbal spondylodiscitis with direct spread of infection to the psoas muscles.

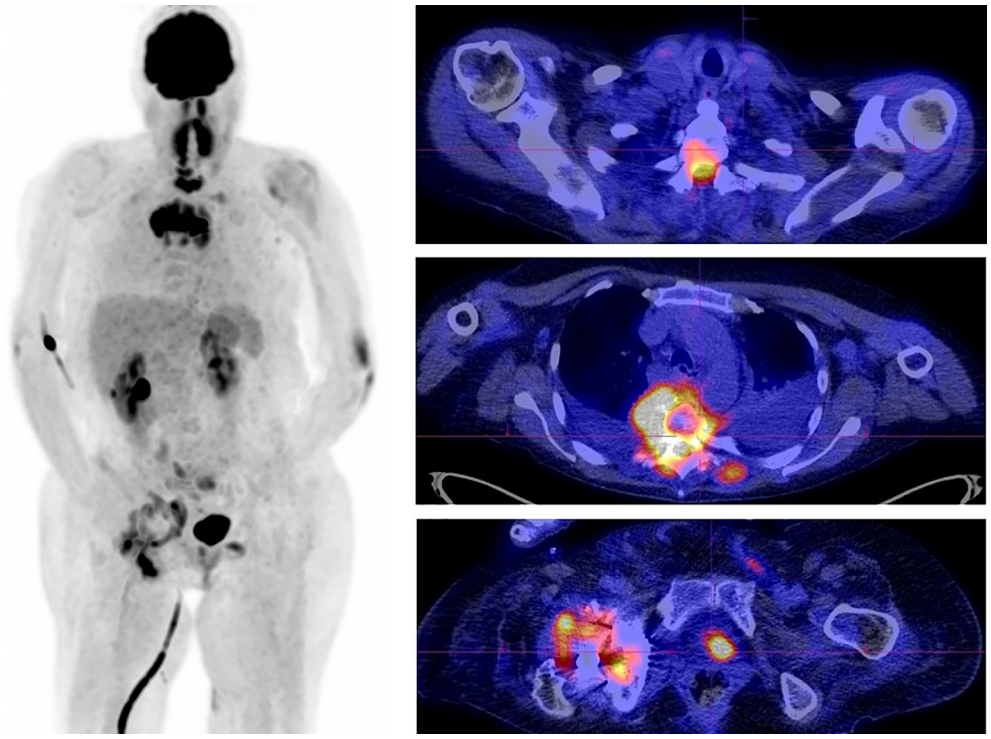

Fig. 5 FDG-PET/CT (left MIP image, right transaxial fused PET/CT images) in a patients with a PJI, and spread of infection to the thoracic spine (spondylodiscitis).

diabetic foot infection revealed a pooled sensitivity of 74% and a specificity of 91% on a per patient-based analysis (Treglia et al., 2013). In another study in 110 diabetic patients with clinical suspicion of pedal osteomyelitis, FDG-PET was compared to MRI. FDG-PET was found less sensitive, but more specific (Nawaz et al., 2010). Regarding semi-quantitative analysis (with SUV calculations) results are discordant. In a study with FDG-PET in 63 patients, a higher SUVmax was found in patients with osteomyelitis compared with patients with Charcot and uncomplicated diabetic foot (Basu et al., 2007). Another study, however, found no correlation between SUVmax and soft tissue infection or osteomyelitis or Charcot and found a superior diagnostic accuracy of WBC scintigraphy in detecting osteomyelitis when compared to FDG-PET/CT (Familiari et al., 2011).

At present, no well-defined interpretation criteria exist to differentiate between infection, inflammation, soft tissue infection, osteomyelitis and Charcot. Therefore, at this moment, white blood cell scintigraphy remains the nuclear imaging modality of choice in patients with suspected diabetic foot infection, according to the EANM/SNMMI guideline (Jamar et al., 2013). Large prospective studies comparing FDG-PET/CT, WBC scintigraphy and MRI in the same patients should be performed to decide which imaging technique is preferred.

Sternal bone/wound infections

In suspected sternal wound infections after sternotomy, the choice of which nuclear medicine modality to use is the same as for peripheral bone infections. Three phase bone scintigraphy is only the first modality of choice in patients without recent surgery and a low probability of an infection. A negative three phase bone scan excludes an infection of the breast bone. In all other cases—and especially when also soft tissue infection is suspected, FDG-PET/CT is a better option. It is well known that after surgery with a sternotomy, the breast bone remains positive for almost a year at FDG-PET due to healing, regeneration and modulation. So when the referring clinician really wants to know if there is an osteomyelitis of the breast bone within the first year after sternotomy it is best to perform a white blood cell scintigraphy (including SPECT/CT). However, when there is already a known infection and the referring clinician wants to know if there is expansion to the soft tissue or mediastinum then FDG-PET/CT is the best option because of the better spatial resolution and the possibility to search for dissemination of infection.

In chronic sternal infections often a cold area can be observed at WBC scintigraphy because of the presence of necrotic bone into the physiological uptake of the labeled cells in the normal bone marrow. In these cases, only a peripheral faint uptake can be the only sign that confirms a breast bone infection. So, FDG-PET/CT might then the best choice.

In general, in patients with suspected sternal bone and/or wound infection, FDG-PET/CT is the best method to start for the search of an infection, for the extent of an already known infection, or to detect dissemination of the infection. However, in inconclusive cases, or after recent sternotomy, WBC scintigraphy with SPECT/CT can be a perfect solution (Fig. 6).

Non-FDG PET tracers

At this moment, FDG is the only tracer that is routinely used in daily clinical practice for infections in the musculoskeletal system. In cases where the conventional bone scan plays a role, the PET tracer ^{18}F-sodium fluoride (NaF) could be used instead. The uptake mechanism of NaF is nearly the same as that of the labeled diphosphonates. However, NaF-PET has several advantages above the conventional bone scan. The faster blood clearance and the twofold higher uptake in developing bone cells of fluoride makes it possible to image faster (1 h after injection, late phase imaging of the conventional bone scan is 3 h after injection) and leads to better ratios between pathological and physiological bone uptake. Furthermore, the use of PET instead of SPECT leads to better resolution and better quantification methods. Limitations, however, are the higher costs and lower availability of this technique and the fact that only late phase imaging is possible (no flow and bloodpool phase).

^{68}Ga-citrate has been used to image osteomyelitis (Nanni et al., 2010). The uptake of this tracer is due to transferrin-dependent and independent mechanisms, but like FDG, Ga-citrate lacks specificity and also accumulates in sterile inflammatory processes or malignancy. Other developments are the use of specific bacterial tracers, such as ^{18}F-sorbitol (Yao et al., 2016). For Gram-negative, and ^{18}F-vancomycin in Gram-positive bacteria. These tracers, however, have not been validated in large patient numbers, so we have to wait for the first results to see if these tracers are able to make it into clinical practice.

New camera developments

Together with the ongoing search for a radiopharmaceutical that is able to differentiate between infection and inflammation, there are also huge developments in hybrid camera systems. The hybrid PET/MRI system is on the market since 2012, and although theoretically there are several advantages to use this system, there are only a few centers that have access to it. In theory, PET/MRI offers an absolute match between the tissue information of both modalities under the same physiological conditions, with better localization of the PET signal within the soft tissues, and without radiation burden from the MRI part (Glaudemans et al., 2012). Especially in patients with suspected spondylodiscitis or suspected infected diabetic foot, PET/MRI could have synergistic value. The facts that costs are high, acquisition time is long, and attenuation correction with MRI is difficult, probably prohibits use of PET/MRI on large scales at this moment.

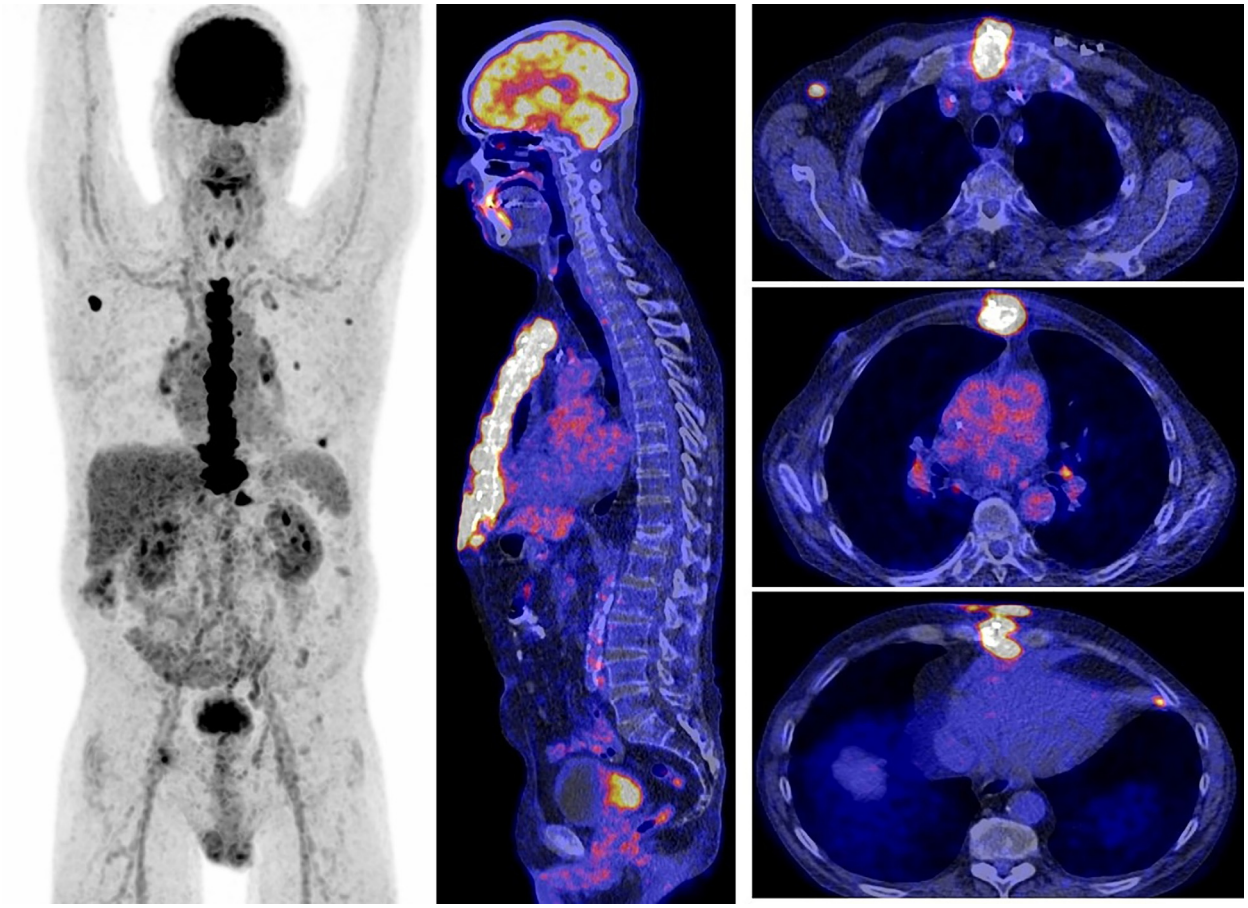

Fig. 6 FDG-PET/CT (left MIP image, middle sagittal FDG-PET/CT fusion image, right transaxial fused PET/CT images) in a patient with osteomyelitis of the breast bone with soft tissue infection ventral of the breast bone, mediastinitis, multiple septic lung emboli, and reactive lymph nodes.

Another very recent development is the so called long axial field of view (LAFOV) PET/CT camera system, indicating any scanner with a significantly extended axial FOV (longer than 1 m), thereby enabling to scan torso and head within the same FOV, and the possibility to provide simultaneous coverage of all major internal organs. The advantage of a LAFOV PET/CT system is the substantial increase in sensitivity compared with conventional PET scanners. This allows for faster scans (whole body scan within 2 min, leading to higher patient throughput) and/or significant reduction in injected dose, and may lead to new clinical indications, patient populations, and research possibilities (Slart et al., 2021). Just recently developed, only a few centers already have this camera system installed, but a future can be expected where these LAVOF PET/CT scanners play a huge role and maybe will be a game changer within the nuclear medicine community.

Conclusions

In conclusion, nuclear medicine modalities play a very important role in patients with suspected musculoskeletal infections. FDG-PET/CT shows good results for most indications, but be careful with interpreting a FDG-PET/CT scan in the early postoperative period, after a recent fracture and with metallic implants in situ. In those cases, WBC scintigraphy is still preferred. We are still in need of large prospective trials to directly compare all imaging techniques (also radiological) with each other in the same patient to really have evidence based data available. For now, both the referring clinician and the nuclear medicine specialist should really adhere to the available guidelines and protocols from the EANM to correctly perform the imaging techniques. For the future, the search toward specific tracers should be continued, and eventually lead to tracers that are able to differentiate between infection and inflammation. The new LAFOV PET/CT camera systems may deliver more comprehensive information to the clinicians, and may be able to detect smaller foci of infections.

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