Nononcologic Applications of PET/CT and PET/MRI in Musculoskeletal, Orthopedic, and Rheumatologic Imaging: General Considerations, Techniques, and Radiopharmaceuticals

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PET is often underutilized in the field of musculoskeletal imaging, with key reasons including the excellent performance of conventional musculoskeletal MRI, the limited spatial resolution of PET, and the lack of reimbursement for PET for nononcologic musculoskeletal indications. However, with improvements in PET/CT and PET/MRI over the last decade as well as an increased understanding of the pathophysiology of musculoskeletal diseases, there is an emerging potential for PET as a primary or complementary modality in the management of rheumatologic and orthopedic patients. Specific advantages of PET include the convenience of whole-body imaging in a single session, the relative resilience of the modality compared with CT and MRI in the imaging of metallic implants, the ability to evaluate deep joints not amenable to palpation, and the potential for improved specificity of diagnosis with novel radiopharmaceuticals. In this review, we discuss multiple radiopharmaceuticals and technical considerations for PET/CT and PET/MRI that can be used in imaging of nontumoral bone and soft-tissue disorders. Both PET/CT and PET/MRI hold significant promise in the field of musculoskeletal imaging, and with further radiopharmaceutical development and clinical research, these hybrid modalities can potentially transform the current management of patients with orthopedic and rheumatologic disease.

Key Words: PET/CT; PET/MRI; rheumatoid arthritis; septic arthritis; osteomyelitis; polymyalgia rheumatica

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PET was introduced 4 decades ago and has rapidly become the standard of care for the diagnosis and monitoring of a wide range of diseases, particularly in the field of oncology. In addition, as a metabolic and molecular imaging modality, PET has significantly advanced our understanding of normal human physiology as well as pathophysiology (*1,2*). PET is now most commonly used as a hybrid modality, typically combined with CT or MRI for better anatomic localization and attenuation correction purposes (*3–5*).

Despite the widespread application of PET/CT and PET/MR for oncology, the role of PET imaging in musculoskeletal disorders, especially nononcologic applications, has not been widely appreciated. PET has traditionally been underutilized in musculoskeletal imaging for several reasons, such as the limited spatial resolution of PET and the excellent performance of musculoskeletal MRI, a modality that does not use ionizing radiation. However, with improvements in PET/CT and PET/MRI over the last decade as well as increased understanding of the pathophysiology of musculoskeletal diseases, there is an emerging potential for PET as a primary or complementary modality in the management of rheumatologic and orthopedic patients. In fact, the low metabolic activity of osseous and tendinous structures is an advantage for detecting pathology in the skeletal system, because of the low physiologic background activity leading to a high target-to-background ratio in imaging of these disease processes. In this review, we discuss the technical details of, and different radiopharmaceuticals for, PET/CT and PET/MRI in the management of nonneoplastic musculoskeletal diseases.

PET RADIOPHARMACEUTICALS

PET is a powerful molecular imaging technique in which a positron-emitting radiotracer is administered to a patient and then subsequent imaging visualizes the in vivo distribution

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and kinetics of that radiotracer. Multiple PET radiopharmaceuticals have been developed that interact with biologic systems, such as radiotracers studying glucose, amino acid, and nucleotide metabolism; cellular receptors and transporters; and bone and cell turnover metabolites.

^{18}F-FDG is by far the most common radiotracer used in clinical PET imaging. Its biodistribution follows the pattern of in vivo glucose metabolism, with increased glucose metabolism typically associated with neoplastic and inflammatory pathologies. Increased ^{18}F-FDG uptake is indeed seen both in neoplastic cells and in cellular elements of inflammation, such as macrophages, fibroblasts, neutrophils, and capillaries (*6,7*). ^{18}F-FDG continues to be widely used because of its availability and low cost, as well as the wealth of evidence and years of experience demonstrating its clinical utility. However, ^{18}F-FDG imaging suffers from the disadvantage of relatively limited specificity. Although this is a major limitation in the imaging evaluation of neoplastic disorders, it probably is not a major issue in the imaging approach to nonneoplastic disorders of the musculoskeletal system, where the diagnosis of diseases relies on mainly nonimaging clinical and serologic findings. In fact, in these cases, the high sensitivity of ^{18}F-FDG can be an advantage in identifying mild and clinically silent stages of the disease.

^{18}F-NaF is a Food and Drug Administration–approved positron-emitting radiotracer used as a marker of osteoblastic activity. The main advantage of this radiotracer is that its uptake is minimal in bone marrow and its activity originates almost exclusively in the cortical bone. Uptake of ^{18}F-NaF in the skeletal system is flow-dependent and consists of fast chemisorption on hydroxyapatite crystals, forming fluoroapatite. ^{18}F-NaF PET is a highly sensitive imaging probe for the detection of osseous metastases and other nonneoplastic bone lesions, such as traumatic (Fig. 1) and metabolic pathologies (*8*). Uptake of ^{18}F-NaF is up to 10 times higher in osteoblastic lesions than in normal bone, leading to excellent image contrast. Contrast is further improved by the fact that ^{18}F-NaF does not bind to plasma protein and thus has fast renal excretion and therefore low background activity. It has been shown that ^{18}F-NaF PET/CT offers a higher sensitivity than MRI in the detection of osteoblastic bone lesions (*9,10*). Combining ^{18}F-NaF PET with MRI is a powerful approach that incorporates the high sensitivity of PET and the robust specificity of MRI for early diagnosis and accurate posttreatment follow-up of osteoblastic lesions (*11*).

Several other PET radiotracers are being studied for use in the musculoskeletal system. There has been increased interest in developing radiotracers with increased specificity compared with ^{18}F-FDG and ^{18}F-NaF, as well as radiotracers using shorter-lived positron-emitting radioisotopes that take advantage of newer PET equipment to limit radiation exposure and reduce image acquisition time (*12*).

^{68}Ga-Citrate and ^{68}Ga-Transferrin

^{68}Ga-citrate and ^{68}Ga-transferrin were originally used for tumor imaging but have recently been studied for possible

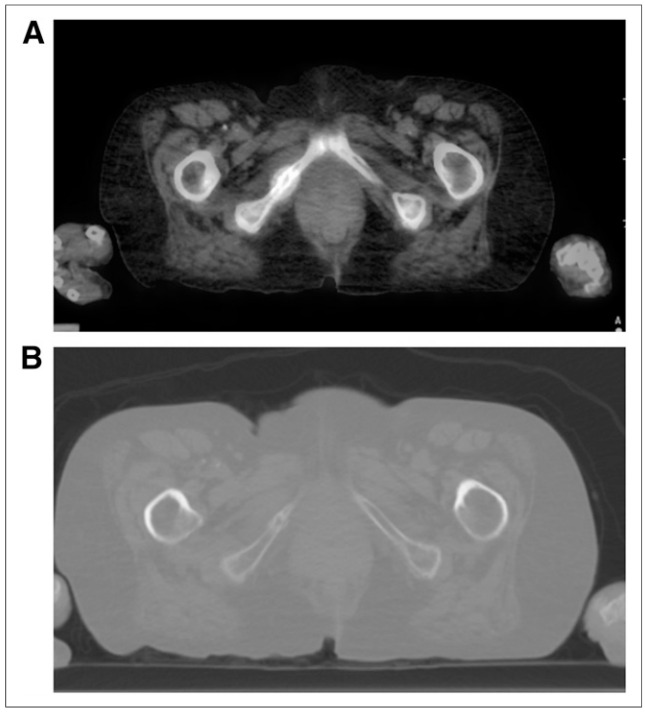

FIGURE 1. 67-y-old woman with bilateral breast cancer underwent ^{18}F-NaF PET/CT for evaluation of osseous metastasis. Focus of intensely increased radiotracer uptake in right ischiopubic junction (A) corresponded to healing fracture identified on low-dose CT (B).

imaging of inflammation and infection in the musculoskeletal system (*13*). ^{68}Ga has a half-life of 68 min, with high blood-pool activity and liver and bone uptake but low soft-tissue activity. It binds to lactoferrin, which is present in high concentrations in neutrophils and abscess fluid as well as in siderophores produced by different infectious microorganisms (*12,14*). In clinical studies, these agents have been successful in detecting the infection site as early as 30 min after injection, but current protocols allow 60 min after injection to reduce background activity and improve image quality. High background activity in the thorax and upper abdomen may interfere with detecting thoracic and upper abdominal lesions; therefore, ^{68}Ga-citrate and ^{68}Ga-transferrin are most useful for lower abdominal and extremity infection sites. Imaging with these ^{68}Ga agents is useful not only for the initial diagnosis of infection but also for planning surgery, monitoring treatment (Fig. 2), and differentiating prosthetic infection from aseptic loosening of a prosthesis (*15*).

^{68}Ga-DOTA-Sialic Acid–Binding Immunoglobulin-like Lectin-9 (^{68}Ga-Siglec-9)

^{68}Ga-Siglec-9 is a PET radiotracer introduced for the assessment of synovitis and the in vivo imaging of inflammation. Siglec-9 is a leukocyte ligand of vascular adhesion protein 1, which, during inflammatory processes, rapidly translocates from the intracellular space to the endothelial surface of cells, including vessels in human rheumatoid synovium (*16*). This is an important step in the regulation

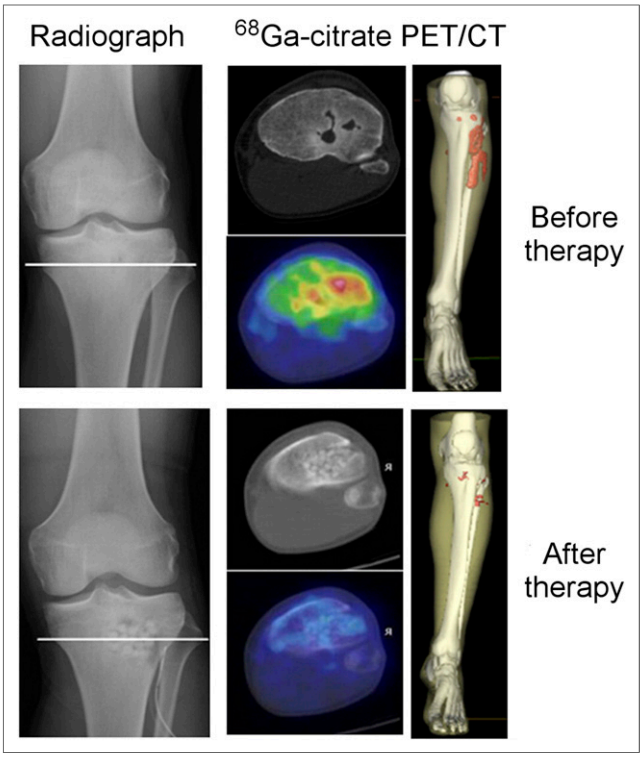

FIGURE 2. Comparison of pre- and posttreatment ^{68}Ga-citrate PET/CT scans in patient with acute osteomyelitis. Pretreatment scan showed increased radiotracer uptake involving proximal tibia. Posttreatment scan showed no significant uptake, representing complete response to treatment. (Reprinted from (*13*).)

of leukocyte migration to sites of inflammation (*17*). However, as a PET radiotracer, ^{68}Ga-Siglec-9 is somewhat nonspecific and detects vascular adhesion protein 1 not only in the vasculature at sites of inflammation but also in cancer tissues (*18*). ^{18}F-labeling of Siglec-9 peptide has also been performed in the preclinical setting (*19,20*).

^{89}Zr-Labeled Rituximab

^{89}Zr-labeled rituximab has been introduced as a specific radiotracer for noninvasive B-cell imaging by PET/CT (*17*). The CD20+ B-cell count in the lymph nodes of subjects who underwent ^{89}Zr-rituximab PET imaging correlated positively with quantitative lymph node PET data. B cells are key players in the pathogenesis of autoimmune inflammatory arthropathies, such as rheumatoid arthritis and systemic lupus erythematosus. ^{89}Zr-rituximab has been successfully used in identifying potential responders before treatment (Fig. 3) (*17*).

^{11}C-Methionine

^{11}C-methionine is used for PET imaging of amino acid metabolism. It was originally used to try to distinguish neoplastic from inflammatory lesions (*12,21*). However, it was subsequently found to accumulate in both categories of lesions. Currently, the radiotracer is being studied for the imaging of musculoskeletal infectious and inflammatory processes (*22*). Soft-tissue and bone uptake of ^{11}C-methionine is relatively low in the extremities, making it a promising radiotracer for evaluation of limb musculoskeletal infections, particularly in the pediatric and adolescent population (*12,23*).

^{11}C-PK11195

^{11}C-PK11195 is a radiolabeled form of PK11195, a specific ligand for the peripheral benzodiazepine receptor, which is highly expressed on activated mononuclear phagocytic cells (*12,24*). This radiotracer has primarily been investigated for the diagnosis of neuroinflammation (*25*), but more recent work has proposed a role in nonneurologic inflammation, such as inflammation of vascular structures and periprosthetic soft tissues in animal models (*24,26*).

1-(2′-Deoxy-2′-Fluoro-β-D-Arabinofuranosyl)-5-Iodouracil (FIAU)

FIAU has been found to be a substrate for bacterial thymidine kinase. ^{124}I-FIAU has been tested in humans as an infection-imaging radiotracer (*27,28*).

^{18}F-Labeled Leukocytes

^{18}F-labeled leukocytes have been shown to be effective in the diagnosis of various infectious and inflammatory pathologies. The underlying mechanism of labeled leukocyte imaging is based on chemotaxis exerted on activated leukocytes by chemoattractants, resulting in cell-bound radionuclide trafficking from the blood-pool compartment to the lesion. The use of ^{18}F labeling is facilitated by the avidity of inflammatory cells for ^{18}F-FDG (*29,30*).

Integrin $\alpha_v\beta_3$

Integrin $\alpha_v\beta_3$ has been suggested as a target for imaging of angiogenesis, as it is expressed on activated endothelial cells. ^{18}F-galacto-RGD (arginine-glycine-aspartate) has been introduced as a radiotracer for PET imaging of integrin $\alpha_v\beta_3$ expression. Although this tracer is mainly studied for oncologic applications, some authors have suggested that it can be also used for the evaluation of inflammatory disorders (*31*).

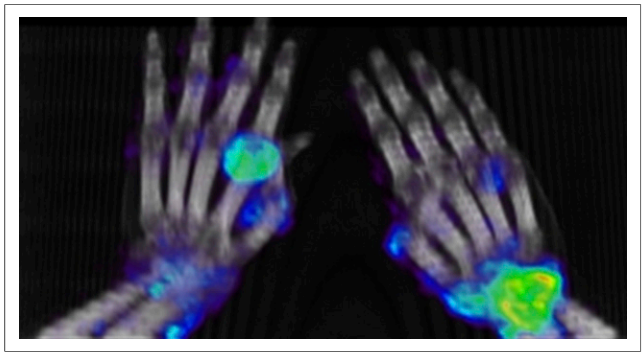

FIGURE 3. ^{89}Zr-rituximab PET/CT scan of patient with active rheumatoid arthritis, demonstrating increased radiotracer uptake involving left second metacarpophalangeal joint and right wrist. (Image courtesy of Dr. Conny van der Laken, Afdeling Reumatologie, VU Universitair Medisch Centrum, Amsterdam.)

Others

Several other radiotracers, such as ^{11}C-choline, ^{11}C-tyrosine, and ^{18}F-fluorothymidine, have also been studied for PET imaging of the musculoskeletal system (*31*). However, their main applications were the study of neoplastic disorders, which is beyond the scope of this review.

IMAGING PROTOCOL

A detailed discussion of PET/CT and PET/MRI protocols is beyond the scope of this article. Generally, when ^{18}F-FDG PET is performed, imaging of the patient 60 min after radiotracer injection is recommended. However, several modifications in imaging protocols have been used to increase the specificity of ^{18}F-FDG PET for nononcologic indications.

Dual–time-point PET imaging has been suggested for the diagnosis of osteomyelitis. It has been shown that dual–time-point imaging with ^{18}F-FDG is more accurate than single–time-point imaging in the differentiation of benign lesions from malignant neoplastic pathologies (*32*,*33*). Sahlmann et al. demonstrated that dynamic dual–time-point ^{18}F-FDG PET elicits a characteristic pattern in chronic osteomyelitis—like that in inflammatory processes in other locations—that differentiates it from neoplastic pathologies. In chronic osteomyelitis, the SUV_{max} of scans obtained between 30 and 90 min after injection remains stable or decreases, with a median decrease of 6%, whereas in malignant lesions, the SUV_{max} and SUV_{mean} between 30 and 90 min after injection both increase (*32*).

Brown et al. also tested this hypothesis on an experimental rabbit model of postsurgical osteomyelitis to distinguish between acute infection and sterile postsurgical inflammation (*34*). In their study, images were acquired 7 and 14 d after surgical intervention, with continuous PET image acquisition for 90 min after ^{18}F-FDG administration. However, their findings were not promising, and they concluded that in the complicated clinical context of acute postsurgical and posttraumatic inflammation versus infection, the diagnostic accuracy of ^{18}F-FDG PET is limited. This limitation is due to the fact that increased glucose utilization is the main basis of PET imaging and that this type of hypermetabolism is generally characteristic of all inflammatory processes, including infectious pathologies, but is not specific to any of them. The conclusion of Brown et al. was concordant with what was previously concluded by Kälicke et al. from their clinical study on 21 patients with suspected osteomyelitis—that PET is not able to differentiate between postsurgical reactive changes and further infection in the early postoperative phase (*35*).

QUANTITATIVE PET IMAGING

Quantification of the metabolic data obtained from PET images offers several benefits in the diagnostic management of diseases, including assessment of response to therapy in serial and follow-up imaging. Several methods of quantification have been proposed, categorized into semiquantitative measures and absolute quantitative analysis. Semiquantitative methods include measures such as SUV and SUV corrected for factors such as lean body mass, target-to-background ratio, and other variants. They are routinely used in the daily clinical practice of nuclear medicine as simple but practical and objective indicators of the metabolic activity of the lesion. However, these semiquantitative measures are prone to interreader and intrareader variability (*36*).

Absolute quantitative techniques use various mathematic models on PET data, including nonlinear regression and Patlak–Gjedde graphical analysis, and may require dynamic or parametric whole-body PET image acquisition. In dynamic image acquisition, time series of PET data are dynamically acquired, enabling simulation of physiologic processes through tracer kinetic modeling. The models may use region-of-interest–based kinetic analysis or voxel-based kinetic modeling (*36*), the detail of which is beyond the scope of this review. More sophisticated techniques for the quantification of PET data have allowed for specialized applications such as static and dynamic ^{18}F-NaF PET quantification of tracer plasma clearance (inhibition constant) in osteoporosis. Compartmental and noncompartmental machine learning models have already been tested in animal models (*37*), and there is great potential for the use of quantitative PET to better understand biologic systems.

PET/CT VERSUS PET/MRI

The hybrid modality PET/CT has become widely used and widely available since its introduction, with combination of the two modalities providing major advantages such as improved anatomic localization and improved attenuation correction. PET/CT is currently the standard of care for most clinical applications of PET imaging.

Technologic advances during the past decade, including the development of digital detector technology that is not disturbed by the magnetic field, has allowed the development of PET/MRI. These advances also include Dixon sequences, which allow acquisition of whole-body MRI in a reasonable time frame. PET/MRI, as a hybrid modality, provides several advantages over PET/CT, particularly with respect to evaluation of the musculoskeletal system. For example, the lower ionizing radiation exposure of PET/MRI than of PET/CT is particularly important for the pediatric population and for young adults who may need repeated follow-up imaging studies for an extended period. In these cases, PET/MRI can spare patients from a significant amount of radiation (*1*).

More importantly, PET/MRI provides higher soft-tissue contrast than PET/CT, which is crucial for appropriate diagnosis of ligamentous, tendinous, and muscular pathologies (*1*,*2*). In addition, because MRI with multisequence multiparametric protocoling is usually required for the diagnostic work-up of these soft-tissue pathologies, PET/MRI

can potentially serve as a 1-stop shop for patient work-up, where both diagnostic MRI of the pertinent anatomy and whole-body PET/MRI can be performed during the same imaging session.

In some applications, PET/MRI can be superior to PET/CT by way of its more accurate coregistration and better MRI-based motion correction of PET data (*1*). Although no head-to-head comparisons of PET/CT and PET/MRI have been reported for musculoskeletal applications, the currently available PET/MRI machines generally provide image quality comparable to PET/CT (*3–5*). In addition, no significant negative effects of the PET hardware on MR image quality and machine functionality have been identified.

However, compared with PET/CT, PET/MRI does have some disadvantages in the evaluation of musculoskeletal pathologies. For example, attenuation correction continues to be better for PET/CT than for PET/MRI. PET/CT is also much more widely available and is lower in cost. PET/MRI scanners not only are more expensive but generally have a lengthier image acquisition time that further increases the cost. MRI of the extremities also often needs special coils, such as those for the knees or wrists. These coils are often an additional expense, and third-party coils are not necessarily PET-friendly. Also, some patients have contraindications to MRI, including permanent pacemakers, intraaortic balloon pumps, and left and right ventricular assist devices, but can be safely imaged by PET/CT.

There are also differences in the quantification of ^{18}F-FDG uptake and metabolic activity using the measure of SUV. Although SUV can be used in PET/MRI, the values are scanner-dependent and not entirely comparable to those obtained from PET/CT. MRI also is weaker than CT in the evaluation of cortical bone, though newly introduced techniques such as ultrashort echo time sequences may help to overcome this difference. However, such sequences also have their own drawbacks, including artifacts at larger fields of view and longer image acquisition times (*2,38,39*). No experience with these sequences on PET/MRI has been published, and more investigation is warranted to confirm the usefulness in PET/MRI for musculoskeletal applications.

Both PET/CT techniques and PET/MRI techniques continue to advance. At present, the two are considered comparable for most clinical applications, though evidence is building that PET/MRI may be superior for certain applications, such as the confident diagnosis of osteomyelitis (*40*). PET/CT remains the more commonly performed examination because of its greater availability and lower cost (*41*).

FUTURE PERSPECTIVES

Multiple PET radiotracers with potential applications in the musculoskeletal system have been developed. Many of these radiotracers have been tested only in animal models, but there are many promising opportunities for future human clinical trials using agents that have favorable diagnostic performance and safety profiles.

The use of hybrid PET/MRI is rapidly evolving in the diagnostic management of different disorders, with the major advantage being combination of the morphologic information of MRI and the functional information of PET (*40,42*). PET/MRI in the management of musculoskeletal disorders is currently a hot topic for investigation, with scarce reports of its use in nononcologic applications. The combination of PET using ^{18}F-FDG or other more specialized radiotracers with novel MRI sequences tailored for the musculoskeletal system raises numerous exciting possibilities.

CONCLUSION

As investigations of the use of PET in the musculoskeletal system increase, measurement of the diagnostic performance and clinical outcomes of PET modalities will continue to be important, particularly in children, for whom exposure to ionizing radiation will always remain a drawback. Comparisons of PET with competing modalities that use less or no ionizing radiation must be performed to ensure appropriate care.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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