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Applications of PET-CT-MR in the management of benign musculoskeletal disorders

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Synopsis

While CT and MRI alone have been used extensively to evaluate various musculoskeletal disorders, hybrid imaging modalities of PET-CT and PET-MRI have been recently developed. These hybrid systems combine the advantages of each imaging method-molecular information from PET and anatomical information from CT or MRI. Furthermore, different radiotracers can be used in PET in order to uncover different disease mechanisms. In this review, potential applications of PET-CT and PET-MRI for benign musculoskeletal disorders are organized by benign cell proliferation/ dysplasia, diabetic foot complications, joint prostheses, degeneration, inflammation, and trauma, metabolic bone disorders, and pain (acute and chronic) and peripheral nerve imaging.

Keywords

Positron emission tomography-computed tomography (PET-CT); positron emission tomography-magnetic resonance imaging (PET-MRI); musculoskeletal disorders; imaging

Introduction

The advancement of different imaging modalities has allowed further understanding of the musculoskeletal system and its disorders. Imaging methods, such as radiography, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), have different benefits depending on the anatomy and pathophysiology being examined. For example, CT imaging gives detailed structure of cortical and trabecular bone. MRI provides soft-tissue contrast so that bone marrow, muscles, tendons, ligaments, cartilage, and fat can be assessed. Therefore, both CT and MRI provide the needed

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anatomical detail for musculoskeletal assessment. PET imaging provides functional information that CT and MRI cannot through positron-emitting radiotracers, but it is inferior to CT and MRI in regards to spatial resolution (1). Given the complicated manifestation and processes of musculoskeletal disorders, a single imaging method may not be sufficient for understanding a given disorder. Furthermore, there has been a need for earlier detection of musculoskeletal disorders so that treatment and prevention plans can be more effective.

The introduction of hybrid imaging systems, such as PET-CT and PET-MRI, allow for the fusion of the advantages for each single imaging modality so that the complex diseases and disorders of the musculoskeletal system can be better understood. In this review, we give background information on hybrid PET-CT and PET-MRI and how these hybrid modalities can be applied to various musculoskeletal disorders.

PET-CT and PET-MRI

PET-CT scanners have been used in clinical medicine since the early 2000s and combine the molecular information from PET with the high-resolution of CT (2,3). PET-CT has the appeal of obtaining detailed images of the bone and its associated molecular information, which can be useful in musculoskeletal disorders. The radiotracer provides information on glucose or bone metabolism, while the CT provides anatomic localization and detailed bony structure.

PET-MRI systems have been more recently introduced and attempt to combine the advantages that each of the single imaging modalities present for musculoskeletal imaging, much like PET-CT scanners (4,5). PET-MRI utilizes lower radiation doses when compared to PET-CT since the CT exposure component is eliminated, which is important when considering how these modalities can be applied to patient populations (6). Furthermore, MRI is a favorable modality compared to CT for numerous musculoskeletal disorders because the superior soft tissue contrast of MRI and how prominent soft tissue is in musculoskeletal disorders.

PET Tracers

Two most commonly used radiotracers for PET imaging for musculoskeletal disorders are ^{18}F -fluorodeoxyglucose (^{18}F -FDG) and ^{18}F -sodium fluoride (^{18}F -NaF). ^{18}F -FDG is the most extensively used PET radiotracer in clinical practice (7,8) due to it being an analog of glucose. The use of ^{18}F -FDG for musculoskeletal disorders is appealing because tumors, activated inflammatory cells, and sites of infection have high metabolic needs and could potentially be marked with high intensity signals on PET images (9).

On the other hand, ^{18}F -NaF is useful for the imaging of bony disorders because bone tissue is continuously remodeling and the ^{18}F ions can exchange with the hydroxyl ions ($-\text{OH}$) on the surface of hydroxyapatite to form fluoroapatite (10,11), which is one of the main components of bone. Therefore, ^{18}F -NaF uptake on PET images can help to elucidate blood flow as well as osteolytic and osteoblastic activity (12,13) for bone breakdown or formation, respectively. As for musculoskeletal disorders, ^{18}F -NaF can be useful for the assessment of metabolic bone diseases, bone graft viability, fracture healing, osteonecrosis, and tumors.

Various tissues take up these PET tracers, and interpretation of the PET signals is necessary. While there are different ways to quantify PET tracer uptake, the most commonly used way is via standard uptake values (SUV), which is the tissue activity concentration normalized by the fraction of the injected dose/unit weight.

Applications

The following sections will describe various applications of PET-CT and PET-MRI to different categories of benign musculoskeletal disorders. The categories include benign cell proliferation/dysplasia, diabetic foot complications, joint prostheses, inflammation, metabolic bone disorders, and pain (acute and chronic) and peripheral nerve imaging.

Benign Cell Proliferation/Dysplasia

PET-CT and PET-MRI has showed promise in the imaging of primary, benign tumors of the musculoskeletal system. Tumors of the musculoskeletal system may be present in the bone, bone marrow, cartilage, or other types of soft tissue sarcomas. Like most disorders of the musculoskeletal system, radiographs or CT have been used for a longer period of time for imaging while the value of MRI has only recently been utilized. Radiography or CT have been valuable imaging modalities in the detection of subtle matrix calcifications and hence can be useful in confirming the diagnosis of a bone- or cartilage-forming tumor (14,15,16,17,18).

On the other hand, MRI alone is generally accepted as the most sensitive imaging method for defining the extent of bone tumors, but it is thought to be less specific than x-ray based techniques in differential diagnosis (19). MRI is useful for the evaluation of primary tumors that originate from anatomic sites that are not optimally evaluated with CT, such as connective tissue, soft-tissue, and bone marrow, due to the soft-tissue contrast providing high spatial resolution definition of tumor volume and staging (20,21). The feasibility of MRI-based bone marrow segmentation by using software techniques for quantitative calculation of pure red marrow metabolism at FDG PET has been reported (22), which could be useful in the clinical evaluation of benign bone marrow disorders.

FDG PET can be used to examine red marrow activity and to detect involvement in benign processes, such as chronic anemia and myelofibrosis, since these processes lead to increased hematopoiesis and reconversion of yellow to red marrow (1). The advantage of using FDG PET is that it can detect metabolically active lesions while CT can provide spatial information regarding the bone marrow. A disadvantage of using FDG PET to image bone marrow happens when a patient is undergoing granulocyte colony-stimulating factor therapy, which causes a physiological response of increased metabolic processes in the bone marrow. The increased FDG uptake in the bone marrow can mimic diffuse metastatic disease, so caution needs to be applied if PET imaging is being used to image bone marrow.

Myelofibrosis is a hematopoietic stem cell neoplasm characterized by bone marrow inflammation, reactive bone marrow fibrosis, and extramedullary hematopoiesis. One study used ^{18}F -FDG PET-CT to noninvasively visualize and quantify the extent and activity of bone marrow involvement in patients with myelofibrosis (Figure 1) (23). The authors concluded that the intensity of bone marrow ^{18}F -FDG uptake decreases as bone marrow

fibrosis increases, and ^{18}F -FDG PET-CT is a promising technique for the quantitation of bone marrow inflammation in myelofibrosis. Further studies are needed to assess ^{18}F -NaF PET and possible PET-MRI for myelofibrosis.

Fibrous dysplasia is a benign disorder where fibrous tissue replaces bone. One of the issues with imaging fibrous dysplasia is that it may show an increase in FDG uptake and therefore mimic malignant bone involvement in FDG PET. Being able to distinguish fibrous dysplasia from malignant tumors or lymphoma is important for patients and clinicians. A case study that used combined FDG PET-CT scanning on a patient with known fibrous dysplasia found an elevation in the uptake of FDG in numerous locations that were identified as fibrous dysplasia by CT (24). The authors concluded that FDG PET coregistered with CT might help to distinguish fibrous dysplasia from osseous malignancies. Furthermore, since fibrous dysplasia is characterized by changes in bone remodeling, or the loss of bone, ^{18}F -NaF PET imaging with CT or MRI might help to assess the severity of the disease and track patients' responses to bisphosphonate therapy.

Since ^{18}F -NaF PET imaging is not specific for malignant tumors and can accumulate in benign osseous abnormalities, hybrid imaging via PET-CT or PET-MRI can help to differentiate tumors with accuracy better than PET alone. For example, one study compared ^{18}F -NaF PET-CT to PET alone and found the specificity for lesions to be 97% and 72%, respectively, and for patients to be 88% and 56%, respectively (25).

Diabetic Foot Complications

Diabetes can lead to a number of complications in the foot, including vascular disease, Charcot neuropathy, soft-tissue infection, and osteomyelitis (26). It can be challenging to form a definitive diagnosis from MRI since signal abnormalities in the bone and bone marrow can be nonspecific to the different diseases. PET-MRI has the potential to differentiate between each of these diseases so that the patient can be optimally treated and further damage can be halted.

For example, Basu et al (27) found that there was a significant difference in FDG uptake in an uncomplicated diabetic foot, a foot with Charcot neuroarthropathy, and a foot with osteomyelitis. The sensitivity and accuracy for diagnosis of Charcot neuroarthropathy were 100% and 93.8% for FDG PET, and 76.9% and 75.0% for MRI. Additionally, in a patient population with a complicated diabetic foot, FDG PET had a sensitivity, specificity, and accuracy of 81%, 93%, and 90% for osteomyelitis diagnosis, and 91%, 78%, and 81%, respectively, for MRI (Figure 2) (28). These results demonstrate that FDG PET and MRI can differentiate between Charcot neuroarthropathy and osteomyelitis, but more research is needed to investigate if PET-MRI hybrid imaging can increase the sensitivity, specificity, and accuracy of diagnosing patients within the diabetic foot population.

Joint Prostheses

Joint replacement can be commonly accompanied with post-operative pain. Aseptic loosening or infection can cause this pain, and it is a clinical challenge to differentiate between these two causes of pain (29). CT and MRI are used for patients who have pain related to arthroplasty, but the images from CT and MRI can be inconclusive due to the

metal artifacts from the prosthesis. Recent methods have been shown to improve MRI around joint replacements (30).

FDG PET has a potential role in detecting infections in hip and knee prostheses since the imaging modality is not affected by metal artifacts. Chryssikos et al (31) performed a study on patients with hip prostheses and pain. PET images were suggestive of septic loosening if increased FDG uptake was found at the stem-prosthesis interface while uptake adjacent to the prosthesis neck was interpreted as a nonspecific reaction. 28 out of 35 positive studies were confirmed as infected while 87 out of 92 negative studies were confirmed aseptic. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FDG PET were 85%, 93%, 80%, and 95%, respectively. Furthermore, a study involving 38 hip prostheses and 36 knee prostheses found the sensitivity, specificity, and accuracy of FDG PET for detecting infection were 90%, 89.3%, and 89.5%, respectively, for hip prostheses, and 90.9%, 72.0%, and 77.8%, respectively, for knee prostheses (32). These studies demonstrate how FDG PET can be used to accurately diagnose and differentiate septic and aseptic causes of pain in hip and knee prostheses. Combining these PET techniques with methods for multispectral MRI (33) may provide an effective way of diagnosing total joint infection without an invasive fluid aspiration and correcting for distortions from metal artifacts. There have been studies using PET-MRI and PET-CT-MRI that have had success in metal artifact correction (34,35) so using PET-CT or PET-MRI to image prostheses is possible and continues to be researched.

F-NaF PET can also be used to measure bone blood flow and bone viability when determining if a joint replacement is necessary or has been successful. Schiepers et al. found that a decrease in blood flow or a decrease in ^{18}F -NaF uptake predicted the need for joint arthroplasty (36). Furthermore, two studies that investigated the uptake of ^{18}F -NaF in the bone graft used in hip arthroplasties found that the uptake in the allograft was similar to the adjacent cortical bone immediately after surgery. However, the uptake decreased in the allograft compared to the adjacent cortical bone (9 months to 5 years post-surgery), which indicated normal bony incorporation (37,38).

Degeneration, Inflammation, and Trauma

The metabolic information of PET and the anatomical differentiation from MRI are complementary for the evaluation of various arthritides and for treatment monitoring. Musculoskeletal disorders involving degeneration, inflammation, and trauma have the potential to be identified through FDG PET since activated inflamed cells have higher metabolic activity and through ^{18}F -NaF PET since some of these disorders involve bone remodeling. The combination of PET and MRI has promise in these musculoskeletal disorders since there is a need for biomarkers to detect these diseases at a reversible stage before tissue loss and degeneration.

OSTEOARTHRITIS

Osteoarthritis (OA) is a disease of the entire joint, which affects tissues such as bone, cartilage, menisci, ligaments, and synovial tissue (39). Although it is expected to affect 25% of U.S. adult population by 2030 (40), the disease process of OA is still poorly understood,

especially the early changes. Recent advances in understanding of OA have shown that the disease process involves multiple joint tissues, is influenced by biomechanics, and may have an inflammatory component in some patients.

MRI alone is a non-invasive imaging technique that has been used to study OA. The appeal of MRI is its ability to produce varying contrasts, which allows for the assessment of soft tissue quality (i.e. cartilage, menisci, ligaments), bone changes (i.e. bone marrow lesions, cysts, osteophytes), and synovitis presence (39,41). Even with the high utility of MRI in identifying structural changes associated with OA, these changes are typically at a later stage in the OA disease process where tissue loss has occurred, and anatomical MRI cannot give insight into the physiological mechanisms leading to OA.

^{18}F -NaF PET can help detect changes in bone remodeling, which can be applied to OA since increased bone remodeling leading to changes in bone and cartilage has been linked to the progression of OA (42,43). For example, SUV_{max} was significantly elevated in hip joints with abnormal findings in bone on MRI, and the severity of hip pain positively correlated with SUV_{max} (44). Similarly, patellofemoral pain coincided with increased metabolic activity in bone at the patellofemoral joint (45). Furthermore, abnormal findings in bone on MRI overlapped with areas of increased ^{18}F -NaF uptake on PET images, but, notably, increased SUV_{max} on ^{18}F -NaF PET did not always match to bone or cartilage degeneration found on MRI (46). The associations between symptoms of OA, increased ^{18}F -NaF uptake, and abnormal findings on MRI shows how PET-MRI hybrid imaging needs to be studied further, as it presents an opportunity to combine the metabolic information of PET with the structural information of MRI to detect OA progression.

Similar to ^{18}F -NaF, ^{18}F -FDG has the potential to elucidate OA progression but through its role of characterizing inflammation via increased glucose usage in tissues. Synovitis is inflammation of the synovial membrane in joints and has been recognized as a part of the progression of OA (47,48). According to studies that assessed patients with clinically diagnosed OA of the shoulder and knee, there was an increase in ^{18}F -FDG uptake when comparing the patients to healthy volunteers, which was interpreted as presence of synovitis (49,50). FDG PET-MRI could allow for identification of synovitis while visualizing the entire joint for other abnormalities that are present in OA.

Furthermore, bone marrow lesions (BMLs) are hypothesized to have an inflammatory element, and they play a role in the progression of OA (51). Typically, BMLs are identified through MRI, but PET-MRI could be a resource to further study the inflammatory mechanism of BMLs. A study on the use of PET-MRI for possible OA identification found that BMLs observed on MRI correlated with high ^{18}F -fluoride PET uptake identified as volumes of interest (VOI_{High}) 33 out of 34 times (97%) (Figure 3) (52). Also, the SUV_{max} in all subchondral bone lesions (BMLs, osteophytes, sclerosis) was significantly elevated compared to the SUV_{max} for normal-appearing bone, as identified on MRI. Of note, the uptake of ^{18}F -FDG in subchondral BMLs was much lower than the uptake of ^{18}F -fluoride, which suggests that bone remodeling processes might play a larger role in BMLs compared to inflammatory processes. The overlap in information from MRI and PET in the study demonstrates the reliability of the two modalities in identifying BMLs and other

mechanisms thought to play a role in osteoarthritis development. Therefore, PET-MRI imaging could be used to detect BMLs and other mechanisms at an earlier time in the progression of OA.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis and affects 1% of the population (53). It is a systemic inflammatory autoimmune disorder and affects joints of varying sizes. Although the disease has numerous etiologies, it is predominantly characterized by degenerative synovitis with leukocyte infiltration and proliferation, which leads to cartilage and bone degradation. RA typically progresses more rapidly than OA and most diagnoses for RA occur at a late stage in the disease process. Furthermore, better patient outcomes are dependent on administering aggressive anti-inflammatory drugs early in the disease progression; earlier detection of RA through novel methods has become imperative.

Given that FDG builds up in activated leukocytes and inflammation is a key part of RA pathogenesis, FDG-PET is a logical tracer that could be used to reveal the inflammatory process before further changes such as hyperemia and erosion are seen on other radiographic imaging modalities (54,55,56). A study that used FDG-PET to examine the joints of patients with RA found that the number of PET-positive joints and the cumulative SUV were significantly correlated with RA disease activity (Figure 4) (57). Animal models with induced RA have shown that increased FDG uptake correlated with imminent bone destruction and pannus formation (58).

Alternatively, other PET tracers may be able to elucidate parts of RA processes. One study found that both the uptake of (11)C-choline, a measure of cell proliferation, and the uptake of (18)F-FDG correlated highly with the volume of synovium, which suggests ¹¹C-Choline could be a promising tracer for quantitative imaging of proliferative arthritis changes (59). Additionally, the PET tracer, ¹¹C-(R)-PK11195, tags macrophages in the inflammatory response so it could provide a direct measure of the inflammation associated with RA (60,61).

Similar to osteoarthritis, rheumatoid arthritis has been studied with hybrid imaging modalities with further research still ongoing. MRI enables synovial inflammation to be delineated as contrast-enhanced lesions with high anatomical resolution, especially for finger lesions in RA (62). MRI also has recently advanced capabilities that could aid in the diagnosis and treatment for RA. For example, early detection of bone erosions can influence the type of treatment (63) and scoring systems that evaluate RA features based on MRI can be used to monitor responses to treatments (64). Furthermore, measurement of apparent diffusion coefficient (ADC) and pharmacokinetic modeling of Gadolinium enhancement and washout are new MRI methods that could allow for more understanding of RA pathogenesis (65). There has been a study that used a hybrid PET-MRI system to study early RA in the hand, and it found that FDG uptake overlapped with sites of synovitis and tenosynovitis, which are components of RA progression (Figure 5) (66). It has been demonstrated that PET-MRI can be used to image the inflammation associated with RA, but further studies using the hybrid modality are needed. Furthermore, RA is usually not isolated to a single

joint and affects joints throughout the body, so the application of PET-MRI needs to have the possibility of imaging many joints.

Relative to PET-MRI studies on RA, PET-CT has been utilized for a longer period of time. A study that examined patients with RA found that whole-body FDG PET-CT delineated large joint lesions in patients with RA, and the metabolic activity of inflammation was accurately overlaid on the anatomy of the joints (67). Furthermore, the authors concluded that the FDG PET-CT findings represented the inflammatory activity in large joints in patients with RA accurately and sensitively and could be helpful for early evaluations of the extent of RA throughout the whole body, including high-risk lesions of the atlantoaxial joint. The PET-CT system also could differentiate increased FDG uptake by enthesopathies from synovitis due to RA.

TRAUMA

Musculoskeletal trauma includes injuries to bone, cartilage, tendons, ligaments, and muscle. These injuries are accompanied by the body's inflammation response, so theoretically PET-CT and PET-MRI could be used to assess these injuries and manage the recovery process, molecularly and structurally. For example, PET-MRI cannot only be used to depict meniscal tears and their exact locations, but also the severity of the tear and the associated synovitis (1,68,69). This specific information could help to reduce exploratory arthroscopies/ surgeries and aid in the surgical repair or meniscectomy.

Similarly, PET-MRI and PET-CT could be used to reveal the presence, severity, and recovery of ligament and tendon tears with greater accuracy. Anterior cruciate ligament (ACL) injuries are of particular interest due to the high frequency of them and the associated post-injury osteoarthritis development (70). One study investigated the development of post traumatic osteoarthritis (PTOA) after anterior cruciate ligament transection (ACLT) of the knee in 5 in vivo canine models with Na¹⁸F PET-CT coregistered with MRI scanning (Figure 6) (71). It was found that prior to ACLT, both knees of all canines did not show Na¹⁸F uptake above background. The uptake of Na¹⁸F in the bone of the ACLT knees post-transection increased exponentially, presenting significantly higher uptake at 12 weeks in every region compared to the ACLT knees at baseline. The authors concluded that Na¹⁸F PET-CT co-registered with MRI is a feasible molecular imaging biomarker to assess knee osseous metabolic changes serially in an in vivo canine model of knee PTOA. Therefore, PET-CT co-registered with MRI could be used to track ACL reconstruction healing and associated PTOA development.

A recent study examined ACL grafts after ACL reconstruction surgery in a human population using PET-MRI (Figure 7) (72). The study found that metabolic activity was significantly lower in grafts that were imaged greater than 2 years post-reconstruction relative to those grafts that had been in place for shorter periods of time. The authors concluded that ¹⁸FDG PET-MRI can assess the metabolic activity of ACL grafts in vivo. ¹⁸FDG PET-MRI can provide insight into the process of graft ligamentization in patients following ACL reconstruction, which could impact graft selection and recovery timelines for patients.

Metabolic Bone Disorders

Metabolic bone disorders are often associated with changes in bone turnover and metabolism that can lead to bone fractures, bone deformities, and disability if untreated. Hence, ^{18}F -NaF and FDG are logical PET tracers to use when tracking these diseases, and MRI and CT provide the anatomical detail needed. Studies have shown that maximum standardized uptake values (SUV) for ^{18}F -NaF PET correlate well with net uptake of fluoride to bone mineral and osteoblastic activity due to disease (73). Furthermore, treatments that lead to a decrease in osteoblastic activity correlate with a decrease in SUV, so SUV can be used to assess these metabolic bone disorders.

Paget's disease involves increases in the resorption and formation of bone, which leads to fragile and misshapen bones (74). Treatment for Paget's disease relies on reducing the breakdown of bone, typically through the administration of bisphosphonates (75), so ^{18}F -NaF PET could be used to assess patients' responses to medication (76).

A study used ^{18}F -NaF PET to examine patients with renal osteodystrophy and found that the incorporation of ^{18}F -NaF into bone correlated closely with serum alkaline phosphatase, a marker of bone turnover and serum parathyroid hormone levels (77). Additionally, the incorporation of ^{18}F -NaF into bone correlated well with histomorphometric indices of bone turnover in iliac crest biopsies. The indices were higher in patients with high-turnover renal osteodystrophy and lower in patients with low bone turnover or healthy subjects.

^{18}F -NaF PET has been used to study osteoporosis, specifically in postmenopausal women. Compared to premenopausal women, postmenopausal women have been found to experience increased bone turnover (78,79). A study on postmenopausal women used ^{18}F -NaF PET and found a significant difference in bone turnover between patients treated with hormone replacement and untreated women (80), which demonstrates the utility of using ^{18}F -NaF PET to monitor changes in bone turnover in patients undergoing treatment for osteoporosis.

^{18}F -FDG PET has the potential to differentiate between traumatic fractures and fractures due to malignancies. Studies have found that acute osteoporotic or traumatic fractures do not show increases in ^{18}F -FDG uptake (81,82). On the contrary, fractures due to malignant or infectious processes do show increases in ^{18}F -FDG uptake via increased glucose needs of macrophages and other inflammatory cells. Therefore, ^{18}F -FDG could be used to distinguish fracture types throughout the body.

The metabolic information from PET about bone remodeling/ strength could supplement the information from CT or MRI for metabolic bone disorders such as osteoporosis, osteomalacia, Paget's disease, parathyroid disorders, and renal osteodystrophy. One of the advantages of using hybrid PET-CT or PET-MRI systems for imaging metabolic disorders is that the molecular changes often precede the structural changes (i.e. fractures, bone deformities) so hybrid imaging could highlight both of these changes if they are present.

Pain (Acute and Chronic) And Peripheral Nerve Imaging

Acute and chronic pain continues to be a heavily researched topic given patients' varying experiences and the frequency of patients seeking medical assistance for pain. The imaging of pain is challenging and focuses on potential anatomical abnormalities. However, anatomical variation is present throughout patient populations, so a consistent, quantitative imaging modality could help to elucidate potential causes or sites of pain.

FDG PET imaging has shown promise in identifying pain since uptake of FDG is increased when inflamed or overactive neurons have increased metabolic needs for glucose. For example, a study that used rat models found that there was an increase in FDG uptake in injured nerves after the rats had unilateral, induced neuropathic limb pain (Figure 8) (83). Additionally, there was not an increase in FDG uptake in the contralateral, or uninjured, limbs or in the control animals. FDG PET-CT scanning has been done on a human subject that initially presented with progressive difficulty walking, and an increase in FDG uptake was found in his lower spinal cord and sciatic nerves (84). A biopsy of the nerves confirmed neuropathy. A study using PET-MRI on patients with neuropathic pain of the lower extremities found that FDG uptake could be localized to the affected nerves (85).

Other PET tracers have the potential to identify pain-related activity, such as ^{11}C -PK11195 and ^{18}F -FTC-146. ^{11}C -PK11195 can image neuroinflammation since it can mark activated microglia and macrophages (86,87). ^{18}F -FTC-146, a recently discovered tracer, has the potential to directly assess signaling pathways since it marks sigma 1 receptors, which have been implicated in nociception (88). It has been recently determined that ^{18}F -FTC-146 is safe for use in humans, and human studies using PET-MRI have been initiated (89).

According to the Global Burden of Disease 2010 Study, the estimated prevalence of low back pain was 9.4% (90). PET has the potential to identify low back pain and back pain in general, especially in spondylolysis. Since ^{18}F -NaF PET characterizes bone remodeling, it may be able to show osseous changes before fractures develop. In a study assessing adolescents with back pain, the authors concluded that ^{18}F -sodium fluoride PET-CT can detect spinal lesions with high diagnostic accuracy (91). Another study that included patients who presented with back pain found that ^{18}F -sodium fluoride PET-CT showed abnormal uptake in the spine of 84% of the patients (92).

While MRI and CT provide high-resolution images of peripheral nerves and general anatomy, they have difficulty specifying sites of nerve inflammation or injury. Hybrid PETMRI and PET-CT imaging modalities can combine the PET information that can potentially localize pain with the MRI or CT information that can identify abnormal anatomy. Given the novelty of imaging pain and using hybrid imaging modalities, more research in human subjects is warranted.

Conclusion

PET-MRI and PET-CT are recently available advanced tools for the diagnosis of musculoskeletal disorders. These methods show considerable promise to improve early detection and characterization of disorders. Currently ^{18}F -FDG is useful for detection of

changes in glucose metabolism, while (18)F-NaF is useful to see early areas of bone remodeling. New radiotracers combined with these modalities promise even more specificity for diagnosis of benign musculoskeletal disease.

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Key Points

- Musculoskeletal disorders' etiologies and mechanisms can be complex where molecular changes precede structural changes
- Earlier detection and further understanding of musculoskeletal disorders is needed for better treatment and prevention
- Hybrid imaging systems (PET-CT and PET-MRI) can combine molecular information from PET with anatomical information from CT or MRI
- PET-CT and PET-MRI have been used for imaging musculoskeletal disorders with success
- Both hybrid modalities have the potential to be applied to more musculoskeletal disorders

Figure 1.

PET-CT images of 60-year-old male with histopathological grade I myelofibrosis. (A) Maximum intensity projection image with high ^{18}F -FDG uptake in the spleen and bone marrow extending into the small bones of the feet. (B) Transaxial PET, (C) CT, and (D) PET/CT show splenic uptake. (E) Transaxial PET, (F) CT, and (G) PET/CT images show femoral bone marrow uptake (arrows). The increased ^{18}F -FDG uptake in this patient with histopathological grade I myelofibrosis indicates an early and highly active state of the disease. [From Derlin T, Alchalby H, Bannas P, et al. Assessment of bone marrow inflammation in patients with myelofibrosis: an ^{18}F -fluorodeoxyglucose PET/CT study. *Eur J Nucl Med Mol Imaging* 2015;42:696. (23) with permission].

Figure 2.

Diabetic male presented with an ulcer of the right great toe. (A) T1-weighted sagittal MRI of right foot with loss of signal intensity in great toe, suggestive of osteomyelitis. (B) PET with increased FDG uptake at the corresponding site of abnormality. The PET scan further confirmed the diagnosis of osteomyelitis in the great toe. [From Nawaz A, Torigian DA, Siegelman ES, et al. Diagnostic performance of FDG-PET, MRI, and plain film radiography (PFR) for the diagnosis of osteomyelitis in the diabetic foot. *Mol Imaging Biol* 2010;12(3): 335–42. (28) with permission].

Figure 3.

¹⁸F-Fluoride PET (SUV) and MRI images of a male patient with posttraumatic osteoarthritis showing concordance between a BML (blue arrowhead) and osteophytes (red diamond arrows) on MRI with high ¹⁸F-fluoride uptake on PET. Additionally, a focal region of high uptake on PET (magenta line arrow) did not exhibit bone abnormalities on MRI but was adjacent to a grade 2 cartilage defect (light blue solid arrow). [From Kogan F, Fan AP, McWalter EJ, et al. PET/MRI of metabolic activity in osteoarthritis: A feasibility study. *J Magn Reson Imaging* 2017;45(6):1736–45. (52) with permission].

Figure 4. ^{18}F -FDG PET images. (A and B) Healthy control subject (C and D) RA patient with active disease. (A) 3D projection image of normal tracer distribution in knee. (B) Normal distribution in hand and wrist. (C) Rheumatoid knee and (D) rheumatoid hand and wrist with elevated FDG uptake (57). [Data from JNM. Beckers C, Ribbens C, André B, et al. Assessment of disease activity in rheumatoid arthritis with (^{18}F) -FDG PET. *J Nucl Med* 2004;45:956–64. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.].

Figure 5.

Hybrid 18F-FDG PET-MRI of the hand in early rheumatoid arthritis. (A) Axial and coronal images of PET co-registered with (B) axial and coronal T1-weighted MRI. (C) True hybrid 18F-FDG PET-MRI of the hand. [From Miese F, Scherer A, Ostendorf B, et al. Hybrid 18F-FDG PET-MRI of the hand in rheumatoid arthritis: initial results. *Clin Rheumatol* 2011;30:1247–50. (66) with permission].

Figure 6.

Knee MRI, Na18F PET, and Na18F PET-MRI coregistered (left to right). Axial views of the knee femoral condyles at baseline, 3 weeks, and 12 weeks post-anterior cruciate ligament transection (ACLT) (top to bottom). The images show Na18F background uptake at baseline, higher uptake at 3 weeks, and significantly higher uptake at 12 weeks post-ACLT (bottom row). The elevated uptake represented increased bone metabolism, caused by the injury-induced trauma. [From Menendez MI, Hettlich B, Wei L, Knopp MV. Feasibility of Na18F PET/CT and MRI for Noninvasive In Vivo Quantification of Knee Pathophysiological Bone Metabolism in a Canine Model of Post-traumatic Osteoarthritis. *Molecular Imaging* 2017;16:1536012117714575. (71) with permission].

Figure 7.

(A) PET image, (B) MRI image, and (C) combined PET-MRI of an ACL graft. PETMRI can help to track and manage ACL reconstruction recovery. [From Magnussen RA, Binzel K, Zhang J, et al. ACL Graft Metabolic Activity Assessed by 18FDG PET-MRI. *Arthroscopy: The Journal of Arthroscopic & Related Surgery* 2017;33(10):e79. (72) with permission].

Figure 8.

(A) Spared-nerve injury (SNI) (top row) and control (bottom row) rat models showing sciatic nerves (arrows) on transaxial MRI, PET, and PET-MRI. ^{18}F -FDG PET-MRI showed significantly increased ^{18}F -FDG uptake on the side with spared-nerve injury (left), compared with control side (right). Control animals did not show any significant difference between right and left nerves. (B) Autoradiography of sciatic nerve specimens from sparednerve injury animals showed that normalized radiotracer uptake is higher in injured sciatic nerve (left) than in control sciatic nerve (right) (83). [Data from published in JNM. Behera D, Jacobs KE, Behera S, et al. (18)F-FDG PET-MRI can be used to identify injured peripheral nerves in a model of neuropathic pain. *J Nucl Med* 2011;52:1308–12. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.].