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Applications of PET-MRI in Musculoskeletal Disease

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Abstract

New integrated PET-MRI systems potentially provide a complete imaging modality for diagnosis and evaluation of musculoskeletal disease. MRI is able to provide excellent high-resolution morphologic information with multiple contrast mechanisms that has made it the imaging modality of choice in evaluation of many musculoskeletal disorders. PET offers incomparable abilities to provide quantitative information about molecular and physiologic changes that often precede structural and biochemical changes. In combination, hybrid PET-MRI can enhance imaging of musculoskeletal disorders through early detection of disease as well as improved diagnostic sensitivity and specificity. The purpose of this article is to review emerging applications of PET-MRI in musculoskeletal disease. Both clinical applications of malignant musculoskeletal disease as well as new opportunities to incorporate the molecular capabilities of nuclear imaging into studies of non-oncologic musculoskeletal disease are discussed. Lastly, we discuss some of the technical considerations and challenges of PET-MRI as they specifically relate to musculoskeletal disease.

Keywords

Musculoskeletal Disease; PET-MRI; Molecular Imaging; Bone; Joint

Introduction

Magnetic resonance imaging (MRI), with its excellent depiction of soft tissues and multiple contrast mechanisms, has become a hallmark for imaging of musculoskeletal disease. However, as assessment of multiple tissue types and functional processes is necessary for optimized detection and diagnosis of musculoskeletal diseases, as well as for studying disease pathogenesis and treatment response, one imaging modality may not be ideal. To address this concern, multimodality imaging systems have been introduced into clinical radiology to combine the strengths and overcome the limitations of various individual

imaging modalities. In particular, hybrid positron emission tomography (PET) and MRI (PET-MRI) systems are an emerging technology which aim to combine the high-resolution soft-tissue information from MRI with simultaneous functional and molecular information from PET and may have numerous indications for clinical and research studies of musculoskeletal disease^{1,2}.

While the first commercial hybrid PET-MRI system were only recently installed in 2010, their numbers have been increasing steadily. There have been several exemplary reviews of both the technical aspects of simultaneous PET-MRI³⁻⁹ as well as their clinical application in oncology^{10,11} and neurology¹². In this review article, we focus on the emerging applications of PET-MRI in musculoskeletal disease. Both oncologic and non-oncologic applications are discussed with a focus on the comparative advantages of PET-MRI over hybrid PET-computed tomography (PET/CT) systems or MRI alone. Lastly, we discuss some of the technical considerations and challenges as they specifically relate to PET-MRI of musculoskeletal disease.

PET-MRI: A logical Pair for Evaluation of Musculoskeletal Disease

Over the last few decades, MRI has become the benchmark for musculoskeletal imaging due to its ability to non-invasively evaluate soft tissue, articular and osseous structures. MRI provides excellent characterization of tissue through an assortment of pulse sequences that each offer a unique contrast mechanism. In the clinical setting, MRI is the primary modality used in orthopedics for diagnosis of soft tissues injuries such as intervertebral disc injuries; tears in the menisci, ligaments and tendons; and occult bone injuries¹³. In evaluation of musculoskeletal tumors, MRI has been traditionally utilized to identify the extent of disease for treatment planning, but new MRI methods such as diffusion-weighted imaging (DWI), chemical shift MRI, perfusion imaging and MR spectroscopy (MRS) have shown the potential to screen, diagnose and characterize musculoskeletal neoplasms¹⁴. Additionally, advanced quantitative MRI techniques that can provide unique cellular information are used to study pathogenesis in many musculoskeletal disorders¹⁵⁻¹⁷.

While MRI is unmatched in its ability to evaluate soft tissue and bone marrow pathology, it has some limitation for imaging osseous abnormalities. Specifically, the lower water content and rapid signal decay of bone, particularly cortical bone, make quantitative MRI difficult. New methods such zero echo time (ZTE) MRI and ultra-short echo time (uTE) have shown promise for visualization of cortical bone¹⁸ and for assessment of fracture risk¹⁹. Nevertheless, functional imaging of bone with MRI remains a challenge.

PET offers incomparable ability to provide quantitative information about molecular and metabolic activity that often precedes structural and even biochemical changes. Many different PET radiotracers have been applied to imaging musculoskeletal applications (Table 1). In particular, two commercially available PET tracers are commonly utilized to study musculoskeletal disease. Fluorine-18 (¹⁸F) labeled [¹⁸F]Fluoro-2-deoxy-2-D-glucose (FDG), an analog of glucose, is the most widely used PET radiotracer in clinical practice and is able to relay information about tissues with increased metabolic activity and glucose consumption²⁰. FDG is extensively used in oncology for tumor staging, detection of

metastasis and tumor recurrence, and for monitoring response to therapy. FDG PET is also a useful tool to identify musculoskeletal inflammation and infection due to increased glucose utilization by activated inflammatory cells²¹.

Additionally, ¹⁸F-sodium fluoride (¹⁸F-NaF) is a long-recognized PET bone-seeking agent^{22,23}. ¹⁸F-fluoride ion is able to exchange with the hydroxyl groups in hydroxyapatite crystals on the surface of bone matrix to form fluoroapatite²⁴. Thus, uptake of ¹⁸F-NaF is concentrated preferentially at sites of newly mineralizing bone and provides a marker of bone metabolism²⁵. ¹⁸F-NaF is used in the detection and evaluation of skeletal metastasis, particularly in tumors with low FDG affinity such as thyroid and renal cell cancers^{23,26}. Further, ¹⁸F-NaF provides an excellent opportunity to study bone turnover and repair in non-oncologic musculoskeletal disorders such as metabolic bone diseases, arthritic diseases and fracture healing^{23,27}.

While PET imaging is unmatched for molecular imaging, it needs the assistance of higher-resolution, anatomic information to localize these physiologic processes. It is most often combined with CT imaging, which is able to provide not only high resolution anatomic detail but also attenuation correction information for acquired PET data²⁸. While PET/CT has become essential for evaluation of oncologic disease, its utility as a stand-alone modality for characterization of musculoskeletal disease (including cancers) has been limited, largely due to the unparalleled soft tissue contrast of MRI.

New integrated PET-MRI systems potentially provide a complete imaging modality for musculoskeletal imaging, combining simultaneous molecular and physiologic information from PET with the high spatial resolution and soft tissue contrast information of MRI to provide a superior level of anatomic and functional information. Other comparative advantages of PET-MRI include no additional ionizing radiation for anatomic localization and the ability of MRI to provide supplementary functional information such as DWI. Hybrid PET-MRI can enhance imaging capabilities and efficiency for clinical examinations of malignant musculoskeletal disease and offer new opportunities to incorporate the molecular capabilities of nuclear imaging into studies of non-oncologic musculoskeletal disease.

Applications of PET-MRI in Oncologic Musculoskeletal Disease

Bone and Soft Tissue Sarcomas

Bone sarcomas (BS) and soft tissue sarcomas (STS) represent a rare and heterogeneous group of mesenchymal-derived malignancies, accounting for approximately 1% of adult cancers. Imaging plays a pivotal role in the diagnosis, staging, and restaging of these tumors. Therapy is typically multimodal and includes surgery, radiation therapy, and both cytotoxic and targeted chemotherapy.

Staging BS and STS relies upon a multi-faceted approach. MRI is the gold standard modality for assessing T-stage given its excellent soft tissue contrast, high spatial resolution, and multiplanar capability. It is critical in preoperative and radiation planning, depicting tumor relationship to neurovascular structures, fascial planes, muscular compartments, and

adjacent joints^{29–31}. Interestingly, a retrospective study examining the diagnostic accuracy of FDG PET/CT and conventional imaging (including MRI) of a heterogeneous cohort of 117 BS and STS showed slightly better T-staging by FDG PET/CT (overall accuracy 96%) compared to conventional imaging (94% accuracy)³². FDG PET has also been shown to help identify tumor-free surgical margins prior to surgical resection³³. Therefore, combined PET-MRI may confer some advantage in T-staging compared to standalone MRI.

The addition of novel MRI techniques like DWI with apparent diffusion coefficient (ADC) mapping, dynamic contrast enhancement (DCE), and MRS may improve diagnostic accuracy compared to conventional MRI^{30,34,35}. Combining these with metabolic measures such as standardized uptake values (SUV), total lesion glycosynthesis (TLG), and metabolic tumor volume (MTV) provides powerful multiparametric evaluation. Indeed, the combination of metabolic and spectroscopic evaluation on FDG PET-MRI has been explored in STS³⁶, and a radiomics model combining texture features from FDG PET-MRI has been used to identify factors most predictive of lung cancer metastases in 51 patients with extremity STS³⁷.

Additional benefits of adding localized PET evaluation to MRI for primary BS and STS assessment include prognostication and guiding biopsy. Baseline BS and STS FDG activity has been shown to independently predict survival in several studies^{38–42}. More recently, two larger meta-analyses have confirmed the prognostic value provided by baseline PET/CT in BS and STS⁴³. Dedicated PET evaluation of the primary lesion may also allow sampling of the most FDG avid and highest-grade areas of tumor⁴⁴. This can be especially critical in large and high-grade sarcomas, which may exhibit extensive necrosis and heterogeneity, and thus be prone to nondiagnostic biopsy or undersampling (Fig. 1).

Although BS and STS sarcomas most commonly metastasize to the lungs⁴⁵, retroperitoneal and visceral sarcomas may hematogenously spread to the liver, myxoid liposarcomas have a propensity for bone (especially spine) and soft tissue metastases, and several STS including synovial sarcoma and rhabdomyosarcoma have a predilection for nodal metastases⁴⁶. The metabolic information afforded by FDG PET/CT has been shown to confer superior sensitivity to conventional imaging (CI) techniques for detecting nodal metastases (N-stage), in both BS and STS^{47,48}. It has also proven superior in detecting distant metastases (M-stage)^{47,48}, and shown to upstage both Ewings's sarcoma and osteosarcoma patients relative to CI⁴⁹. However, high-resolution chest CT has higher sensitivity for detecting pulmonary metastases^{50,51}, particularly those less than 1 cm⁴⁸, and therefore diagnostic chest CT will remain an essential component of sarcoma staging and follow-up.

A recent study examined the role of FDG PET-MRI in staging of 29 BS and STS patients. T and M stage was identical for PET-MR and CI in all patients. One patient with a thoracic wall rhabdomyosarcoma was found to have N1 disease on PET-MRI versus N0 on CI, but this did not alter therapy. In the remaining 28 patients, PET-MRI and CI yielded identical N stage. ROC analysis for distant metastasis detection showed a sensitivity of 97.8% and specificity of 100% for PET-MRI, compared to 94.4% and 100% for CI, but this was not statistically significant ($p = 0.51$). A number of additional case series and pilot studies have also shown benefit of PET/MRI in evaluating STS^{52–54}.

There are clear advantages to combined PET and MRI for therapy response assessment and disease monitoring. The utility of FDG PET for response assessment after chemotherapy has been demonstrated for both STS⁵⁵ and BS⁵⁶, and quantitative ADC analysis has been used to assess response on MRI^{34,35}. While it seems intuitive that combining PET and MRI would be additive or perhaps synergistic in determining treatment response, early studies have shown discordant results between PET and MRI measures^{57,58}, and further study is needed to examine the role of integrated PET-MRI in assessing therapy response.

Evaluation of local recurrence on MRI in the post-treatment setting may be hindered by signal abnormality and enhancement within the operative bed, and FDG PET can show inflammatory uptake in the same regions. Integrated PET-MRI has been recently shown to have benefit compared to MRI alone for the identification of locally recurrent soft tissue sarcomas. In a study of 41 patients with clinically suspected sarcoma recurrence, the sensitivity, specificity, and diagnostic accuracy for detecting local recurrence was 82%, 86%, and 83% for MRI, versus 96%, 79%, and 90% for PET-MRI, respectively ($p > 0.05$). Further, PET-MRI showed higher confidence levels ($p < 0.05$) for delineating malignant lesions⁵⁹. Earlier studies have shown FDG PET to have similar sensitivity and increased specificity compared to conventional imaging in recurrent osteosarcoma and Ewing's sarcoma⁶⁰, and equal accuracy in assessing locally recurrent and distant metastatic disease in pediatric sarcoma patients⁶¹. Future prospective studies are expected to define the role of integrated PET-MRI in the post-therapy setting. In conclusion, FDG PET-MRI for BS and STS is useful for providing prognostic information, guiding biopsy, and staging disease during initial evaluation, helpful in identifying local recurrence, and holds promise for assessing treatment response.

Multiple Myeloma

Multiple myeloma (MM) is a hematologic malignancy of plasma cells characterized by bone marrow infiltration and immunoglobulin overproduction. In the revised 2014 International Myeloma Working Group (IMWG) criteria, diagnosis requires evidence of clonal marrow plasma cells $\geq 10\%$ or biopsy-proven plasmacytoma and one or more myeloma-defining events, which include CRAB features (hypercalcemia, renal insufficiency, anemia, one or more osteolytic bone lesions $> 5\text{mm}$) or specific biomarkers including clonal bone marrow plasma cells $\geq 60\%$, serum free light chain ratio ≥ 100 , or more than one marrow replacing lesion $> 5\text{mm}$ on MRI⁶². Therefore, imaging plays a key role in diagnosing active MM, although it is not strictly needed for the diagnosis.

Cross sectional imaging is preferred for detection of bone lesions in patients with suspected myeloma, and one of three modalities can be used depending on availability, cost, and/or institutional preference: whole body low dose CT, whole body MRI (WBMRI), or FDG PET/CT. The most recent IMWG consensus guidelines endorse MRI as the gold standard for imaging the axial skeleton, evaluating painful lesions, and for distinguishing benign from malignant compression fractures. It is recommended for the work-up of solitary bone plasmacytoma, and the IMWG recommends whole-body MRI, or spine and pelvic MRI at minimum, in all patients with smoldering or asymptomatic myeloma⁶³. ¹⁸F-FDG PET/CT should be used to confirm a diagnosis of solitary plasmacytoma if whole-body MRI is

unavailable, and to differentiate between smoldering and active myeloma, if whole-body x-ray is negative and WBMRI is unavailable. FDG PET/CT is also the preferred functional imaging modality to evaluate and monitor therapy⁶⁴. There is no current consensus statement on the use of FDG PET-MRI in myeloma patients from the IMWG, but it has been incorporated into the diagnostic algorithm at several institutions⁶⁵.

MRI has been proven to be more sensitive in depicting MM lesions than radiographs, except for rib lesions⁶⁶. Up to 50% of patients with a normal radiographic skeletal survey have lesions depicted on MRI^{67,68}. On MRI, myelomatous lesions appear as T₁ hypointense areas of marrow replacement, with increased signal on T₂ or short tau inversion recovery (STIR)-weighted images. Five patterns of marrow involvement have been recognized: normal, focal, diffuse (homogenous or heterogeneous), variegated (also referred to as “salt and pepper”), or a combination thereof⁶⁷. Importantly MRI depicts marrow infiltration and replacement, while radiographs and CT illustrate osseous destruction, and because of this MRI has superior detection of bone marrow involvement compared to LDWBCT or PET/CT, with a specific advantage in the diffuse patterns of involvement^{69–71}. Incorporation of DWI results in superior lesion conspicuity compared to conventional STIR and contrast-enhanced MRI^{72,73}, and ADC values can be used with excellent accuracy (90% sensitivity and 93% specificity) to differentiate diseased and normal marrow⁷⁴. Quantitative ADC analysis has shown particular value in determining diffuse involvement; a bone marrow ADC greater than $0.548 \times 10^{-3} \text{ mm}^2/\text{sec}$ has been shown to be 100% sensitive and 98% specific for diagnosing a diffuse marrow pattern⁷⁵.

MRI also confers prognosis; the presence of more than one focal lesion on MRI is an independent predictor of progression to symptomatic disease and development of osteolytic bone lesions^{76,77}. The diffuse pattern of involvement has been correlated with worse prognosis, greater burden of disease, and high-risk cytogenetics^{78,79}. MRI’s ability to demonstrate focal and diffuse disease and the quantitative potential of ADC hold promise for monitoring treatment response. Positive response on conventional MRI sequences includes decrease in size and/or number of focal lesions, normalization of a diffuse pattern, and in focal lesions, the appearance of a peripheral halo of T₁ hyperintense fatty marrow, or complete fatty replacement, also called fatty metamorphosis. It has been also been shown that mean ADC increased in 95% of MM responders and a 3.3% ADC increase resulted in 90% sensitivity and 100% specificity in detecting positive treatment response⁸⁰, which has been supported by other studies⁷⁴.

Like MRI, FDG PET/CT is more sensitive than radiographs^{67,68,70}, and performs equally well to MRI in detecting focal lesions, but is inferior for detecting diffuse disease^{67–71}. Some studies have shown correlation between SUVmax on PET/CT and bone marrow cellularity and plasma cell ratios on bone marrow biopsy sample⁸¹. PET/CT also has excellent ability for detecting extramedullary disease (EMD)⁸², which is important given that approximately 10% of MM patients will develop EMD during the course of their disease⁸³.

The prognostic value of FDG PET/CT is better established than MRI. The presence of three or more lesions is an independent predictor of overall survival (OS)⁸⁴, while a SUVmax of

greater than 4.2 and presence EMD adversely affect progression free (PFS) and OS⁸⁵. A positive PET/CT has also been associated with quicker progression of smoldering myeloma to active myeloma⁸⁶. Interestingly, some studies have shown higher probability of progression if focal FDG avid lesions also exhibit osteolysis⁸⁷, while others have not shown osteolysis on PET/CT to be predictive⁸⁶. Despite this, the updated IMWG guidelines necessitate the presence of osteolysis to make the diagnosis of active disease on PET/CT⁶². The benefit of FDG PET/CT in assessing treatment response was well-demonstrated in a recent meta-analysis combining 10 studies involving 690 myeloma patients⁸⁸. PET/CT may demonstrate disease response earlier than MRI, as resolution of FDG activity is typically seen before MRI signal normalization^{89,90}. A negative PET/CT after therapy is an independent predictor for prolonged PFS and OS in patients with complete response⁹¹.

The literature detailing PET-MRI performance in multiple myeloma is limited. A study comparing WBMRI and PET/CT in assessment of active disease in MM found better sensitivity and specificity for MRI, but noted that when used in combination, PET and WBMRI were found to have a specificity and positive predictive value of 100%, heralding a role for integrated PET/MRI⁹². Another study showed equivalency of PET/CT and PET-MRI for detection of myeloma lesions in 30 patients; finding 94% of focal lesions identified on the PET portion of PET/CT were also seen on the PET portion of PET-MRI. PET-MRI missed rib lesions that were seen on PET/CT evaluation, not surprising given that WBMRI has documented limitations in evaluation of skull, ribs, and clavicles⁶⁶. In conclusion, PET-MRI in multiple myeloma shows vast potential given the high accuracy of both PET/CT and MRI to detect focal lesions, MRI's advantage in diffuse disease, prognostic information afforded by both, and PET's well-evidenced ability to determine response to therapy. In our personal experience, PET-MRI has been helpful in cases of diffuse disease, better depicted on MRI than PET (Fig. 2), and also in showing resolution of FDG activity in responding lesions before resolution of signal abnormality on MRI (Fig. 3).

Bone Metastases

The skeleton is one of the most frequent sites of metastatic disease, most commonly from breast and prostate cancer⁹³. Accurate detection is critical given the reduced patient survival and differing treatment strategies associated with presence of osseous metastases⁹³. Both PET/CT and MRI have excellent accuracy for detecting osseous metastases, with one meta-analysis showing overall sensitivity of 98% with PET/CT and 95% with MRI⁹⁴. Other meta-analyses have shown equivalency of PET and MRI⁹⁵, including comparison of PET and MRI with DWI⁹⁶.

A few studies examining the role of FDG PET-MRI in bone metastasis have been performed. A study comparing FDG PET-MRI and PET/CT in 67 oncology patients with a spectrum of primary malignancies found higher detection of osseous metastases for PET-MRI (100%) versus PET/CT (94%), especially in small lesions⁹⁷. Lesion conspicuity was high for both modalities, but greater on PET-MRI ($p < 0.05$). However, this may have been in part because of greater uptake time on PET-MRI (152 minutes) vs. PET/CT (60 minutes). A separate study examined sequential FDG PET/CT and PET-MRI in 24 oncology patients and found similar overall detection rates but higher reader confidence with PET-MRI vs. PET/CT⁹⁸. In

a study of 109 patients with breast cancer undergoing same-day contrast enhanced FDG PET/CT and PET-MRI, PET-MRI demonstrated superior sensitivity (96% vs. 85%), and was positive in 12% of patients deemed negative for osseous metastasis on PET/CT⁹⁹. A retrospective study comparing ⁶⁸Ga-PSMA PET/MRI and PET/CT in prostate cancer showed 100% concordance between PET-MRI and PET/CT in evaluating bone metastases, but overall higher conspicuity of bone lesions on MRI compared with CT ($p < 0.006$)¹⁰⁰. In conclusion, PET/MRI has excellent diagnostic performance in evaluating osseous metastases, and there is growing evidence of an advantage compared to PET/CT given increased lesion conspicuity and reader confidence with PET-MRI.

Applications of PET-MRI in Non-Oncologic Musculoskeletal Disease

Osteoarthritis (OA)

Osteoarthritis (OA) is a leading cause of pain and disability, and is characterized by degeneration of joint tissues¹⁰¹. There is tremendous effort towards understanding OA and development of drugs to address both the causes and symptoms of disease. These endeavors are often undermined by a lack of non-invasive tools to detect early and reversible disease changes. Further, there is increasing evidence that OA is a disease of the whole joint with numerous phenotypes, suggesting that reliable biomarkers are necessary for better understanding, prevention, diagnosis, and treatment of OA.

MRI provides an excellent opportunity to non-invasively study the complex disease processes involved in OA¹⁰². In addition to its excellent high-resolution and multi-contrast morphologic information of joint tissues, advanced quantitative MRI techniques may provide important information about tissue microstructure such as collagen matrix organization, glycosaminoglycan (GAG) content, and hydration, which is thought to degrade before structural changes are seen with conventional imaging methods^{103,104}.

PET imaging with ¹⁸F-NaF provides a method to assess subchondral bone activity in OA. Functional imaging of subchondral bone is vital, as this is the only highly vascularized tissue in the joint and has the ability to reflect rapid changes. Further, increased bone remodeling has been implicated as a mechanism of OA progression that affects not only bone but also adjacent tissues^{105,106}. The gold standard for assessment of bone remodeling with bone biopsy is costly, invasive, and spatially limited. Measurement of biochemical markers of bone resorption and formation in the serum or urine is limited to global changes. Bone activity measured with ¹⁸F-NaF has been shown to correlate with bone histomorphometry²⁵. Early studies in OA patients showed uptake of ¹⁸F-NaF was significantly increased in hip joints which had bone abnormalities on separately performed MRI¹⁰⁷. Further, the uptake of ¹⁸F-NaF in the patellofemoral compartment of the knee has been shown to correlate with the presence of patellofemoral pain¹⁰⁸.

Simultaneous ¹⁸F-NaF PET-MRI has shown promise for comprehensive whole-joint imaging. A feasibility study in patients with knee pain or prior knee injury showed that the ¹⁸F-NaF PET uptake in subchondral bone marrow lesions (BML), osteophytes, and sclerosis identified on MRI was significantly higher than that of normal appearing bone on MRI (Fig. 4a). Furthermore, a correlation was observed between BML and osteophyte grades based on

the MRI Osteoarthritis Knee Score (MOAKS) and SUV_{max} in those lesions. Of interest, more than half of small, grade 1 osteophytes identified on MRI, often described as the earliest morphologic sign of OA, did not correlate with high ^{18}F -NaF uptake (Fig. 4b)¹⁰⁹. This observation suggests that ^{18}F -NaF PET provides a quantitative measure to characterize degenerative lesions and understand which play a more important role in the progression of OA. Importantly, 37% (63/172) of high uptake regions on ^{18}F -NaF PET had no correlative abnormality on MRI (Fig. 4c). Further, in patients with unilateral, reconstructed anterior cruciate ligament (ACL) tears within the last 10 years, who have a known increased risk for developing accelerated OA, significantly increased ^{18}F -NaF PET uptake was observed in the subchondral bone of ACL-Reconstructed knee joints, compared with their uninjured contralateral knees¹¹⁰. As molecular changes often precede changes at the tissue level, these findings suggest increased bone activity detected with ^{18}F -NaF PET may serve as a marker for early OA in this population.

Another benefit of hybrid PET-MR imaging of OA is that it uniquely allows the simultaneous evaluation of not only early mechanisms of disease, but also spatial relationships between them and across tissues. Current whole-joint assessments of OA with MRI largely rely on semi-quantitative scoring systems, which subjectively evaluate tissue structures¹¹¹. In a study of mild to moderate OA patients, increases in cartilage $T_{1\rho}$ relaxation times, which are associated with a loss of cartilage GAG content, were correlated with increased ^{18}F -NaF uptake in the adjoining bone as well as reduced uptake in the nonadjoining compartments¹¹². In a separate study of patients with unilateral, reconstructed ACL tears, a correlation was observed between increased ^{18}F -NaF uptake measures of bone remodeling and increased T_2 values in adjacent cartilage, which is indicative of early collagen matrix breakdown¹¹⁰. This correlation was particularly pronounced in the deep layers of cartilage adjacent to the subchondral bone. This supports an interdependent relationship between bone and cartilage with early degenerative changes in one tissue having an effect on the neighboring tissue.

In addition to ^{18}F -NaF, FDG has been used to study the role of inflammatory processes in OA pathogenesis. In particular, FDG has been applied to study synovitis and the inflammatory component of BMLs in OA. A diffuse increase in FDG uptake was seen in OA patients compared to healthy age-matched controls, which the authors attributed to the presence of synovitis in OA^{113,114}. While contrast-enhanced MRI is often used to detect synovitis, FDG offers a tool for early detection and quantitative characterization of inflammation in the synovial membrane. BMLs, which are identified as regions of increased bone marrow signal on fat-suppressed T_2 -weighted fast spin-echo MRI images, are associated with OA pain and disease progression, but their etiology is difficult to evaluate. The combination of PET and MRI offers a unique combination to identify BMLs and characterize their molecular composition. Preliminary PET-MRI evaluation of BMLs in patients with prior knee injury or knee pain showed that BMLs identified on MRI had high ^{18}F -NaF uptake and negligible increased FDG uptake relative to normal-appearing bone¹⁰⁹ (Fig. 5). This suggests that BMLs in OA are not primarily driven by inflammatory processes. However, further studies are necessary to validate these findings and evaluate the longitudinal progression of molecular processes in these lesions.

In summary, PET-MRI offers a new paradigm for imaging of OA pathogenesis; offering simultaneous acquisition of multiple markers of early disease process across all joint tissues. This can provide new insights into OA pathogenesis and help objectively evaluate the efficacy of new disease modifying therapies.

Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a painful inflammatory autoimmune disease characterized by systemic inflammation, and destruction of articular and periarticular tissues. Conventional radiography has long been used to detect structural changes, including osseous erosions and joint space narrowing. However, new targeted disease modifying anti-rheumatic drugs (DMARDs) have revolutionized treatment of RA by aiming for sustained remission of disease. This has shifted strategies for management of RA from symptom relief to early institution of disease-modifying therapy to prevent structural damage and disability¹¹⁵. Patient outcomes are thus tied to the timing of expensive but powerful therapy. As a result, new imaging methods capable of detection and treatment monitoring of early inflammatory and cellular changes in RA offer the ability to change clinical management of these patients.

MRI is a power tool for detection and treatment of RA. MRI can detect soft tissue and bone marrow affected by inflammation before development of structural lesions seen on radiography or CT. Further, contrast enhancement with intravenous gadolinium can effectively detect synovitis, bursitis, tenosynovitis, osteitis, and bone erosions and differentiate active inflammation. MRI has shown efficacy for disease confirmation when conventional methods were inconclusive, which is vital to optimize initiation of DMARD treatment and maximize long-term outcomes¹¹⁶. MRI can also provide prognostic information. In particular, BMLs detected with MRI are strongly correlated with future radiographic finding of RA and progression on MRI¹¹⁷. For patients undergoing RA therapy and those in remission, MRI scoring systems that evaluate RA features show great potential for monitoring disease, particularly for risk stratification when considering options for tapering biologic therapy¹¹⁸.

FDG PET is able to quantitatively image elevated glucose utilization in cells mounting an immune response and thus offers a quantitative and more sensitive method for evaluation of the joint inflammation and synovitis that are the hallmarks of RA. FDG uptake has been correlated with disease activity and C-reactive protein levels in RA patients¹¹⁹. Further, it has been used to evaluate the extent of whole body involvement in RA¹²⁰, clinical outcomes, and treatment efficacy in early RA patients undergoing DMARD therapy¹²¹. In addition to FDG PET, additional PET tracers may offer new molecular targets with greater sensitivity to inflammation. For example, ¹¹C-choline can target cellular proliferation¹²² while ¹¹C-(R)-PK11195 targets proteins on activated macrophages and may offer more specific molecular marker of inflammation¹²³.

PET-MRI can boost the application of molecular imaging techniques to study RA and improve the clinical utility of imaging in all aspects of disease. PET may provide the most sensitive method for detection and quantitative characterization of inflammation in RA, while MRI provides an optimal technique for musculoskeletal imaging and evaluation of morphologic changes. The feasibility of simultaneous PET-MRI for imaging inflammation

has been demonstrated in early RA of the hand, showing sites of synovitis and tenosynovitis on contrast-enhanced MRI that corresponded to increased uptake on FDG PET (Fig. 6)¹²⁴. This multi-modality approach can potentially change the clinical approach for evaluation of RA; using imaging markers of inflammation as a treatment target and for clinical evaluation of disease remission.

Imaging of Pain Generators

Neuropathic pain is a debilitating pain symptom secondary to neural damage in the somatosensory nervous system¹²⁵. It often accompanies significantly amplified pain responses to mildly painful stimuli, non-painful stimuli, or no stimuli at all. About 10% of the general population in the U.S., corresponding to 15.7% of total pain patients, was estimated to have some form of neuropathic pain in a recent survey¹²⁶. For locating the causative nerve damage of neuropathic pain, electromyography and nerve conduction studies are most widely used. Unfortunately, these tests entail painful, invasive needle electrode placement, and the test outcome is strongly subject to the practitioner's skills¹²⁷. MRI has increasingly gained attention as an alternative diagnostic method to non-invasively identify a variety of nerve damage¹²⁸. However, the detected structural nerve abnormalities are often very subtle or can be even irrelevant to the pain symptom¹²⁹. Therefore, there is a pressing need for non-invasive diagnosis with improved sensitivity and specificity to identify sources of neuropathic pain.

FDG PET-MRI has shown promising results in diagnosis for neuropathic pain. The main assumption of this approach is that the neuroinflammatory process in the painful nerve lesion may result in hypermetabolic activity, presenting as focally high FDG uptake in the PET image. Here, co-registration of the PET image with high-resolution MRI facilitates identification and localization of increased FDG uptake within nerve tissues. An animal study validated this assumption with a rat-model experiment by demonstrating significantly increased FDG uptake at the site of spared-nerve injury compared to the contralateral side and controls¹³⁰. The feasibility of FDG PET-MRI for human study was recently demonstrated with chronic sciatica patients. Sciatica is one of the most common neuropathic pain sources, characterized by radiating pain from the lower back to lower extremities along the sciatic nerve. Spinal nerve impingement by a herniated disc is the most likely cause of sciatica, but it is a structural abnormality with a very high false-positive rate, frequently observed in asymptomatic subjects as well¹²⁹. FDG PET-MRI results showed the sensitivity of FDG to neuroinflammation at the site of the impinging spinal nerve (Fig. 7). Joint analysis using FDG uptake and morphologic MRI features demonstrated potential for detecting non-spinal sources of sciatica and ruling out nerve root impingements irrelevant to the patient's symptoms.

A careful analysis is required to correlate increased FDG uptake with neuropathic pain sources, because there can be many non-pain-related factors that cause elevated FDG uptake. A more specific radioligand, 18F-FTC-146^{131,132}, was recently introduced for PET-MRI with improved specificity to pain. 18F-FTC-146 (6-(3-[18F]fluoropropyl)-3-(2-(azepan-1-yl)ethyl)benzo[d]thiazol-2(3H)-one) specifically binds to sigma-1 receptors, a transmembrane protein that becomes increasingly expressed in the nervous system with

many neurological diseases that cause neuropathic pain^{132,133}. An in-vivo animal study showed the increased uptake of 18F-FTC-146 at the site of nerve injury¹³², demonstrating its feasibility as a neuropathic pain marker. The biodistribution and radiation dosimetry of 18F-FTC-146 in human controls were presented to validate its safety and stability for PET-MRI on human subjects¹³⁴. The recent application of 18F-FTC-146 PET-MRI to patients with complex regional pain syndrome showed that the imaging findings altered the pain management plan for 7 out of 8 patients, and change of therapy in two patients achieved a considerably improved pain-relief outcome¹³⁵.

In conclusion, PET/MRI for neuropathic pain has demonstrated promising results in detection of causative nerve damage, which has altered pain management and achieved better patient outcomes. Novel pain-specific PET tracers can further improve identification of pain generators, allowing PET-MRI imaging to serve as a valuable diagnostic method for challenging neuropathic pain cases when conventional diagnostic methods have been exhausted.

Osteoporosis and Metabolic Bone Diseases

Metabolic bone diseases, such as osteoporosis, osteomalacia, and Paget's disease affect bone strength and result in fractures and bone deformities if left untreated. Clinical assessment in these diseases are aimed at evaluation of bone structure and bone mass to understand the risk of future fractures. Digital X-ray radiogrammetry (DXR) and dual energy X-ray absorptiometry (DEXA) are the most common clinical imaging tests to evaluate bone mass in these subjects, but do not provide information regarding bone architecture, quality, and turnover which are critical features for understanding bone strength.

Measurement of regional bone metabolism with ¹⁸F-NaF PET is appealing to study the metabolic imbalance in bone formation and resorption that may underlie metabolic bone disorders. ¹⁸F-NaF PET uptake in women has been shown to positively correlate with age in the humeral shaft and negatively correlate with age in the lumbar spine, with significant differences in uptake in both regions observed between pre- and postmenopausal women¹³⁶. ¹⁸F-NaF PET has also been applied to evaluating therapeutic efficacy in osteoporosis. Kinetic modeling of ¹⁸F-NaF PET uptake in 18 women with osteoporosis showed an increase in bone mineralization after 6 months of treatment with Teriparatide, an anabolic agent that increases bone density and reduces the risk of fragility fractures¹³⁷. The increase in uptake varied regionally, with the largest response to treatment seen in the femoral shaft and the smallest observed in the spine. The authors interpreted these findings as teriparatide having a greater effect in formation of cortical bone than trabecular bone, given the greater proportion of cortical bone in the femur and trabecular bone in the spine. These findings are in conflict with previous studies of bone densitometry, and highlight the potential for PET to evaluate regional changes of bone turnover and provide biomarkers in metabolic bone disease.

CT is appealing for studying metabolic bone disorders due to its high-resolution contrast of bone architecture and ability to provide quantitative information about bone mineral density. However, MRI may offer a more optimal modality for studying fracture risk and high-resolution morphologic imaging to pair with nuclear medicine techniques. While direct

imaging of bone is challenging with MRI, the trabecular microstructure and volume can be accurately measured from signal void in high-signal-intensity fatty bone marrow¹⁵. Additionally, MRI can better visualize bone marrow and can differentiate between red and yellow marrow. Recent work that applied ¹⁸F-NaF PET and MRI sequentially to image the femoral neck showed that FDG uptake was dependent on the composition of bone marrow¹³⁸. This is particularly interesting as yellow bone marrow contains mesenchymal stem cells that can differentiate into osteoblasts and directly affect bone metabolism. In addition to morphology and bone marrow composition, MRI can quantitatively evaluate cortical bone water content as a surrogate of bone porosity¹³⁹. uTE MRI measures of cortical bone water have been correlated to measures of bone quality and strength in bone specimens and has been used to show that cortical bone pore water increases in populations with increased fracture risk¹⁴⁰. In summary, PET-MRI provides complementary information which can improve quantitative assessment of bone strength and prediction of fracture risk in characterization of disease and evaluation of therapeutic efficacy.

Osteomyelitis and Spondylodiscitis

Simultaneous PET-MRI may also provide superior diagnostic capabilities in suspected osteomyelitis and spondylodiscitis. Accurate and timely diagnosis of these infections is critical as antibiotic therapy can be curative and prevent bone or spinal deformity, neurologic deficits or amputation¹⁴¹. As the typical clinical presentation of osteomyelitis and spondylodiscitis is usually heterogeneous and non-specific, imaging often plays a crucial role in diagnosis and characterization of disease. Similar to the previously discussed applications, the superior contrast in bone marrow, vertebra, intervertebral discs, and neural structures have made MRI the current imaging method of choice to confirm suspected bone or spinal infection. However, presence of edema on MRI, usually seen as high signal on T₂-weighted sequences or after injection of intravenous contrast, may lack specificity in osteomyelitis.

FDG PET can be utilized to differentiate between active inflammation and degenerative changes seen on MRI, thereby improving specificity. In a retrospective study of patients who underwent both MRI and FDG PET for a suspected diagnosis of osteomyelitis, a simulated imaging strategy showed that if PET or MRI was equivocal for osteomyelitis, the addition of the other modality resulted in the correct diagnosis¹⁴². Further, recent work showed that simultaneous FDG PET-MRI significantly increased diagnostic certainty for detection of spondylodiscitis in patients with inconclusive clinical or MRI findings (Fig. 8)¹⁴³. In that prospective study of 30 patients, simultaneous ¹⁸F-FDG PET-MRI improved the sensitivity from 54% to 100% and the specificity from 71% to 88% compared to MRI alone. MRI included pre- and post-contrast standard MRI spine sequences and histopathology or clinical follow-up were used as a reference standard. In this study, neither the C-reactive protein level nor the leukocyte count showed any relationship to the reference standard diagnosis of spondylodiscitis. In conclusion, PET-MRI in osteomyelitis and spondylodiscitis shows promise for improved diagnostic certainty to allow for earlier initiation of treatment and improved clinical outcomes in these patients.

Other Non-Oncologic Musculoskeletal Applications

PET-MRI has been applied to study muscle activation¹⁴⁴. FDG PET, which measures glucose uptake and is thus sensitive to muscle metabolism and activity, was used as a reference standard to study the relationship between T₂ relaxation time changes and glucose uptake in skeletal muscle after exercise. Simultaneous acquisition of PET and MRI data allowed for analysis of the two quantitative measures following the same exercise paradigm on the same time course, which would not have been possible with sequential scanning. Thus, integrated PET-MRI systems are necessary for dynamic imaging of acute changes in physiology with both modalities. Further, PET-MRI presents an excellent opportunity to use the superior molecular sensitivity of PET to validate functional MRI methods that may offer higher resolution and applicability without ionizing radiation.

PET-MRI has also been applied to the diagnosis of stress fractures. Stress fractures are common overuse injuries in athletes that result from abnormal increased stress on normal bone. Radiographs have poor sensitivity to stress fractures and positive findings may take several weeks to months to appear. MRI can detect bone marrow edema well in advance of changes on radiographs, differentiate fractures from soft tissue injuries, thus becoming an important imaging for stress fractures. PET imaging with ¹⁸F-NaF can detect increased bone turnover at the site of new bone formation around a stress fracture within a few days after onset of symptoms and thus offers optimal sensitivity to detect the earliest signs of stress fractures. PET-MRI was shown to be useful for diagnosis of stress fractures and stress reactions in cases where no pathological findings were present on X-ray (Fig. 9)¹⁴⁵. A separate study in patients with foot pain of unclear cause showed that in cases of stress fracture, PET-MRI performed better than PET/CT due to earlier depiction of T₁-weighted MRI changes than changes on CT, which provided higher diagnostic confidence¹⁴⁶. Overall, the authors saw that ¹⁸F-NaF PET-MRI provided more diagnostic information and higher diagnostic confidence compared with PET/CT for evaluation of foot pain of unclear cause. This was largely attributed to diagnostically relevant findings from soft-tissue and bone marrow pathology on MRI. The authors also showed a high correlation between SUV measurements of PET-MRI and PET/CT, demonstrating that PET-MRI is technically feasible and robust.

Technical Considerations and Challenges

Technical advancements in solid state photodetectors that are MRI-compatible have made integrated PET-MRI systems possible^{5,147}. There are several commercially available PET-MRI scanner including sequential and now more common, integrated designs. All of these systems use 3 Tesla static magnetic field strengths for MRI. Current technical considerations and challenges in PET-MRI revolve around correction of attenuation of PET photons using MR images, PET-MRI workflow, and quantification and interpretation of data^{3,5,7,9}. The specifics of these technical considerations in musculoskeletal imaging are discussed below.

MR-Based Attenuation Correction (MRAC)

During reconstruction, PET data needs to be corrected to account for attenuation of photons as they pass through tissue and hardware in order to accurately quantify PET uptake. Unlike

CT, where Hounsfield units can directly be converted to linear attenuation at the PET 511 keV energy level, MRI signal is a function of tissue proton density and relaxation properties and does not relay any direct information about attenuation correction (AC) for PET data. Instead, current commercial MR-based attenuation correction (MRAC) methods primarily use a segmentation-based approach where Dixon fat-water separated images are used to identify soft-tissues and fat, which are then assigned known AC coefficients. However, this still leaves challenges to correct for MRI hardware, bone, and metal implants which affect musculoskeletal imaging but do not have signal on conventional MRI.

Bone—Bone has higher PET photon attenuation than soft tissues but is challenging to account for in MRAC due its short T_2 relaxation time which results in a lack of signal on conventional MRI. Attenuation correction for bone is particularly critical for PET-MRI of musculoskeletal disorders, which either involve direct imaging of bone or imaging of structures in close proximity to bone. Misclassifying bone in AC maps may result in underestimation of PET uptake in and around the osseous structures¹⁴⁸. Atlas-based methods, which account for bone by registering MR images to an anatomic atlas, are commonly used to account for bone in the head but do not completely account for variations in patient bone structure and density⁸. Methods based on uTE or zTE MRI have shown promise to not only offer patient-specific bone morphology, but also to estimate continuous-valued attenuation coefficients for bone¹⁴⁹. Further, new methods have been developed using a deep learning based approach for generating pseudo CT attenuation correction maps from acquired ZTE and Dixon images¹⁵⁰. Data is processed with a convolutional neural network that has been taught to learn spatial patterns and multi-parametric correlations in order to generate a continuous-valued AC map. This method is able to capture variations in bone density, and provides substantial improvements in SUV accuracy near bony anatomy.

MRI Hardware—Attenuation correction (AC) for MRI coils is a new challenge for PET quantification that came with the introduction of hybrid PET-MRI systems^{151,152}. The presence of MRI hardware components leads to considerable attenuation of the PET signal¹⁵³. Rigid and stationary MR hardware components with known positions, such as the patient table and fixed rigid coils are commonly corrected for using AC templates of these parts at their known positions⁷. However, flexible radiofrequency (RF) coils are currently disregarded in commercial MRAC as their position and individual geometry are unknown in patient scans. These flexible arrays are commonly used in MSK imaging. Large flexible arrays are employed for body or pelvis exams as well as for efficient whole-body scanning while small flexible extremity coils are optimal for MRI and PET-MRI of the joints. New methods have shown the feasibility of using MR visible markers¹⁵⁴, 3D cameras¹⁵⁵, or uTE sequences¹⁵⁶ to detect the position of flexible MRI surface coils, allowing a template CT-based attenuation map of the coil to be localized and registered in the MRAC map. Further, new coil designs specifically for PET-MRI systems aim to reduce PET attenuation from MR hardware while simultaneously improving MR sensitivity¹⁵⁷.

Metal Implants and Arthroplasty—Another challenge in musculoskeletal PET-MRI is artifacts and attenuation from metal implants. Approximately one million total joint arthroplasty (TJA) cases are performed in the U.S. every year¹⁵⁸ and the prevalence of

orthopedic metal implants is increasing. It is thus becoming more common that subjects with metal implants are in need of PET and/or MRI scans, either directly due to complications involving the implant or unrelated pathology in its vicinity. Recent multi-spectral MRI acquisition techniques for metal artifact correction have greatly advanced MRI investigation of patients with metallic implants^{159,160}. For PET imaging, the metal-induced artifacts in the CT or MRI images used to derive the PET attenuation coefficient map results in errors in the reconstructed PET uptake maps (Fig. 10). Additionally, for MRI, the large attenuation from the implant itself is ignored. A reconstruction approach jointly estimating the attenuation coefficient map and radioactivity showed promise for mitigating the tracer quantification errors in PET near metallic implants¹⁶¹. Adoption of metal-artifact-corrected MRI images was introduced to generate a more accurate attenuation coefficient map near metallic implants for the PET image reconstruction^{162,163}. Further, phantom experiments demonstrated that classification of metal and soft tissues using MRI could be feasible, achieving significant correction for the underestimation of the PET tracer uptake¹⁶⁴.

MRAC Conclusion—MRAC methods have progressed substantially in the last five years since the advent of integrated PET-MRI systems. While many of the advanced methods mentioned above are still not widely available or have been developed for a specific anatomy or pathology, there is an encouraging trend towards incorporation of these techniques in commercially available MRAC methods in the near future.

Workflow Considerations

Hybrid PET-MRI workflow needs to be tailored for each application to optimize data acquisition and is still a work in progress. Scan time is most often constrained by MRI acquisition times. Oncologic studies or imaging of musculoskeletal pain often require 5–8 bed positions for whole-body coverage. This largely limits MRI acquisition time to 3–5 minutes per PET bed. This will often include 1–2 anatomic sequences as well as a mandatory scan for MRAC. As the MRI field-of-view (FOV) in the superior-inferior position can be greater than that of PET bed, MRI sequences can be extended across multiple PET beds to increase the number of MRI contrasts collected. A longer MRI protocol can be used for comprehensive anatomical imaging or for supplemental functional scans such as DWI in specific anatomy of interest but scan time must always be balanced against patient comfort. In contrast, PET-MRI studies where the anatomy of interest is constrained to one PET bed, such as the knee or foot, permit longer MRI protocols. As the entire duration of MRI scan time can be used for PET data acquisition, this allows for a considerable reduction in the injected radiotracer dose. Further, as MRI does not produce any ionizing radiation, PET-MRI can provide a drastic reduction in effective radiation dose to patients, which is vital for imaging of pediatric patients and for the widespread adoption of nuclear medicine techniques for non-oncologic musculoskeletal imaging.

Quantification and Interpretation of PET Uptake

PET imaging is able to provide quantitative information regarding metabolic and molecular processes, but requires an understanding of the tracer uptake mechanisms for proper interpretation. PET uptake is most commonly quantified by using SUV, which measures the tissue activity concentration (in kBq/mL) normalized for the injected activity and the patient

body weight. This method provides the simplest method to express uptake and has been shown to be reproducible and reliable¹⁶⁵. However, SUV provides a semi-quantitative measure of PET radiotracer uptake. As there is only a finite amount of tracer, SUV measurements are affected by the delivery and availability of the tracer at any particular site, and thus can be affected by several biologic and physical factors¹⁶⁶. While SUV has been shown to be effective for detection and characterization of tumors, caution should be taken when comparing SUV between different patient cohorts or in longitudinal evaluation of musculoskeletal disease.

Pharmacokinetic modeling of dynamic PET uptake offers a more quantitative approach to PET image analysis¹⁶⁷. Kinetic modeling requires acquisition of PET list-mode data, usually for 45 minutes or more, immediately after injection of the radiotracer. The PET data is then reconstructed into dynamic frames of varying temporal length, usually shorter frames immediately after injection and longer frames at the end. Lastly, dynamic PET activity is fit to compartmental model to determine rate constants that describe the movement of PET radiotracer between blood, extracellular, and intracellular compartments (Fig. 11). These rate parameters are absolute and can be compared between anatomical regions as well as patient populations. However, compared to static SUV measurements, kinetic modeling of dynamic PET uptake is more challenging, often limited to one PET bed, and requires a considerably longer PET acquisition time. Further, models are dependent on an accurate arterial input function (AIF), a measure of tracer activity in arterial blood¹⁶⁸. Nevertheless, in PET-MRI applications of musculoskeletal disease where one anatomic region is being evaluated and extended scan times are necessary for MRI evaluation, kinetic modeling can provide accurate quantification as well as additional metabolic information. Additionally, PET-MRI may provide an optimal method to calculate an accurate image-derived input function (IDIF). High resolution MR angiography can provide a true arterial volume, which in combination with dynamic PET data, can provide an accurate IDIF that is localized to the anatomy of interest without the time delay and invasiveness that may be present with arterial blood sampling¹⁶⁹.

Conclusion

While widespread application of integrated PET-MRI in musculoskeletal disease is still limited, in part due to the more limited availability of the systems and challenges in workflow and reimbursement, these multimodality systems offer great promise. As MRI is often the imaging modality of choice in many musculoskeletal disorders, and new UTE and ZTE methods provide enhanced visualization of osseous anatomy, it is reasonable that PET-MRI may replace PET/CT in many musculoskeletal exams. This is particularly true for applications where PET/CT and MRI are already performed sequentially as part of clinical care. Further, the addition of molecular PET information to established MRI applications might offer earlier detection, improved sensitivity, and greater specificity in many non-oncologic musculoskeletal diseases. In applications where only one anatomic region is of interest, PET-MRI can be performed with minimal increase in scan time and substantially reduced PET radiotracer dose. While several technical and workflow considerations require further innovation and improvement for accurate and optimized PET-MRI, there is an encouraging trend in recent scientific developments to resolve these limitations. The

remaining challenge for adoption of PET-MRI into routine clinical practice will be demonstration of sufficient benefit to justify the cost and added complexity of these systems.

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Figure 1.

61-year-old female with a large pelvic mass discovered on CT and non-diagnostic biopsies taken during laparoscopic exploration at an outside institution. [a] T₂-weighted fat-saturated (FS) and [b] FS post-gadolinium spoiled gradient recalled (SPGR) images demonstrate a large heterogeneously T₂-hyperintense pelvic mass extending through the right sciatic notch with perilesional edema and extensive central necrosis. [c] Corresponding fused T₂-weighted FS and [d] FS post-gadolinium SPGR FDG PET/MRI images demonstrate intense peripheral FDG activity. An FDG-avid area was targeted during subsequent CT-guided biopsy, with pathology showing a high-grade malignant peripheral nerve sheath tumor.

Figure 2.

54-year-old female with multiple myeloma undergoing staging FDG PET/MRI. [a] Maximum intensity projection PET image shows normal FDG biodistribution throughout the skeletal bone marrow. [b] Sagittal T2-weighted FS MRI image of the thoracolumbar spine shows diffuse T2-hyperintense marrow infiltration, consistent with diffuse involvement by multiple myeloma. [c] Corresponding fused T2-weighted FS PET/MRI image shows only normal low-grade marrow activity throughout the spine. Subsequent bone marrow biopsy demonstrated involvement by 80–90% clonal plasma cells.

Figure 3.

43-year-old woman with multiple myeloma undergoing restaging FDG PET/MRI after chemotherapy. [a] Axial T1-weighted MRI image demonstrated a rounded, T₁-hypointense marrow-replacing lesion in the posterior right iliac bone (arrow). [b] Corresponding fused T₁-weighted PET/MRI image demonstrates no FDG activity within the lesion, consistent with a treated lesion showing resolution of FDG activity prior to normalization of MRI signal.

Figure 4. MRI, ¹⁸F-NaF PET and Fusion images of 3 patients with posttraumatic osteoarthritis. [a] Concordance is seen between a BML (blue arrowhead) and large osteophytes (red diamond arrows) on MRI and high ¹⁸F-NaF Uptake on PET. However, PET was able to provide additional information about metabolic activity in the knee. [b] Many small osteophytes identified on MRI (orange arrows) did corresponded to elevated metabolic bone activity on PET. Further, ¹⁸F-NaF was able to identify areas of increased metabolic activity (magenta line arrows) that appeared unremarkable on MRI. From Ref 109 with permission.

Figure 5.

[a] ^{18}F -NaF and [b] FDG PET overlaid on a T2-weighted, fat suppressed FSE MRI image acquired simultaneously of a 52 yr-old male subject with OA. A large grade 3 BML (blue arrowhead) seen on MRI corresponded to considerably elevated ^{18}F -NaF uptake ($\text{SUV}_{\text{max}} = 26.2$) and only marginally elevated FDG uptake ($\text{SUV}_{\text{max}} = 1.4$) relative to normal appearing bone on MRI. Imaging with multiple tracers may offer a better understanding the etiology of features associated with OA pain and progression such as BMLs. From Ref 109 with permission.

Figure 6.

Axial and Coronal [a] FDG PET, [b] T1-weighted MRI and [c] overlaid fusion images of the hand in early RA acquired on an integrated PET-MRI system. The highest uptake is seen at the palmar portion of metacarpophalangeal joint II which corresponds to synovial thickening and contrast enhancement on MRI. Reprinted by permission from SpringerNature: *Clinical Rheumatology*. (Miese et al. Hybrid 18F-FDG PET–MRI of the hand in rheumatoid arthritis: initial results) (2011)¹²⁴.

Figure 7. Normal FDG PET and MRI patterns of lumbar spine (top row) and abnormal FDG PET and MRI patterns of a sciatica patient with a herniated disc (bottom row). The left sided L4–5 paracentral disc protrusion causes compression of descending L5 spinal nerve (red arrows), showing increased FDG uptake on the site of the nerve compression.

Figure 8.

Simultaneous ^{18}F -FDG PET-MRI of a [a] 71-yr-old and a [b] 59-yr-old patient with suspected spondylodiskitis. In both cases, MRI was inconclusive with typical hyperintense signal alterations on IR-FSE and moderate [a] to poor [b] postcontrast signal on T1-weighted MRI. Fused ^{18}F -FDG PET-MRI images in case [a] showed increased uptake in the suspected discs (blue arrows) which signaled active inflammation and confirmed a diagnosis of spondylodiskitis, while the lack of elevated uptake (red arrows) in [b] excluded active inflammation resulting in a diagnosis of no spondylodiskitis but post fracture changes. This research was originally published in JNM. Fahnert et al. Use of Simultaneous ^{18}F -FDG PET/MRI for the Detection of Spondylodiskitis. *J Nucl Med.* 2016;57:1396–1401.

Figure 9.

[a] X-ray, [b] CT, [c] MRI and [d] ^{18}F -NaF PET-MRI fusion of the ankle of a 58 yr-old female patient. X-ray images were negative while CT show sclerotic lesions in the dorsal calcaneus (*red arrow*) and degenerative changes in the talonavicular region but no signs of acute stress fractures. On MRI, a fracture line in the dorsal calcaneus with little edema is seen, due to an older stress fracture that corresponds to elevated ^{18}F -NaF PET uptake (*red arrow*). Additionally, another stress fracture is shown on PET-MRI in the mediiodorsal parts of the cuboid with bone marrow edema on MRI and elevated uptake on ^{18}F -NaF PET (*dotted arrow*)¹⁴⁵. Reprinted from Cronlein et al. Visualization of stress fractures of the foot using PET-MRI: a feasibility study. *Eur J Med Res* 2015;20:99 under the terms of the Creative Commons Attribution 4.0 International License.

Figure 10.

Challenge of MRAC in a subject with total knee arthroplasty. [a] Source MRI image acquired with the conventional 3D gradient echo sequence, [b] attenuation coefficient (AC) map derived from the source MRI image, and [c] MAVRIC-SL metal artifact reduction MRI image. The severe signal loss artifact in the source MRI image near the metallic knee implant caused misclassification of metal (green arrow), femoral bone (yellow arrow), and soft tissues (red arrow) as air (white arrows) in the derived AC map. The attenuation coefficients of the misclassified materials are much higher than that of air, which can lead to significant underestimation of the tracer uptake in the reconstructed PET image.

Figure 11.

[a] Hawkins compartmental model for pharmacokinetic analysis of ^{18}F -NaF Uptake. [b] Dynamic analysis of tracer distribution (input function (IDIF)) and uptake (time activity curve (TAC)) allows for modeling of tracer kinetics. This permits a quantitative analysis of rate constants that describe bone perfusion (K_1) as well as mineralization (k_3).

Table 1

Select radiotracers for PET imaging of musculoskeletal disease

PET Tracer	Mechanism	Primary MSK Applications	Half-Life	Cyclotron Requirements
^{18}F -FDG	Glucose Metabolism	MSK tumor staging, restaging and evaluation of treatment response, Bone metastases, Inflammation and Infection	109.8 Minutes	Regional
^{18}F -NaF	Calcium Analog	Bone metastases, Bone turnover	109.8 Minutes	Regional
^{68}Ga -PSMA	Binding to PSMA	Metastasis in prostate cancers	68 Minutes	Generator (Cyclotron Independent)
^{11}C -choline	Cell Proliferation	Proliferative changes in arthritic synovium	20.4 Minutes	On-Site
^{11}C -(R)-PK11195	Activated Macrophages	Specificity to active inflammation	20.4 Minutes	On-Site
^{18}F -FTC-146	Binding to Sigma-1 Receptor	Active Neuropathic Pain	109.8 Minutes	Regional