JOURNAL OF MAGNETIC RESONANCE IMAGING 36:928–932 (2012)

Original Research

Comparison of MRI and ^{18}F-NaF PET/CT in Patients With Patellofemoral Pain

Christine E. Draper, PhD,[1] Andrew Quon, MD,[1] Michael Fredericson, MD,[2] Thor F. Besier, PhD,[2] Scott L. Delp, PhD,[2,3] Gary S. Beaupre, PhD,[4] and Garry E. Gold, MD[1]*

Purpose: To determine whether bone metabolic activity corresponds to bone and cartilage damage in patients with patellofemoral pain.

Materials and Methods: We acquired magnetic resonance imaging (MRI) and ^{18}F-NaF positron emission tomography (PET) / computed tomography (CT) scans of the knees of 22 subjects. We compared locations of increased tracer uptake on the ^{18}F-NaF PET images to bone marrow edema and cartilage damage visualized on MRI.

Results: We found that increased bone activity on ^{18}F-NaF PET does not always correspond to structural damage in the bone or cartilage as seen on MRI.

Conclusion: Our results suggest that ^{18}F-NaF PET/CT may provide additional information in patellofemoral pain patients compared to MRI.

Key Words: patellofemoral pain; MRI; ^{18}F-NaF PET/CT
J. Magn. Reson. Imaging 2012;36:928–932.

PATELLOFEMORAL PAIN is characterized by dull, achy pain originating from behind the patella and is exacerbated by activities that place large loads on the joint, such as running and stair climbing. Patellofemoral pain accounts for a large fraction of knee disorders seen in sports medicine clinics (1), yet treatment is challenging because the underlying causes of pain are often unclear (2). Musculoskeletal disorders are commonly diagnosed using magnetic resonance imaging (MRI), which provides excellent bone and soft tissue contrast; however, a number of patients with patellofemoral pain do not appear to have structural damage to the bones or cartilage at the joint (3). This makes diagnosis challenging. It is commonly thought that elevated stress in the subchondral bone of the patellofemoral joint is one cause of pain (4). Unfortunately, while structural and morphological information can be derived from MRI, bone stress cannot be directly measured using this modality.

Elevated subchondral bone stress may result in alterations in tissue physiology that either accompany or precede pathological changes to tissue structure. Methods to directly image bone metabolic activity could provide insight into the relationship between bone stress and tissue structure. Technetium-99m hydroxymethylene diphosphonate (Tc-99m MDP) bone scintigraphy has revealed increased bone turnover in patients with knee osteoarthritis (OA) (5) and patellofemoral pain (6). These studies have provided valuable insight into potential alterations in bone activity in some musculoskeletal disorders; however, the poor spatial resolution of tracer uptake in these scans can limit the diagnostic potential.

^{18}F-NaF positron emission tomography (PET) / computed tomography (CT) offers a number of advantages over bone scintigraphy. This technique was used because of the selective uptake of ^{18}F-NaF in bone. In this technique, ^{18}F-NaF radiotracer becomes incorporated into the bone at sites of bone remodeling with high metabolic activity. The injected ^{18}F fluoride ions exchange with hydroxyl ions in bone crystal to form fluorapatite and become naturally incorporated into bone (7). Incorporation of the ^{18}F fluoride ion in bone is thought to be due to the activity of osteoblasts and osteoclasts. Therefore, processes such as increased bone remodeling or blood perfusion will result in increased tracer uptake (7). While 18F-NaF PET/CT is more expensive than Tc-99m MDP bone scintigraphy, there are a number of benefits of this modality. The advantages of ^{18}F-NaF PET/CT over bone scintigraphy techniques are improved spatial resolution, more accurate anatomical localization of tracer uptake

[1]Department of Radiology, Stanford University, Stanford, California, USA.
[2]Department of Orthopedics, Stanford University, Stanford, California, USA.
[3]Department of Bioengineering, Stanford University, Stanford, California, USA.
[4]Rehabilitation R&D Center, VA Palo Alto Health Care System, Palo Alto, California, USA.

Contract grant sponsor: National Institutes of Health (NIH); Contract grant numbers: EB0002524, EB005790, U54 GM072970, RO1HD33929, RO1HD046814, R90 DK071508; Contract grant sponsor: Office of Research and Development, Department of Veterans Affairs; Contract grant number: Rehabilitation R&D Service grant A2592R; Contract grant sponsor: GE Healthcare; Stanford PET/CT Joint Venture.

*Address reprint requests to: Garry E. G., Department of Radiology, 300 Pasteur Dr. SO-68B, Stanford University, Stanford, CA 94305. E-mail: gold@stanford.edu

Received August 9, 2011; Accepted March 16, 2012.
DOI 10.1002/jmri.23682
View this article online at wileyonlinelibrary.com.

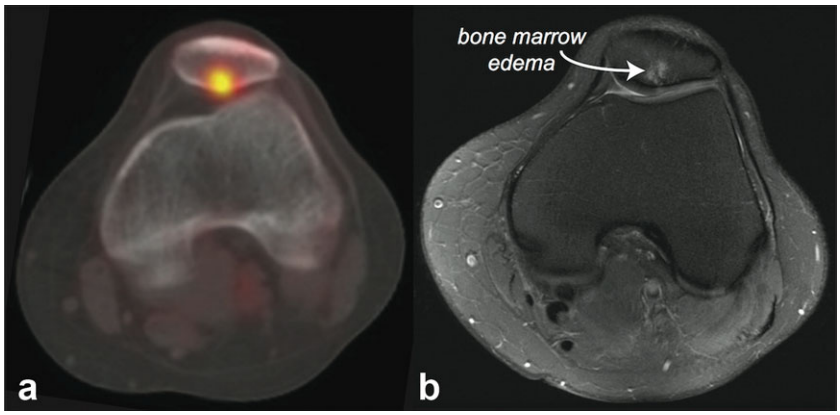

Figure 1. a: Sample ^{18}F-NaF PET/CT image of the patellofemoral joint of a 40-year-old female with patellofemoral pain. **b:** Sample MR image of the patellofemoral joint of the same subject. Notice the colocalization of the region of increased tracer uptake and the bone marrow edema in the apex of the patella.

using coregistered CT, larger ratio of bone uptake to soft-tissue uptake, and faster study times (8).

Recent studies have suggested that this technique may be promising for the evaluation of nononcologic orthopedic conditions (9), such as bone fractures (10), foot pain (11), and back pain (12,13); however, few studies have shown whether bone activity is related to structural information about the joint. Previous work studying patients with foot pain has shown agreement between MRI and ^{18}F-NaF PET in only 40% of the patients studied (11). Furthermore, moderate correlations were found between bone uptake on Tc-99m MDP bone scintigraphy and subchondral bone lesions on MRI in patients with early knee OA (14). It remains unclear whether regions of increased ^{18}F-NaF uptake correspond to structural defects in the bone or cartilage visualized using MRI in patients with patellofemoral pain.

The goal of this study was to evaluate whether regions of increased tracer uptake in the knee detected using ^{18}F-NaF PET/CT correspond to structural damage seen on MRI. We hypothesized that regions of bone marrow edema, subchondral bone cysts, and cartilage thickness loss correspond to increased ^{18}F-NaF tracer uptake.

MATERIALS AND METHODS

The knees of 22 subjects (12 male: 31 ± 8 years, 1.8 ± 0.09 m, 78 ± 12 kg; 10 female: 34 ± 8 years, 1.6 ± 0.04 m, 60 ± 6 kg) diagnosed with patellofemoral pain by an experienced sports medicine physician were studied. Subjects were included if they experienced reproducible anterior knee pain during at least two of the following activities: stair ascent/descent, kneeling, squatting, prolonged sitting, or isometric quadriceps contraction. Subjects were excluded if they met any of the following criteria: knee ligament instability, patellar tendonitis, joint line tenderness or knee effusion, previous knee trauma or surgery, or patellar dislocation. Prior to participating in the study, all subjects were informed about the nature of the study and provided consent according to the University Institutional Review Board. Both knees of each subject were imaged. Three knees were excluded due to prior surgery, for a total of 41 knees imaged.

All subjects received an ^{18}F-NaF PET/CT scan of both knees (Fig. 1a). To minimize the effects of recent physical activity and blood flow on tracer uptake, subjects remained seated for 30 minutes prior to tracer injection. Subjects then received 5–10 mCi of ^{18}F-NaF intravenously (0.08 mCi/kg) and remained seated until the PET/CT scan. Scanning was performed an average of 69 ± 24 minutes following tracer injection using a GE Discovery LS PET/CT scanner (GE Healthcare, Milwaukee, WI). Subjects were positioned in a supine position with their legs strapped together to minimize movement and facilitate registration between the PET and CT scans. The PET images were acquired with the following scan parameters: single

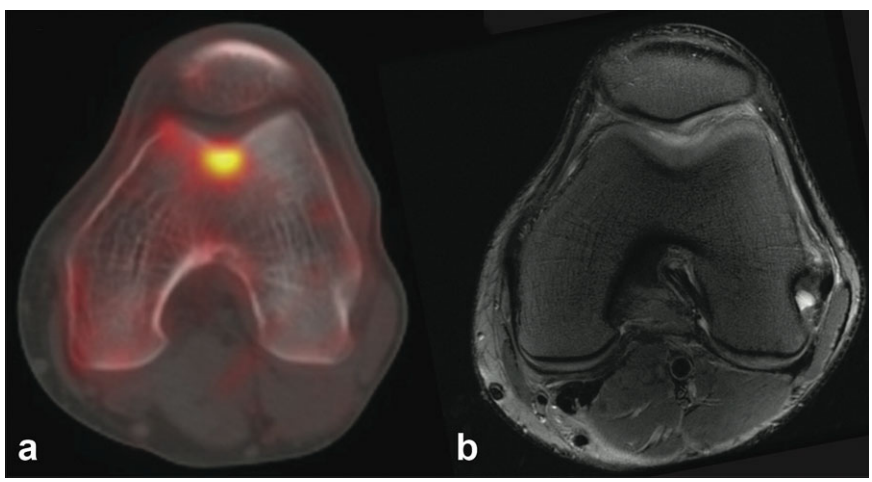

Figure 2. a: Sample ^{18}F-NaF PET/CT image of the patellofemoral joint of a 24-year-old male with patellofemoral pain. **b:** Sample MR image of the patellofemoral joint in the same subject. The region of increased tracer uptake in the trochlea seen on the PET/CT image does not correspond to bone or cartilage damage visualized on the MR image.

Table 1
Corresponding PET and MRI Scores of All Regions of All Knees

A MRI Bone Score

PET Score	0	1	2
0	985	19	0
1	27	1	0
2	22	6	6

B MRI Cartilage Score

	0	1	2
0	987	14	3
1	26	2	0
2	20	11	3

field of view (SFOV): 55 cm, matrix: 128 × 128, slice thickness: 4.25 mm, 5-minute acquisition/bed position, 1 bed position, ordered subsets expectation maximization (OSEM) iterative reconstruction. The resolution of PET images from this type of scanner has been shown to be ≈7–8 mm full-width at half-maximum (FWHM) (15). Corresponding noncontrast CT images of the subjects in the same position were obtained immediately prior to the PET scan using the following parameters: SFOV: 50 cm, matrix size: 512 × 512, slice thickness: 4.25 mm, 140 kVp, 90 mAs. PET and CT images were displayed using both a GE Xeleris 2.1220 workstation (GE Healthcare) and Osirix 3.7.1 software (Antoine Rosset, Geneva University Hospital, Switzerland). Axial, coronal, and sagittal PET, CT, and PET/CT fused images were analyzed and interpreted.

MR images of both knees of all subjects were acquired using a GE Signa HDx 3.0T MRI scanner (GE Healthcare) and an 8-channel knee coil. Scans sensitive to bone marrow edema and cartilage damage were acquired using fat-suppressed, fast spin-echo sequences (Fig. 1b): (axial proton-density) TR: 4200 msec, TE: 35 msec, FOV: 14 × 14 cm, matrix size: 416 × 320, slice thickness: 4 mm, flip angle: 90° and (sagittal T2-weighted) TR: 7000 msec, TE: 77 msec, FOV: 16 × 16 cm, matrix size: 320 × 224, slice thickness: 4 mm, flip angle: 90°. On average, MRI scans were acquired within 1 month of the PET/CT scans.

For image analysis, each knee was divided into 26 anatomical regions (patella: 12 regions, femur: 10 regions, tibia: 4 regions) and each region was evaluated for abnormalities. The PET images were evaluated by a nuclear medicine radiologist with 10 years of experience, blinded to the MR images. Signal abnormalities within the bones were qualitatively identified using the following scoring system: 0 = no signal uptake; 1 = mild: uptake noticeably above soft-tissue background; 2 = severe: uptake substantially above bone background. The registered CT images were used for anatomic localization. A musculoskeletal radiologist with 15 years of experience, blinded to the PET/CT images, rated the bone and cartilage in each region using the MR images. The following scoring systems were used: 1) Bone: 0 = no edema or cysts; 1 = mild: edema or cysts <50% region volume; 2 = severe: edema or cysts > 50% region volume; and 2) Cartilage: 0 = healthy; 1 = mild: signal change or fray/fissure; 2 = severe: partial or full thickness loss. Within each region, the scores from the PET and MR images were compared. ^{18}F-NaF PET only enables bone to be assessed; therefore, regions of bone closest to the cartilage regions were used when comparing cartilage and bone abnormalities.

The symmetry between the number of colocalized regions of abnormal uptake detected by PET and regions of bone or cartilage damage detected using MRI was compared using the Bowker test for symmetry (16). A symmetric relationship indicates that both MRI and PET detect similar numbers and grading of abnormalities, whereas an asymmetric relationship indicates that one modality detects abnormalities that are not detected (or are not of the same grade) using the second modality.

RESULTS

We observed more regions of increased tracer uptake on PET (62 abnormal foci) than regions of bone abnormalities (32 abnormal regions) or cartilage damage (33 abnormal regions) on MRI. Bone marrow edema, subchondral bone cysts, and cartilage damage tended to coincide with regions of increased tracer uptake on the PET scans (Fig. 1). However, the relationship between increased tracer uptake and bone or cartilage damage was highly asymmetric (Table 1). This indicates that increased tracer uptake on the PET scan did not always correspond to structural damage in cartilage or bone detected using MRI. For example, there were 22 severe PET/CT foci of intense ^{18}F-NaF activity with no corresponding bone structural abnormality detected by MRI (Fig. 2), whereas all severe bone abnormalities seen on MRI (MRI score = 2) also exhibited an increase in bone metabolic activity (PET score = 2) (Table 1A). This asymmetry existed in the comparison of both the cartilage and bone MRI scores with the bone PET scores ($P < 0.00001$); however, the comparison between cartilage and bone integrity scored from MRI was symmetric ($P = 0.65$) (Table 2), indicating a more consistent relationship between the presence of bone marrow edema and cartilage damage.

A lesion-based analysis was performed on the most painful knee of each subject ($n = 22$). Lesions were defined to be any region receiving a score of 1 or 2 from either MRI or PET. We found that 49% of the abnormal regions consisted of increased tracer uptake detected by PET alone (Fig. 2). Only 12% of all abnormal regions were detected by MRI alone. The remaining 39% of the abnormal regions were localized by both PET and MRI (Fig. 1).

A subject-based analysis was also performed on the most painful knee of each subject. Of the 22 subjects, 14 exhibited at least one region of increased tracer uptake on PET that did not correspond to bone marrow edema or cartilage damage on MRI. In four of these subjects, no region of increased tracer uptake on PET corresponded to structural damage visualized on MRI, whereas the other 10 subjects had multiple abnormal regions, some of which were colocalized with abnormalities on MR and some of which were only detected by PET. In seven out of 22 subjects, the PET and MRI overlapped completely: all regions of increased tracer uptake corresponded to either bone or cartilage damage. The remaining subject exhibited

Table 2
Corresponding MRI Bone and Cartilage Scores of All Regions of All Knees

Bone Score	Cartilage Score 0	1	2
0	1017	15	2
1	16	7	3
2	0	5	1

multiple abnormal regions, including one region of cartilage damage only identified by MRI.

DISCUSSION

This study evaluated whether regions of increased ^{18}F-NaF uptake were colocalized with bone and cartilage structural abnormalities imaged using MRI in patients with anterior knee pain. The results of this study suggest that, while bone marrow edema and cartilage damage often correspond to regions of increased tracer uptake, metabolic abnormalities in the bone also occur in the absence of structural changes seen using MRI.

The increased sensitivity of PET resulted in a number of regions of increased tracer uptake that were not colocalized with either bone or cartilage damage. In fact, 49% of all lesions were only identified with PET, whereas only 39% of the lesions were colocalized with both PET and MRI. The increased sensitivity of PET was also highlighted by the fact that in only 32% of the subjects did the MRI and PET/CT scans correlate completely. The implication of these results is that 18F-NaF PET/CT may be a potential diagnostic tool that could complement other imaging modalities. Future work investigating ^{18}F-NaF sensitivity to pain will help determine the clinical significance of the regions of increased tracer uptake that occur in the absence of structural joint damage.

No previous study has compared ^{18}F-NaF PET/CT to MRI in the knee, but our results can be compared to studies of other joints or studies using bone scintigraphy. A study comparing ^{18}F-NaF PET/CT and MRI in patients with foot pain found agreement between imaging modalities 40% of the time (11). This is consistent with our result that 39% of the abnormal regions were colocalized by both PET and MRI. Another study correlating bone scintigraphic activity with MRI in patients with knee pain found moderate correlations between bone uptake and subchondral lesions ($\kappa = 0.49$) (14); however, correlations between bone activity and osteophytes and cartilage lesions were fair or poor ($\kappa = 0.03$–0.18) (14). While we found that a number of subchondral lesions corresponded to increased tracer uptake, the overall correlation between imaging modalities was poor for both bone and cartilage due to the number of PET lesions detected that did not correspond to structural defects on MRI. The improved correlation between bone uptake and MR-detected subchondral lesions in the previous study may be explained by the differences in joint degeneration in the patient populations studied. In the current study, young patients were chosen to minimize the occurrence of degenerative joint changes, whereas in the previous study most patients had evidence of radiographic knee OA and structural damage to the bone. This discrepancy in results may indicate that increased bone metabolic activity could occur prior to the development of structural changes to the bone.

A significant factor differentiating our study from previous studies is that we used fused PET/CT images, allowing for excellent anatomical coregistration and correlation with MRI findings. It would not have been feasible to accurately subdivide an ^{18}F-NaF PET scan into 26 anatomical regions without the aid of a coregistered CT image.

Subchondral bone abnormalities can be associated with the development of pain (17) and cartilage degeneration (18). Based on our results, bone marrow edema and/or cartilage damage was often associated with increased bone metabolic activity; however, our results also suggest that in patients with patellofemoral pain, changes in bone metabolic activity can occur in the absence of structural damage to the joint. The increased bone metabolic activity might be related to the pain felt by the subjects and it could indicate a metabolic abnormality that will eventually lead to degenerative joint changes. As a result, treatments aimed at decreasing bone metabolic activity may be successful in this patient population. Future work evaluating the ability of ^{18}F-NaF PET/CT to predict bone and cartilage degeneration at the knee is needed to confirm this hypothesis.

A limitation of our study was the cross-sectional design that did not include a follow-up of subjects to assess whether increased bone metabolic activity predicted subsequent structural changes in the bone and cartilage. This study was also limited by the small number of subjects studied, the fact that only two radiologists evaluated the images, and the limited resolution of the PET images. Furthermore, we did not evaluate other MRI techniques, such as spectroscopy, which may be more sensitive to metabolic changes and might detect bone metabolic abnormalities without ionizing radiation. Future studies comparing PET/CT to MR spectroscopy or T2 maps are needed to determine whether these imaging modalities can provide similar information. While we did not examine pain-free controls due to the ionizing radiation involved in PET/CT scanning, all subjects were free of tibiofemoral pain. Only six (out of 41) tibia were found to exhibit increased tracer uptake on the PET/CT scan, suggesting that increased tracer uptake is not common in pain-free bones. No tibia had any cartilage or bone abnormalities based on the MRI.

While this imaging modality may complement other imaging techniques and could provide additional insights into the diagnosis of patellofemoral pain, the cost of PET/CT may be prohibitive in some cases. Nonetheless, in patients for whom this scan is feasible the insight gained may aid in the treatment of patellofemoral pain.

In conclusion, our results suggest that ^{18}F-NaF PET/CT may detect abnormalities in the knee unseen using MRI. This technique could complement MRI to detect sources of bone pain in patients and may prove to be a promising tool for early detection of osteoarthritis.

ACKNOWLEDGMENTS

We thank the following nuclear medicine technologists for their help acquiring the PET/CT images: Christine Fuji, Paulo Castaneda, Lincoln Sanders, and Matthew Gabriele. We thank the PET/CT research coordinator, Lindee Burton. We thank Jarrett Rosenberg for advice on statistics and Erik Mittra for helpful discussions.

REFERENCES

1. Devereaux MD, Lachmann SM. Patello-femoral arthralgia in athletes attending a Sports Injury Clinic. Br J Sports Med 1984;18: 18–21.
2. LaBella C. Patellofemoral pain syndrome: evaluation and treatment. Primary Care 2004;31:977–1003.
3. Pihlajamaki HK, Kuikka PI, Leppanen VV, Kiuru MJ, Mattila VM. Reliability of clinical findings and magnetic resonance imaging for the diagnosis of chondromalacia patellae. J Bone Joint Surg Am 2011;92;927–934.
4. Fulkerson JP. Diagnosis and treatment of patients with patellofemoral pain. Am J Sports Med 2002;30:447–456.
5. McCrae F, Shouls J, Dieppe P, Watt I. Scintigraphic assessment of osteoarthritis of the knee joint. Ann Rheum Dis 1992;51:938–942.
6. Naslund JE, Odenbring S, Naslund UB, Lundeberg T. Diffusely increased bone scintigraphic uptake in patellofemoral pain syndrome. Br J Sports Med 2005;39:162–165.
7. Blau M, Ganatra R, Bender MA. 18 F-fluoride for bone imaging. Semin Nucl Med 1972;2:31–37.
8. Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with 18F-fluoride: applying new technology to an old tracer. J Nucl Med 2008;49:68–78.
9. Even-Sapir E, Mishani E, Flusser G, Metser U. 18F-Fluoride positron emission tomography and positron emission tomography/computed tomography. Semin Nucl Med 2007;37:462–469.
10. Hsu WK, Feeley BT, Krenek L, Stout DB, Chatziioannou AF, Lieberman JR. The use of 18F-fluoride and 18F-FDG PET scans to assess fracture healing in a rat femur model. Eur J Nucl Med Mol Imaging 2007;34:1291–1301.
11. Fischer DR, Maquieira GJ, Espinosa N, et al. Therapeutic impact of [(18)F]fluoride positron-emission tomography/computed tomography on patients with unclear foot pain. Skeletal Radiol 2010;39:987–997.
12. Lim R, Fahey FH, Drubach LA, Connolly LP, Treves ST. Early experience with fluorine-18 sodium fluoride bone PET in young patients with back pain. J Pediatr Orthop 2007;27:277–282.
13. Strobel K, Fischer DR, Tamborrini G, et al. (18)F-Fluoride PET/CT for detection of sacroiliitis in ankylosing spondylitis. Eur J Nucl Med Mol Imaging 2010;37:1760–1765.
14. Boegard T, Rudling O, Dahlstrom J, Dirksen H, Petersson IF, Jonsson K. Bone scintigraphy in chronic knee pain: comparison with magnetic resonance imaging. Ann Rheum Dis 1999;58: 20–26.
15. Schmidtlein CR, Kirov AS, Nehmeh SA, et al. Validation of GATE Monte Carlo simulations of the GE Advance/Discovery LS PET scanners. Med Phys 2006;33:198–208.
16. Bowker AH. A test for symmetry in contingency tables. J Am Stat Assoc 1948;43:572–574.
17. Sowers MF, Hayes C, Jamadar D, et al. Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and X-ray-defined knee osteoarthritis. Osteoarthritis Cartilage 2003;11:387–393.
18. Dieppe P, Cushnaghan J, Young P, Kirwan J. Prediction of the progression of joint space narrowing in osteoarthritis of the knee by bone scintigraphy. Ann Rheum Dis 1993;52:557–563.