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Patients with patellofemoral pain exhibit elevated bone metabolic activity at the patellofemoral joint

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Summary

Patellofemoral pain is characterized by pain behind the kneecap and is often thought to be due to high stress at the patellofemoral joint. While we cannot measure bone stress *in vivo*, we can visualize bone metabolic activity using ^{18}F NaF PET/CT, which may be related to bone stress. Our goals were to use ^{18}F NaF PET/CT to evaluate whether subjects with patellofemoral pan exhibit elevated bone metabolic activity and to determine whether bone metabolic activity correlates with pain intensity. We examined 20 subjects diagnosed with patellofemoral pain. All subjects received an ^{18}F NaF PET/CT scan of their knees. Uptake of ^{18}F NaF in the patella and trochlea was quantified by computing the standardized uptake value and normalizing by the background tracer uptake in bone. We detected increased tracer uptake in 85% of the painful knees examined. We found that the painful knees exhibited increased tracer uptake compared to the pain-free knees of four subjects with unilateral pain ($p=0.0006$). We also found a correlation between increasing tracer uptake and increasing pain intensity ($r^2 = 0.55$; $p = 0.0005$). The implication of these results is that patellofemoral pain may be related to bone metabolic activity at the patellofemoral joint.

Keywords

patellofemoral pain; ^{18}F NaF PET/CT; bone metabolic activity

Introduction

Patellofemoral pain syndrome is often characterized by dull, achy pain that is exacerbated by activities such as running, squatting, and stair climbing. Patellofemoral pain accounts for a large fraction of knee disorders seen in sports medicine clinics[1], but treatment is challenging because the underlying causes of pain are unclear[2]. Often, patients with patellofemoral pain do not appear to have structural damage to the bones or cartilage at the joint[3], making diagnosis from imaging challenging. Elevated stress in the subchondral bone of the patellofemoral joint is hypothesized to be one cause of pain[4]; however, stress cannot be measured *in vivo*. Bone remodels in response to applied joint loads[5]; therefore, elevated subchondral bone stress may result in increased bone remodeling activity. Bone remodeling activity may also be related to nerve growth and the development of pain[6].

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Methods to directly image bone metabolic activity can provide insight into the relationship between bone stress and pain. Technetium-99m hydroxymethylene diphosphonate (Tc-99m MDP) bone scintigraphy previously revealed increased bone turnover at the knee in patients with patellofemoral pain[7] and knee osteoarthritis[8,9]; however, the poor spatial resolution of this technique makes it difficult to localize the specific regions of tracer uptake. ^{18}F NaF PET/CT is an alternative to Tc-99m MDP bone scintigraphy that may provide additional insight due to its ability to more specifically localize regions of elevated bone metabolic activity. In this imaging technique, ^{18}F fluoride ions, which have a high affinity for bone mineral[10], are injected intravenously. The ^{18}F fluoride ions exchange with hydroxl ions in bone crystal to become naturally incorporated into cortical bone[11]. Incorporation of the ^{18}F fluoride ion in bone is due to the activity of osteoblasts and osteoclasts during bone remodeling; therefore, processes that increase bone remodeling or bone metabolic activity will result in increased uptake of the tracer[11]. The advantages of ^{18}F NaF PET/CT over bone scintigraphy are improved spatial resolution, more accurate anatomical localization of tracer uptake using co-registered CT, larger ratio of bone uptake to soft-tissue uptake, and faster study times[12].

Characterizing bone metabolic activity using ^{18}F NaF PET/CT in patients with patellofemoral pain has not previously been performed. This information may aid in the diagnosis and treatment of this disorder; therefore, the goals of this study were: to determine whether subjects with patellofemoral pain exhibit elevated bone metabolic activity at the patellofemoral joint and evaluate whether the location of elevated bone metabolic activity corresponds to the specific location of pain; and to assess whether the level of bone metabolic activity correlates with reported pain intensity.

Materials and Methods

We studied the knees of 20 subjects (12 male: 29 ± 5 yrs, 1.8 ± 0.1m, 80 ± 15kg; 8 female: 32 ± 6 yrs, 1.6 ± 0.04m, 61 ± 6kg) diagnosed with chronic patellofemoral pain by an experienced sports medicine physician. Subjects experienced pain for a minimum of 3 mos. 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 injuries or surgery, or patellar dislocation. Both knees of every subject were imaged although only the more painful knee at the time of scanning was analyzed. Due to the radiation exposure of PET/CT scanning, pain-free subjects were not recruited. Four subjects were diagnosed with unilateral pain, and their pain-free knees were used as controls. During the physical exam, the physician determined the region of the joint most sensitive to palpation. This was recorded for comparison with the location of tracer uptake. Furthermore, subjects rated the maximum pain experienced during the past year on a verbal rating scale from 0 to 10, where 0 represents no pain and 10 represents the worst pain imaginable. Prior to participating in the study, all patients were informed about the nature of the study and provided consent as approved by the University Institutional Review Board.

All subjects received an ^{18}F NaF PET/CT scan of both knees. To minimize the effects of recent physical activity and blood flow on tracer uptake, subjects were seated for 30 mins prior to tracer injection. Subjects then received 5-10mCi of ^{18}F NaF intravenously (0.08mCi/kg) and remained seated until the PET/CT scan. This is an equivalent dose of 5-10mSv and is approximately 1.5 to 3 yrs of background radiation. The PET/CT scan was acquired an average of 69 ± 23 mins following tracer injection. A GE Discovery LS PET/CT scanner (GE Healthcare, Milwaukee, WI) was used. Subjects were scanned in a supine position with their legs strapped together to minimize movement between the CT and PET

scans. This improves registration between the two scans. Non-contrast CT images of both knees of the subjects were obtained immediately prior to the PET scan using the following parameters: SFOV: 50cm, matrix size: 512×512, slice thickness: 4.25mm, 140kVp, 90mAs. The PET images were acquired using the following parameters: SFOV: 55cm, matrix: 128×128, slice thickness: 4.25mm, 5 min acquisition/bed position, 1 bed position, ordered subsets expectation maximization (OSEM) iterative reconstruction. The resolution of PET images from this type of scanner is 7 to 8mm (full width at half maximum)[13].

Uptake of the ^{18}F NaF tracer was quantified by computing the standardized uptake value (SUV):

$$\mathrm{SUV\,(g/ml)} = \frac{\text{pixel value (Bq/ml)} * \text{patient weight (g)}}{\text{dose corrected by tracer half-life and duration between injection and scan (Bq)}}$$

The background tracer uptake in bone was computed for each subject. Since all subjects were free of tibiofemoral abnormalities, we defined the average SUV of an axial slice through the tibial epiphysis just proximal to the tibial tuberosity to be representative of typical bone background uptake. We then defined a region of increased tracer uptake to be any group of two or more adjacent pixels that were greater than twice the background tracer uptake. We computed the mean and peak SUV of the regions of tracer uptake. In cases where subjects did not exhibit increased tracer uptake, we computed the mean and peak of the entire patella. To account for variations in uptake between patients, we normalized all SUV values by the background bone SUV for each subject. A Student's t-test was used to assess the significance of differences in tracer uptake between the painful and pain-free knees. A Kappa test was used to evaluate the relationship between the location of pain and the location of tracer uptake, and a Pearson's correlation test was used to evaluate the correlation between pain intensity and tracer intensity.

Results

We detected regions of increased tracer uptake (Fig. 1), indicative of elevated bone metabolic activity in 17 of the 20 painful knees analyzed. The average volume of the regions of increased tracer uptake was 1cm^3 (range 0.05 to 3cm^3). Regions of increased uptake were found in 15 patellae and four femoral trochleae (two subjects exhibited increased uptake in both the patella and trochlea). None of the four pain-free knees exhibited regions of increased uptake.

Due to the fusion of the PET images onto CT images, we could accurately localize the regions of increased tracer uptake. Seven subjects exhibited increased tracer uptake on the lateral patellar facet, seven exhibited increased tracer uptake on the medial patellar facet, one exhibited increased tracer uptake on the inferior pole of the patella, two exhibited increased uptake in the medial trochlea, one on the lateral trochlea, and one in the center of the trochlea.

Sixteen subjects localized pain to specific regions of the patellofemoral joint during the physical exam: 7 subjects had pain on the lateral facet, 7 had pain on the medial facet, and 2 experienced pain on the inferior pole of the patella. The remaining four subjects did not exhibit tenderness during the palpation assessment, and we were unable to localize pain in these subjects. Additionally, three subjects did not exhibit increased tracer uptake and were not included in the analysis, leaving a total of 14 subjects for the analysis. We found that in 10 of the 14 subjects the region of pain during palpation corresponded to the region of

increased tracer uptake, resulting in a moderate correlation between pain location and location of tracer uptake ($\kappa = 0.44$).

The normalized mean and peak SUV of the region of tracer uptake were greater in the 20 painful knees compared to the four pain-free knees (Fig. 2). The mean normalized SUV was 36% lower in the pain-free knees compared to the painful knees ($p = 0.01$). The peak normalized SUV was 59% lower in the pain-free knees compared to the painful knees ($p = 0.0006$).

Increasing pain intensity tended to correlate with increasing tracer uptake (Fig. 3). We found a moderate correlation between pain intensity and normalized mean SUV ($r^2 = 0.55$; $p = 0.0005$). A modest correlation was found between pain intensity and the normalized peak SUV ($r^2 = 0.29$; $p = 0.02$).

Discussion

Our goal was to use ^{18}F NaF PET/CT to determine whether subjects with patellofemoral pain exhibit elevated bone metabolic activity at the patellofemoral joint. We also evaluated whether bone metabolic activity correlates with pain. We hypothesized that pain results from elevated stress at the patellofemoral joint that could lead to elevated bone remodeling activity at the joint. Our results suggest that patellofemoral pain is related to increased ^{18}F fluoride tracer uptake, indicative of elevated bone metabolic activity at the joint.

Previous studies investigating whether patients with patellofemoral pain exhibit increased bone activity using Tc-99m MDP bone scanning revealed diffuse tracer uptake at the knee in 44% of the painful knees examined[7]. Of the knees with diffuse tracer uptake, over half exhibited increased tracer uptake in the patella[7]. In our study, we observed increased ^{18}F fluoride uptake in 85% of the knees. This increase in the percentage of subjects with increased uptake may be due to increased sensitivity of ^{18}F PET/CT. In agreement with the previous study, we also found that the majority of the knees exhibited increased uptake in the patella compared to the femur.

While Tc-99m MDP bone scintigraphy is beneficial for identifying diffuse regions of uptake and can differentiate uptake in the patella from uptake in the femur, a significant factor differentiating our study from previous work using bone scintigraphy is that we used registered PET/CT images, allowing for excellent anatomical localization of tracer distribution. This enabled us to accurately identify the specific regions within a bone that exhibited elevated bone metabolic activity.

Increased bone metabolic activity was more often observed in the patella compared to the femur. Among those with increased metabolic activity in the patella, the metabolic activity was located on the posterior surface in 12 of the 15 knees. The increased metabolic activity may be a result of excessive stress in the subchondral bone of the patella. While stress cannot be measured *in vivo*, previous studies estimated patellofemoral joint stress during activities such as walking, stair climbing, and squatting in patients with patellofemoral pain[14-16] and revealed increased joint stress in knees with patellofemoral pain[16]. Furthermore, octahedral shear stress is greater in patellar cartilage compared to femoral cartilage[17], which may be one explanation for our observation that more subjects exhibited increased metabolic activity on the patella compared to the femur. Though these estimates of bone stress used data acquired during weight-bearing activities, they can still provide insight into a potential mechanism of bone metabolic activity measured during the non-weight-bearing conditions of this study.

The presence of increased metabolic activity in the patella may have significant implications. Histological studies demonstrated the presence of sensory nerve fibers containing substance-P, a nociceptive neurotransmitter, in the patella [18], suggesting that this region may be sensitive to mechanical stress. This observation along with our results suggests that the patella is likely to be more affected in patellofemoral pain syndrome and could be the source of pain. Additionally, we saw a moderate correlation between the region of the joint most sensitive to palpation and the location of the elevated bone metabolic activity. We also observed a moderate correlation between the intensity of pain and the intensity of bone metabolic activity, further suggesting a relationship between bone metabolic activity and pain. Treatments aimed at decreasing the stress in the patella may be effective in decreasing bone metabolic activity and alleviating pain.

An additional implication of these results is that ^{18}F NaF PET/CT may be a potential diagnostic tool for evaluating elevated bone stress in patients with patellofemoral pain and identifying specific regions of elevated stress. Future work correlating mechanical stress with bone metabolic activity is needed to confirm the hypothesis that tracer uptake is related to bone stress.

A limitation of our study was that we did not evaluate pain-free controls due to the ionizing radiation involved in PET/CT scanning. We chose to measure bone metabolic activity in the knees of subjects with unilateral pain as an alternative. This limits the number of pain-free knees that we could study, as only four subjects had unilateral pain. Additional subjects are needed for a more complete analysis. Furthermore, the pain-free knee of a subject with unilateral patellofemoral pain may have altered bone metabolic activity patterns compared to a knee of a subject who has never experienced knee pain. Nonetheless, the comparison of pain-free and painful knees provides interesting insights in the absence of true control knees. Another limitation is that the definition of increased tracer uptake (greater than twice the bone background) was chosen arbitrarily, and our results may differ if we choose a different threshold. We did have a nuclear medicine radiologist independently examine the images, and his assessment of regions of increased tracer uptake was in agreement with the regions we identified using our threshold. This provides confidence that the regions identified in this study correspond to clinically meaningful increases in bone metabolic activity.

Despite these limitations, there are a number of important implications of this study. Our results suggest that subjects with patellofemoral pain exhibit elevated bone metabolic activity that may indicate a source of pain in these patients. We found that the majority of subjects exhibited increased bone metabolic activity in the posterior patella, suggesting that this region may play a role in the development of pain. The implications of these results are that treatments to reduce bone metabolic activity by reducing the stress at the patella may be effective in alleviating pain in these subjects.

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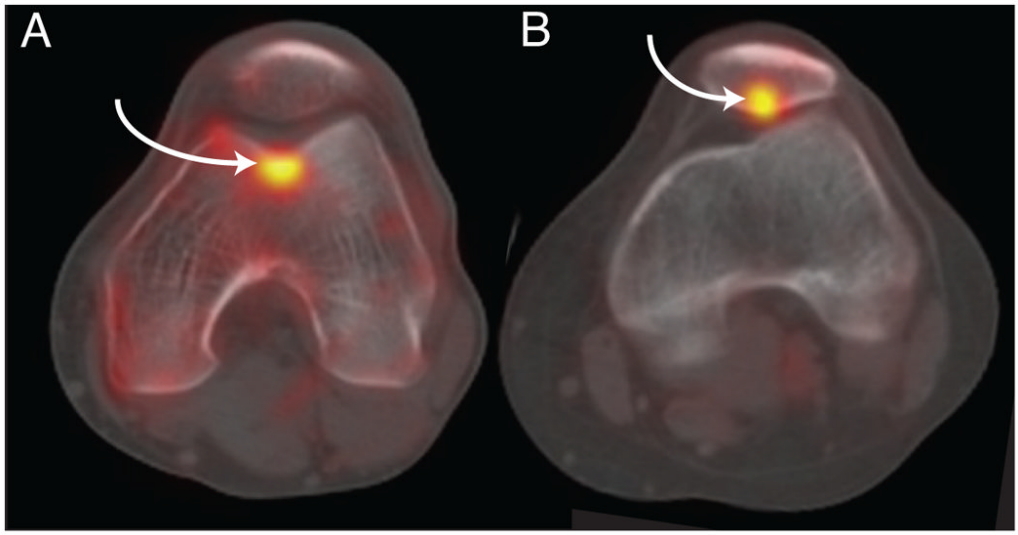

Figure 1.
A) Sample ^{18}F NaF PET/CT image of the patellofemoral joint with a region of increased tracer uptake in the trochlea. B) Sample ^{18}F NaF PET/CT image of the patellofemoral joint with a region of increased tracer uptake in the patella. Regions of increased tracer uptake are indicated by the arrows.

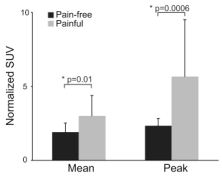

Figure 2.

Comparison of normalized Standardized Uptake Value between the 20 painful knees and the 4 pain-free knees of the subjects with unilateral pain. The painful knees exhibited increased tracer uptake compared to the pain-free knees. The error bars represent one standard deviation.

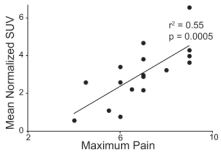

Figure 3.
Correlation between normalized mean Standardized Uptake Value and maximum pain felt during the previous year.