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Quantitative Imaging of Bone-Cartilage Interactions in ACL-Injured Patients with PET-MRI

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Abstract

Objective: To investigate changes in bone metabolism by PET, as well as spatial relationships between bone metabolism and MRI quantitative markers of early cartilage degradation, in ACL-reconstructed knees.

Design: Both knees of 15 participants with unilateral reconstructed ACL tears and unaffected contralateral knees were scanned using a simultaneous 3.0T PET-MRI system following injection of ¹⁸F-sodium fluoride (¹⁸F-NaF). The maximum pixel standardized uptake value (SUV_{max}) in the subchondral bone and the average T₂ relaxation time in cartilage were measured in each knee in 8 knee compartments. We tested differences in SUV_{max} and cartilage T₂ relaxation times between the ACL-injured knee and the contralateral control knee as well as spatial relationships between these bone and cartilage changes.

Results: Significantly increased subchondral bone ¹⁸F-NaF SUV_{max} and cartilage T₂ times were observed in the ACL-reconstructed knees (median[inter-quartile-range(IQR)]:5.0[5.8], 36.8[3.6]ms) compared to the contralateral knees (median[IQR]:1.9[1.4],34.4[3.8]ms). A spatial relationship between the two markers was also seen. Using the contralateral knee as a control, we observed a significant correlation of $r=0.59$ between the difference in subchondral bone SUV_{max} (between injured and contralateral knees) and the adjacent cartilage T₂ (between the two knees) [$p<0.001$], with a slope of 0.49ms/a.u. This correlation and slope were higher in deep layers ($r=0.73$, slope=0.60ms/a.u.) of cartilage compared to superficial layers ($r=0.40$, slope=0.43ms/a.u.).

Conclusions: ¹⁸F-NaF PET-MR imaging enables detection of increased subchondral bone metabolism in ACL-reconstructed knees and may serve as an important marker of early OA

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progression. Spatial relationships observed between early OA changes across bone and cartilage support the need to study whole-joint disease mechanisms in OA.

Keywords

PET-MRI; Bone Remodeling; Osteoarthritis; Bone-Cartilage Interactions

INTRODUCTION

Increasing evidence that osteoarthritis (OA) is a disease of the whole joint with numerous phenotypes suggests that biomarkers are necessary in multiple tissues to not only study multiple mechanisms of early disease but also spatial interactions between tissues. Anterior cruciate ligament (ACL) injuries provide a phenotype to study early changes that occur in osteoarthritis^{1,2}. ACL tears are a common and severe injury to the knee that are known to predispose subjects to an increased risk for development of OA. While ACL reconstruction (ACLR) surgery is able to restore stability of the knee and allow return to an active lifestyle, studies have shown that 50% of these patients may progress to post-traumatic OA within 10–15 years after their injury³. This makes them an optimal population to study early mechanisms of OA as the initiating event is known.

Magnetic resonance imaging (MRI) is used widely for the detection and monitoring of ACL injuries as well as to non-invasively study the complex disease processes involved in OA⁴. MRI provides outstanding high-resolution morphologic information of joint tissue with numerous different contrasts. Furthermore, advanced quantitative MRI methods, including T_2 or $T_{1\rho}$ relaxation measurement, have been associated with tissue microstructure in cartilage and meniscus and show promise for detecting early biochemical changes in OA⁵. While radiographic OA changes may take years to present, changes in cartilage matrix organization as measured by T_2 and $T_{1\rho}$ relaxation times, have been observed as soon as 1 year post ACL tear and reconstruction surgery^{1,6}.

In addition to cartilage, degradation of subchondral bone is another well-recognized feature of OA. While these events are often studied in isolation, there is evidence that the bone–cartilage interface functions as a synergistic unit, with biochemical and molecular crosstalk between bone and cartilage⁷. On MRI, while bone structure can be inferred by the surrounding soft tissues, its lack of signal makes functional imaging of subchondral bone structures in the knee infeasible. Positron emission tomography (PET) imaging with ¹⁸F-Sodium fluoride (¹⁸F-NaF, $T_{1/2} = 110$ minutes) provides a unique way to assess regional bone remodeling^{8,9}. The radiolabeled fluoride ion is able to exchange with the hydroxyl groups in hydroxyapatite crystals on the surface of the bone matrix to form fluoroapatite⁸. Thus uptake of ¹⁸F-NaF is concentrated preferentially at sites of newly mineralizing bone and can be used as a marker of bone metabolism¹⁰. Additionally, ¹⁸F-NaF PET may detect metabolic bone abnormalities that appear normal on MRI and is a promising tool for detection of early metabolic changes in OA¹¹.

Simultaneous PET/MRI systems provide a unique tool to simultaneously image multiple markers of early OA and to study spatiotemporal relationships between degenerative changes in bone and cartilage^{11–13}. This study aims to investigate subchondral bone ¹⁸F-

NaF uptake in ACL-reconstructed knees as well as the spatial relationship between bone ^{18}F -NaF uptake and adjacent cartilage T_2 relaxation times. To account for inter-subject variation, the unaffected contralateral knees were used as a control. We hypothesized that ^{18}F -NaF can depict early abnormalities in bone metabolism and that there is a spatial relationship between this abnormal bone activity and early degenerative cartilage matrix changes as measured by T_2 relaxation times.

MATERIALS AND METHODS

Study population

Fifteen subjects (mean age 32.7 ± 10.5 years, 10 male, 5 female, mean BMI of 26.5 ± 4.3 kg/m^2) with unilateral ACL tears (mean time from injury = 4.0 ± 3.2 years) and unaffected contralateral knees were recruited for the study. All subjects had undergone successful ACL reconstructive surgery. Subjects with a prior history of knee pain or injury in their contralateral knee, known high grade OA, pregnant women, children and those less than 6 months or more than 10 years removed from ACL injury, were excluded from participating. Based on previously research¹¹, we expected to see SUV_{max} differences between subchondral bone abnormalities and normal appearing bone to be greater than one standard deviation. Our sample size of 15 pairs of knees provided 97% power at two-sided 5% error to detect a difference as small as one standard deviation. Prior to participating in the study, all subjects were informed about the nature of the study and provided written informed consent according to the University Institutional Review Board.

PET-MRI Scanning

Both knees of each subject were scanned on a 3T whole-body time-of-flight enabled PET-MR hybrid system (GE SIGNA, GE Healthcare, Milwaukee, WI) following injection of 74–111 MBq of ^{18}F -NaF and a 45-minute delay to allow for tracer uptake. PET data acquisition of the knees was performed in one PET bed (FOV = 26 cm). MRI data was simultaneously acquired on one knee at a time with a 16-channel flexible phased-array wrap coil (NeoCoil, Pewaukee, WI). A quantitative double-echo in steady-state (DESS) sequence was acquired for tissue morphology, segmentation and T_2 relaxation time mapping (TR/TE₁/TE₂ = 24.6/5.8/43.4 ms; FOV = 16.0 cm; matrix = 320×320 (interpolated to 512×512); slice thickness = 1.5 mm)^{14,15}. Additionally, a 2-point Dixon fat-water T_1 -weighted fast spoiled gradient echo MR sequence (TR/TE₁/TE₂ = 4.1/1.1/2.2 ms; FOV = 50×37.5 cm; matrix = 256×128 ; slice thickness/overlap = 5.2/2.6 mm; 120 images/slab; scan time = 18 sec) was acquired for MR-based attenuation correction (MRAC) of PET data¹⁶. PET data was acquired simultaneously for the entire duration of the MRI scans, which lasted 30 minutes for each knee, for a total scan time of about one hour.

Image Analysis

^{18}F -NaF images were reconstructed from 30 minutes of acquired list-mode data using a time-of-flight PET reconstruction (4 iterations and 28 subsets, 50 cm field of view, 192×192 matrix, 2.78 mm slice thickness). Reconstruction included correction for scatter, random counts, dead time, and point-spread function. MRAC images were used for automated anatomic segmentation and tissue-specific linear attenuation coefficients were assigned to

each segmented tissue¹⁶. T_2 relaxation times were determined for articular cartilage using Extended Phase Graph (EPG) modeling of the relationship between the two DESS signals as previously described¹⁵. One experienced reviewer (F.K.) [Intra-reader reliability - 95% limits of agreement: T_2 measurements: -0.62 to 0.62 ms; SUV_{max} measurements: 0 to 0] segmented each knee into 8 cartilage and adjacent subchondral bone compartments [Patella, Trochlea, Central and Posterior Medial Femoral Condyle, Central and Posterior Lateral Femoral Condyle and Medial and Lateral Tibia] (Fig. 1). The cartilage was further subdivided into deep and superficial regions by a midline. The maximum pixel standardized uptake value (SUV_{max}) in each subchondral bone compartment and the average T_2 relaxation time in each cartilage compartment was measured. Additionally, to identify “hot” regions of abnormal tracer uptake on PET SUV maps, subchondral bone areas with SUV greater than 5 times the reference SUV in normal bone (i.e., the mean SUV from a region of normal-appearing trabecular bone in the medial femoral condyle) were identified as high uptake Volumes of Interest (VOI_{High}).

Statistical Analysis

We tested the hypothesis that average compartmental SUV_{max} in subchondral bone on PET images and cartilage T_2 relaxation times on MRI differed between the ACL injured knee and the contralateral control knee using the Wilcoxon signed-rank test. This was performed for cartilage as a whole, as well as for the deep and superficial layers of cartilage. Differences in PET SUV_{max} between compartments within ACL-injured and contralateral knees, respectively, were evaluated using a Wilcoxon signed-rank test. Lastly, the relationship between differences in subchondral bone SUV_{max} (between injured and contralateral knees in each subject for each compartment) and differences in T_2 relaxation time in the adjacent cartilage (between the two knees in each subject for each compartment) were assessed with linear regression using a robust variance estimator and adjusted for clustering within patient. Residuals were tested for normality and homoscedasticity. Statistical analyses were done with Stata Release 15 (StataCorp LP, College Station, TX) and R version 3.3.1 (r-project.org) using version 1.1.3 of the “coin” package and using the statistical toolbox in Matlab (Mathworks, Natick, MA). Nominal (unadjusted) p -values are reported and $\alpha < 0.05$ was considered statistically significant except where a Bonferroni adjustment was applied when $\alpha < 0.05/m$, where m is the number of hypotheses, was considered statistically significant.

RESULTS

While structurally similar on conventional MRI, the ACL injured knee showed considerably higher ^{18}F -NaF uptake compared to the unaffected contralateral knee (Fig. 2). More compartments had areas of high PET uptake (VOI_{High}) in the ACL injured knees (61 out of 120 [51%]) compared to the contralateral knee (7 out of 120 [6%]). Further, SUV_{max} across compartments was significantly higher in the injured knee (median = 5.0, inter-quartile range (IQR) = 5.8) compared with the contralateral knee (median = 1.9, IQR = 1.4) [$p < 0.001$]. Table 1 shows the median and IQR of PET SUV_{max} in each analyzed compartment for the ACL-injured and contralateral knees. With the exception of the trochlear and medial tibial subchondral bone, each compartment had significantly higher

mean SUV_{max} in the ACL-injured knee compared to corresponding compartment of the contralateral knee (Table 1) [Wilcoxon Signed-Rank with Bonferroni adjustment]. Within each knee, while there was some regional variation, no significant differences in SUV_{max} were observed between compartments [Wilcoxon Signed-Rank with Bonferroni adjustment].

In cartilage, T_2 relaxation time was increased in the injured knee compared with the contralateral knee. A median T_2 of 36.8 ms (IQR = 3.6 ms) was observed in the ACL injured knee cartilage, which was significantly greater than the 34.4 ms (IQR = 3.8 ms) observed in the contralateral knee cartilage [$p=0.002$]. When deep and superficial layers of cartilage were considered separately, the increase in compartmental T_2 was more pronounced in the deep layers of cartilage compared to the superficial layers. In the ACL injured knee, median compartmental T_2 relaxation times of 31.0 ms (IQR = 2.5 ms) and 43.1 ms (IQR = 4.0 ms) were observed in deep and superficial layers of cartilage, respectively, compared to 28.0 ms (IQR = 2.8 ms) and 40.7 ms (IQR = 4.2 ms) in the contralateral knee. These differences were statistically significant [$p=0.001$ for deep layers, $p=0.02$ for superficial layers]. Table 2 lists mean T_2 relaxation times for all cartilage as well as by compartment for the ACL injured and contralateral knees. Nominal p -values, as computed by Wilcoxon signed-rank test, are also shown. Statistically significant values with Bonferroni adjustment ($p<0.0063$ [0.05/8]) are noted in bold with asterisks.

In addition to differences in quantitative disease markers in subchondral bone and cartilage between ACL injured and contralateral knees, spatial relationships between these markers were also observed. Figure 3 shows a representative example of increased ^{18}F -NaF PET uptake in subchondral bone adjacent to an area of increased cartilage T_2 relaxation time in the ACL injured knee. Using the contralateral knee as a control, we observed a statistically significant correlation of $r=0.59$ [$p<0.001$], between the difference in subchondral bone SUV_{max} and the adjacent cartilage T_2 , with a slope of 0.49 ms/a.u. (Fig. 4). When the cartilage was further subdivided, this correlation and slope was higher in the deep layers ($r=0.73$ [$p<0.001$], slope=0.60 ms/a.u.) of cartilage compared with the superficial layers ($r=0.40$ [$p<0.001$], slope=0.43 ms/a.u.).

DISCUSSION

In this study, simultaneous PET-MR imaging was used to simultaneously and quantitatively study multiple metabolic and biochemical markers of early OA in bone and cartilage as well as spatial relationships between the two tissues. ACL-injured knees, which are at risk for developing OA, showed significantly increased bone metabolism, as measured by ^{18}F -NaF PET uptake, compared to their unaffected contralateral knee. Further, increased T_2 relaxation times were also observed in the ACL-injured knee and were spatially correlated with ^{18}F -NaF PET uptake. This work strongly supports a spatial relationship between increased bone metabolism and MRI markers of early cartilage matrix degradation.

Increased subchondral bone remodeling has been implicated as a mechanism of OA progression, particularly in the early disease stages^{17,18}. However, measurement of metabolic or biochemical bone markers remains challenging. 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 more practical but is limited to global changes. On the other hand, ^{18}F -NaF PET imaging is able to detect radiolabeled ^{18}F ions after they undergo chemisorption on hydroxyapatite and then rapidly exchange with hydroxyl ions (-OH) the surface of the hydroxyapatite matrix $[\text{Ca}_{10}(\text{PO}_4)_6\text{OH}_2]$ to form fluoroapatite $[\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2]$ ¹⁹. Thus, uptake and retention of ^{18}F -NaF is dependent on areas of “exposed” bone surface. Osteoblastic and osteolytic processes increase exposure of bone surface, providing a higher availability of binding sites and resulting in increased uptake²⁰. Bone activity measured with ^{18}F -NaF has been shown to correlate with bone histomorphometry^{10,21}.

Recent studies have demonstrated the sensitivity of ^{18}F -NaF PET to quantitatively evaluate uptake measures of bone metabolism in established features of OA seen on MRI¹¹. Further, the presence of areas of high PET uptake in areas of normal-appearing subchondral bone on MRI suggested that ^{18}F -NaF uptake may detect early changes in bone metabolism prior to structural damage as seen in the joint. Lastly, PET imaging with ^{18}F -NaF has several advantages compared to other commonly utilized radionuclide imaging methods such gamma camera studies with technetium-99m-methylene diphosphonate ($^{99\text{m}}\text{Tc}$]TcMDP, $T_{1/2}$ = 6 hours) (bone scans). The main advantages of ^{18}F -NaF is the absence of binding to plasma proteins in circulation as well as its exceptionally high and rapid uptake into bone and rapid clearance from soft tissue²². Additionally, PET has better spatial resolution and provides three-dimensional resolution compared to gamma camera studies⁹.

Our results further support the hypothesis that increased metabolic bone activity detected with ^{18}F -NaF PET can serve as a marker for early OA and progression of disease. Patients who experience ACL tears are at a known increased risk for developing OA, and are thus an especially useful population for investigating early mechanisms of OA as the initiating event is known³. ACL-injured knees showed significantly elevated ^{18}F -NaF PET uptake, indicative of increased bone metabolism, compared with the contralateral knee. Further, considerably more regions of high PET uptake (VOI_{High}) were observed in the ACL injured knee compared to the contralateral knee. Very few regions with high PET uptake were observed in the unaffected, contralateral knee of these otherwise healthy subjects, which provides a control measure for the abnormal uptake observed in the ACL-injured knee.

While all regional compartments with the exception of the trochlea and medial tibia showed a statistically significant increase in ^{18}F -NaF SUV_{max} in the ACL-injured knee compared to the contralateral knee, no significant difference in SUV_{max} was observed between various compartments within each knee. The diffuse nature of ^{18}F -NaF uptake may be due to changes in joint loading, knee rehabilitation or other factors that affect the whole-joint. Diffuse increases in cartilage T_2 and $T_{1\rho}$ relaxation times have also been observed after ACL tears²³. High uptake is also often seen surrounding the ACL graft sites, likely as a result from the ACL reconstruction surgery. While this is not subchondral and wouldn't directly affect the results reported in this study, it may have an indirect effect on surrounding tissue as well as joint mechanics as a whole. However, the small sample size and variation in patients' post-injury time may have made it difficult to identify any conclusive trends in regional SUV variation between compartments. Longitudinal studies with larger samples sizes and more targeted patient populations are needed to evaluate regional differences in

bone metabolism and to make conclusions with respect to knee biomechanics in patients following ACL injury and reconstruction.

Advanced quantitative MRI methods, such as T_2 relaxation time mapping, have been extensively utilized to study early cartilage extracellular matrix degeneration. T_2 relaxation times have been associated with cartilage hydration as well as collagen content and structure due to dipolar interactions, and elevated T_2 relaxation times have been linked to future OA disease progression²⁴. Numerous studies have also reported increased T_2 relaxation times in ACL-reconstructed knees at various follow-up times, compared with the uninjured knee or a control population^{1,25,26}. In agreement with prior literature, we observed significantly elevated cartilage T_2 relaxation times in the ACL-injured knee compared to the unaffected contralateral knee. Lamina analysis showed larger T_2 differences between cartilage in the ACL-injured and contralateral knees in the deep layers of cartilage compared to the superficial layers. Additionally, several compartments, and in particular the medial femoral condyle, showed statistically significant differences between T_2 values in deep layers of cartilage between the two knees. The medial femoral condyle is thought to be an area of high weight-bearing load and similar results have been reported by previous studies^{27,28}. However, the small sample size and lack of control for mechanical factors in this and other similar cartilage studies preclude us from making conclusive biomechanical associations between ACL injuries and regional associations with early OA cartilage matrix changes.

Hybrid PET-MR imaging of OA uniquely allows the simultaneous evaluation of spatial relationships across tissues. Our previous studies observed a link between increased ^{18}F -NaF PET uptake and late-stage degenerative cartilage changes¹¹. This study demonstrated a correlation between increased ^{18}F -NaF PET uptake in subchondral bone and increased T_2 relaxation time in adjacent cartilage. This suggests a spatial relationship between metabolic and biochemical markers of early OA in bone and cartilage. Further, this correlation and the slope of this relationship was higher in the deep layers of cartilage that are adjacent to the subchondral bone, compared to the superficial layers. This finding strongly suggests an interdependent relationship between bone and cartilage with early degenerative changes in one tissue having a degenerative effect on the neighboring tissue.

It is also important to point out several limitations to this study. The ^{18}F -NaF radiotracer exposes patients to ionizing radiation. However, due to lack of ionizing radiation in MRI and the long duration of PET data collection, which allowed for a reduced radiotracer dose, the effective dose to patients was less than 3 mSv and presents minimal risk to patients²⁹. Due to the nature of the study, a small sample size was used. Further, patients were recruited only on the basis of prior unilateral ACL injury that was surgically reconstructed (within 5 months to 10 years) and no history of pain or injury to their contralateral knee, without controlling for other factors such as type of injury or reconstruction or patient activity levels. While quantitative MRI results are in agreement with prior longitudinal studies and statistical significance was obtained in evaluation of PET uptake in subchondral bone between ACL injured and contralateral knees, replication and more targeted studies remain warranted. Additionally, this study used the contralateral knee as a control instead of age-matched healthy subjects. Other studies have shown that following ACL injury, the contralateral knee may also show changes due to changes in loading, knee biomechanics, or

other factors²³. However, we felt that in this study, the contralateral knee serves as the ideal control as it minimizes inter-subject variation; in particular, that intra-subject tracer distribution would be equivalent to both knees for comparison of PET SUV.

Another limitation is that PET uptake and T₂ relaxation times were not correlated with changes in tissue morphology such as the presence of bone marrow lesions or bone bruising. Previous work has shown increased PET SUV in bone abnormalities detected on MRI, which may have been the cause of high subchondral bone PET SUV or adjacent cartilage T₂ changes in our ACL patients¹¹. However, ¹⁸F-NaF PET is able to provide a quantitative imaging based measure to characterize these lesions. Further, ¹⁸F-NaF PET may detect changes in bone activity that occur prior to structural changes that are seen on MRI¹¹. As we do not know the etiology of these morphologic features, which may be caused by abnormal bone activity, we did not isolate them in this cross-sectional study. Additionally, T₂ relaxation times may not capture the earliest macromolecular changes that occur in cartilage in OA. It should also be noted that as our analysis was cross-sectional, the observations made in this study are correlative. Longitudinal studies are necessary to evaluate temporal relationships between morphologic changes, increased ¹⁸F-NaF PET uptake and T₂ relaxation times in the development of OA. Lastly, attenuation of PET photons due to our flexible MR coil array was not accounted for in computation of PET SUV maps. This likely led to an underestimation of calculated SUV values, although we expect the tracer distributions to be preserved with and without this coil³⁰.

In conclusion, this study demonstrated significantly increased ¹⁸F-NaF PET uptake in the subchondral bone of knee joints following ACL-injury and reconstructive surgery, which are at known increased risk for developing osteoarthritis, compared to their unaffected contralateral knees. Similarly, and in agreement with prior research, significantly increased cartilage T₂ relaxation times were observed in the ACL injured knees compared with their contralateral control knees. Lastly, a spatial correlation was observed between increased ¹⁸F-NaF PET uptake in subchondral bone and increased T₂ relaxation times in adjacent cartilage, particularly in the deep layers of cartilage, which are adjacent to the subchondral bone. Our study supports the hypothesis of a spatial relationship between early degenerative OA changes across bone and cartilage. Hybrid PET-MRI systems thus provide a unique tool to simultaneously and quantitatively assess several metabolic and biochemical markers of early OA in bone and cartilage as well as spatial relationships between the two tissues. ¹⁸F-NaF PET-MRI holds tremendous potential to provide biomarkers that quantitatively assess early progression of OA, which are crucial to develop and evaluate disease-modifying treatments, and ultimately arrest or reverse the progression of OA.

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Literature Cited

1. Li X, Kuo D, Theologis A, Carballido-Gamio J, Stehling C, Link TM, Ma CB, Majumdar S. Cartilage in Anterior Cruciate Ligament Reconstructed Knees: MR Imaging T1 and T2. Initial Experience with 1-year Follow-up Radiology. 2011; 258(2):505. [PubMed: 21177392]
2. 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 Mol Imaging. 2017; 16:1536012117714575. [PubMed: 28730928]
3. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis The American journal of sports medicine. 2007; 35(10):1756–1769. [PubMed: 17761605]
4. Potter HG, Koff MF. MR Imaging Tools to Assess Cartilage and Joint Structures HSS journal : the musculoskeletal journal of Hospital for Special Surgery. 2012; 8(1):29–32. [PubMed: 23372524]
5. Matzat SJ, Kogan F, Fong GW, Gold GE. Imaging strategies for assessing cartilage composition in osteoarthritis Current rheumatology reports. 2014; 16(11):462. [PubMed: 25218737]
6. Monu UD, Jordan CD, Samuelson BL, Hargreaves BA, Gold GE, McWalter EJ. Cluster analysis of quantitative MRI T2 and T1rho relaxation times of cartilage identifies differences between healthy and ACL-injured individuals at 3T Osteoarthritis Cartilage. 2017; 25(4):513–520. [PubMed: 27720806]
7. Lories RJ, Luyten FP. The bone-cartilage unit in osteoarthritis Nature reviews Rheumatology. 2011; 7(1):43–49. [PubMed: 21135881]
8. Czernin J, Satyamurthy N, Schiepers C. Molecular mechanisms of bone ¹⁸F-NaF deposition Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2010; 51(12):1826–1829.
9. Jadvar H, Desai B, Conti PS. Sodium ¹⁸F-fluoride PET/CT of bone, joint, and other disorders Semin Nucl Med. 2015; 45(1):58–65. [PubMed: 25475379]
10. Piert M, Zittel TT, Becker GA, Jahn M, Stahlschmidt A, Maier G, Machulla HJ, Bares R. Assessment of porcine bone metabolism by dynamic [¹⁸F]-fluoride ion PET: correlation with bone histomorphometry Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2001; 42(7):1091–1100.
11. Kogan F, Fan AP, McWalter EJ, Oei EHG, Quon A, Gold GE. PET/MRI of metabolic activity in osteoarthritis: A feasibility study Journal of Magnetic Resonance Imaging. 2016:n/a–n/a.
12. Savic D, Podoia V, Seo Y, Yang J, Bucknor M, Franc BL, Majumdar S. Imaging Bone-Cartilage Interactions in Osteoarthritis Using [¹⁸F]-NaF PET-MRI Mol Imaging. 2016; 15:1–12. [PubMed: 28654417]
13. Kogan F, Fan AP, Gold GE. Potential of PET-MRI for imaging of non-oncologic musculoskeletal disease Quantitative Imaging in Medicine and Surgery. 2016; 6(6):756–771. [PubMed: 28090451]
14. Staroswiecki E, Granlund KL, Alley MT, Gold GE, Hargreaves BA. Simultaneous estimation of T(2) and apparent diffusion coefficient in human articular cartilage in vivo with a modified three-dimensional double echo steady state (DESS) sequence at 3 T Magn Reson Med. 2012; 67(4): 1086–1096. [PubMed: 22179942]
15. Sveinsson B, Chaudhari AS, Gold GE, Hargreaves BA. A simple analytic method for estimating T2 in the knee from DESS Magn Reson Imaging. 2017; 38:63–70. [PubMed: 28017730]
16. Wagenknecht G, Kaiser HJ, Mottaghy FM, Herzog H. MRI for attenuation correction in PET: methods and challenges Magma. 2013; 26(1):99–113. [PubMed: 23179594]
17. Burr DB, Gallant MA. Bone remodelling in osteoarthritis Nature reviews Rheumatology. 2012; 8(11):665–673. [PubMed: 22868925]
18. Hayami T, Pickarski M, Wesolowski GA, McLane J, Bone A, Destefano J, Rodan GA, Duong LT. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model Arthritis Rheum. 2004; 50(4):1193–1206. [PubMed: 15077302]
19. Hawkins RA, Choi Y, Huang SC, Hoh CK, Dahlbom M, Schiepers C, Satyamurthy N, Barrio JR, Phelps ME. Evaluation of the skeletal kinetics of fluorine-18-fluoride ion with PET Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 1992; 33(5):633–642.

20. Bastawrous S, Bhargava P, Behnia F, Djang DS, Haseley DR. Newer PET application with an old tracer: role of ¹⁸F-NaF skeletal PET/CT in oncologic practice Radiographics. 2014; 34(5):1295–1316. [PubMed: 25208282]
21. Messa C, Goodman WG, Hoh CK, Choi Y, Nissenson AR, Salusky IB, Phelps ME, Hawkins RA. Bone metabolic activity measured with positron emission tomography and [¹⁸F]fluoride ion in renal osteodystrophy: correlation with bone histomorphometry J Clin Endocrinol Metab. 1993; 77(4):949–955. [PubMed: 8408470]
22. Blake GM, Siddique M, Frost ML, Moore AE, Fogelman I. Quantitative PET Imaging Using (18)F Sodium Fluoride in the Assessment of Metabolic Bone Diseases and the Monitoring of Their Response to Therapy PET Clin. 2012; 7(3):275–291. [PubMed: 27157458]
23. Pedoia V, Su F, Amano K, Li Q, McCulloch CE, Souza RB, Link TM, Ma BC, Li X. Analysis of the articular cartilage T1rho and T2 relaxation times changes after ACL reconstruction in injured and contralateral knees and relationships with bone shape Journal of orthopaedic research : official publication of the Orthopaedic Research Society. 2017; 35(3):707–717. [PubMed: 27557479]
24. Prasad AP, Nardo L, Schooler J, Joseph GB, Link TM. T(1)rho and T(2) relaxation times predict progression of knee osteoarthritis Osteoarthritis Cartilage. 2013; 21(1):69–76. [PubMed: 23059757]
25. Li H, Tao H, Hua Y, Chen J, Li Y, Chen S. Quantitative magnetic resonance imaging assessment of cartilage status: a comparison between young men with and without anterior cruciate ligament reconstruction Arthroscopy. 2013; 29(12):2012–2019. [PubMed: 24286800]
26. Bae JH, Hosseini A, Wang Y, Torriani M, Gill TJ, Grodzinsky AJ, Li G. Articular cartilage of the knee 3 years after ACL reconstruction. A quantitative T2 relaxometry analysis of 10 knees Acta Orthop. 2015; 86(5):605–610. [PubMed: 25854533]
27. Chu CR, Williams AA, West RV, Qian Y, Fu FH, Do BH, Bruno S. Quantitative Magnetic Resonance Imaging UTE-T2* Mapping of Cartilage and Meniscus Healing After Anatomic Anterior Cruciate Ligament Reconstruction The American journal of sports medicine. 2014; 42(8):1847–1856. [PubMed: 24812196]
28. Su F, Hilton JF, Nardo L, Wu S, Liang F, Link TM, Ma CB, Li X. Cartilage morphology and T1rho and T2 quantification in ACL-reconstructed knees: a 2-year follow-up Osteoarthritis Cartilage. 2013; 21(8):1058–1067. [PubMed: 23707754]
29. Lin EC. Radiation risk from medical imaging Mayo Clin Proc. 2010; 85(12):1142–1146. quiz 1146. [PubMed: 21123642]
30. Kogan, F., Rosenberg, J., Brazina, S., Fan, A., Holley, D. , Gold, G.. Effect of 16-Channel Flex Array Coil on PET Standardized Uptake Values for PET/MR Imaging of the knee. 2015; Toronto, Canada.

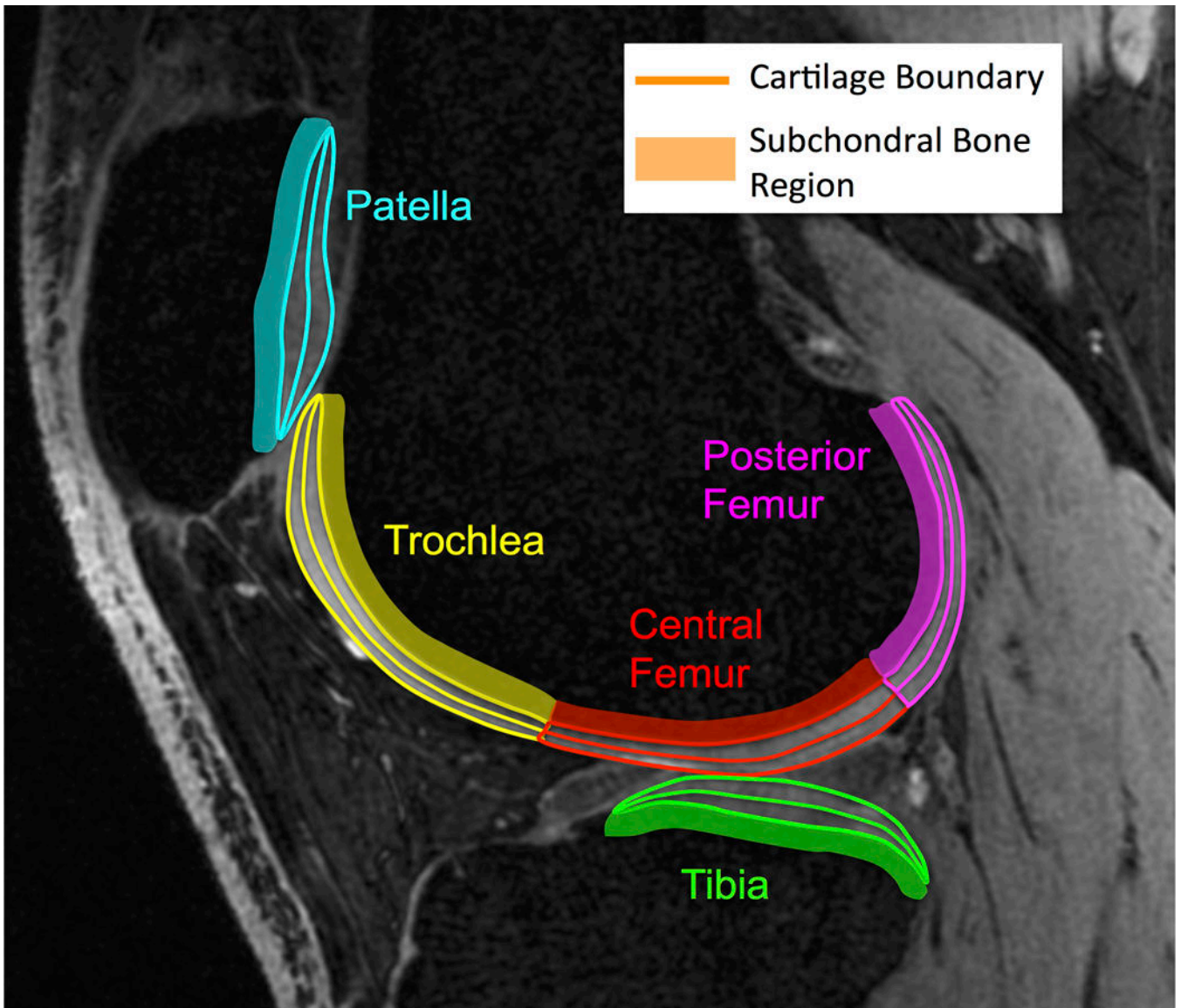


Figure 1: Cartilage and adjacent subchondral bone in each knee were segmented into 8 compartments. For each compartmental region of interest (ROI), an equivalent boundary was selected for cartilage and subchondral bone segmentations. The cartilage was further subdivided into deep and superficial layers. Patellar, trochlear, and lateral central femoral, posterior femoral and tibial cartilage regions are shown here. Medial central femoral, posterior femoral and tibial regions were also segmented [not shown].

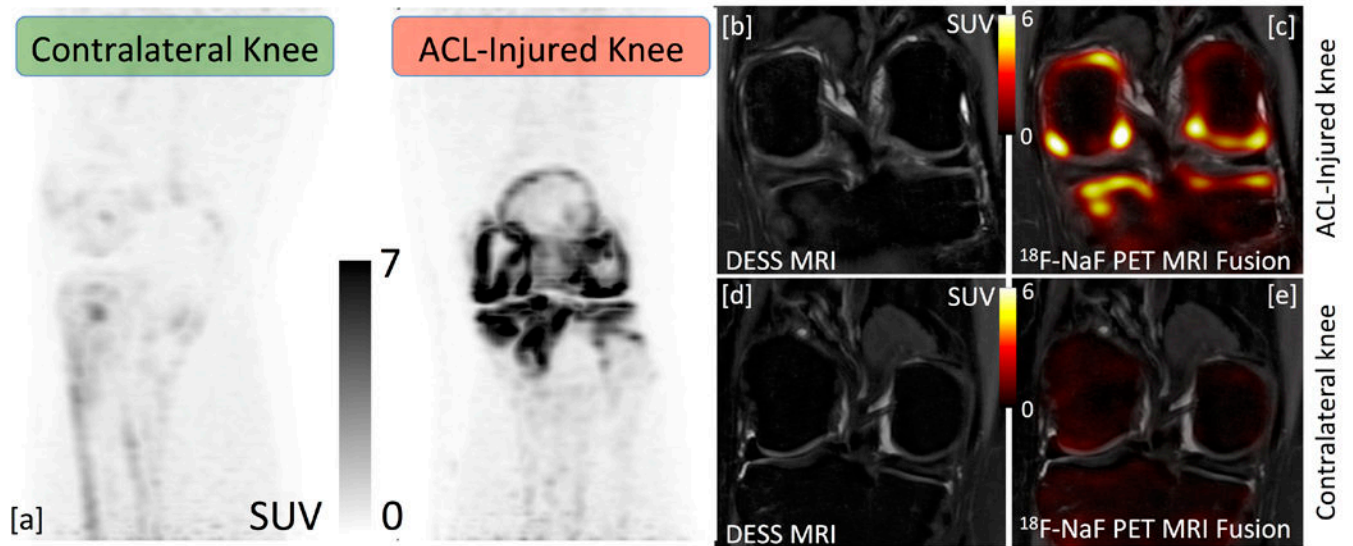


Figure 2:

[a] ^{18}F -NaF SUV map in a 27 year old female subject 1 year post ACL tear and reconstruction surgery. Considerably more uptake is observed in the ACLR knee compared to the contralateral knee. [b] Morphologic MR images of the ACLR knee look unremarkable while the [c] ^{18}F -NaF PET- MRI uptake fusion show the increased metabolic bone activity. [d] MRI and [e] fused ^{18}F -NaF PET- MRI of the unaffected contralateral knee look unremarkable for pathology or increased bone activity.

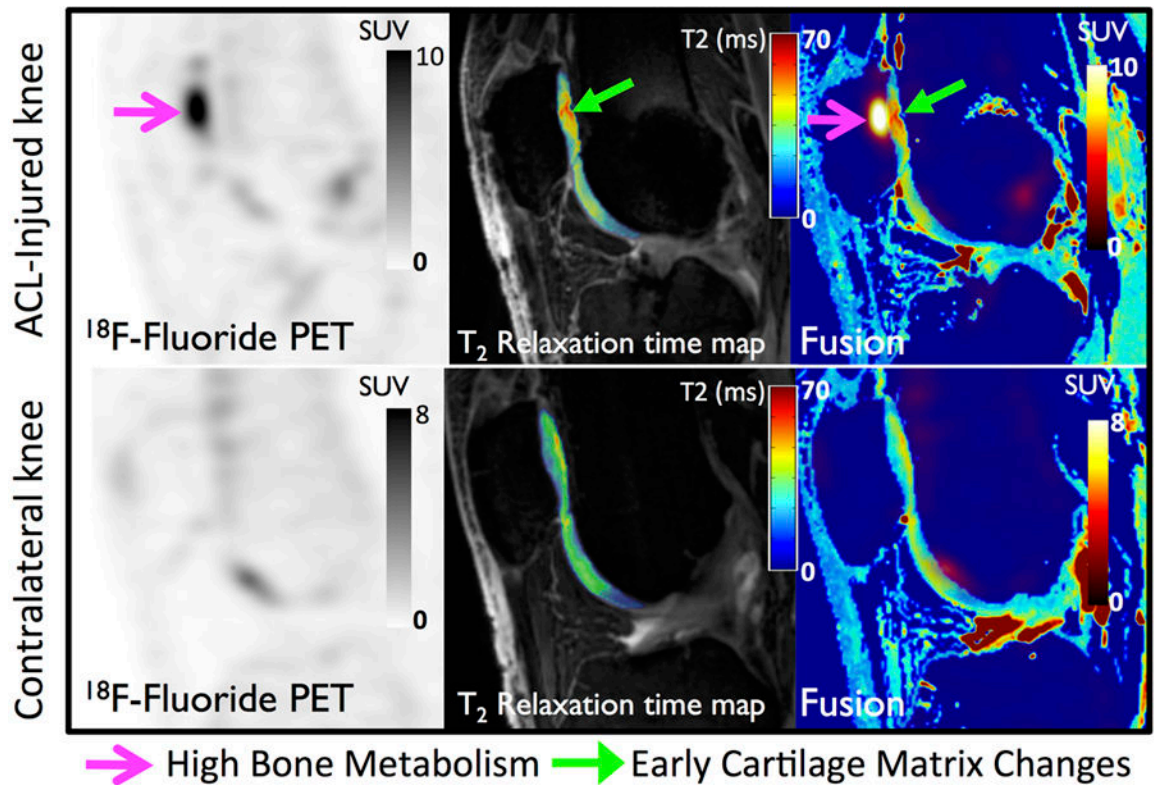


Figure 3:

¹⁸F-NaF PET (SUV), cartilage T₂ relaxation time (ms) and PET-MRI fusion maps of the ACL injured knee [top] and contralateral knee [bottom] of a subject with a unilateral reconstructed ACL tear. A high area of ¹⁸F-NaF uptake (magenta line arrow), indicative of increased bone activity in the patellar subchondral bone is seen adjacent to an area of increased cartilage T₂ relaxation time (solid green arrow), indicative of early cartilage collagen loss. By comparing the difference in subchondral bone ¹⁸F-NaF SUV_{max} and average T₂ in the patella (or other compartment) between injured and contralateral knees, we quantitatively study the correlation between early bone and cartilage changes in this population at risk for developing OA.

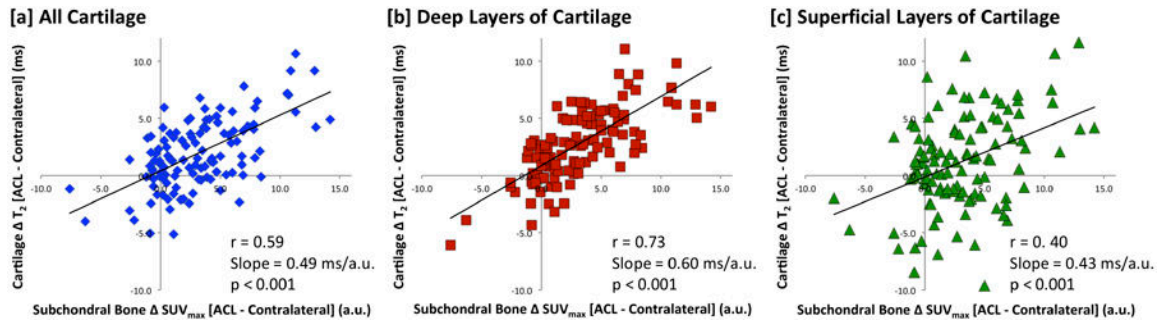


Figure 4:

Difference in subchondral bone SUV_{max} between ACL injured and contralateral knees as a function of difference of adjacent cartilage T_2 relaxation times between the two knees for [a] all cartilage, [b] deep layers of cartilage and [c] superficial layers of cartilage. Each data point represents one of the 8 segmented compartments in the 15 subjects evaluated (120 points total). Correlations (r) suggest a spatial relationship between increased bone metabolism and MRI markers of early cartilage matrix degradation.

Table 1:

Mean (and standard deviation) compartmental ^{18}F -NaF PET SUV_{max} and count of VOI_{High} for all subchondral bone as well as by compartment in the ACL injured and contralateral knees. Statistical significance of difference in uptake between knees is noted by nominal p-value [significant p-values with Bonferroni adjustment in bold with asterisks]

	Median Compartmental ^{18}F -NaF SUV_{max} (Inter-Quartile Range)			PET Positive Compartments (VOI_{High})		
	ACL Injured Knee	Contralateral Knee	ACL Injured Knee	Contralateral Knee	ACL Injured Knee	
Patella	3.0 (4.1)	1.9 (2.0)	0.004*	6	1	
Trochlear Femur	5.0 (4.7)	1.9 (1.6)	0.119	7	1	
Lateral Central Femur	7.4 (7.6)	2.1 (1.7)	0.001*	10	1	
Lateral Posterior Femur	2.6 (3.3)	1.8 (1.1)	0.004*	3	0	
Lateral Tibia	6.0 (4.6)	3.1 (1.7)	0.003*	9	1	
Medial Central Femur	4.8 (7.0)	1.5 (1.3)	0.005*	6	2	
Medial Posterior Femur	6.2 (5.7)	1.8 (1.0)	0.001*	10	0	
Medial Tibia	6.1 (7.1)	1.9 (0.9)	0.012	10	1	

Table 2:

Mean (and standard deviation) cartilage T₂ relaxation times (in ms) by compartment in the ACL injured and contralateral knees. Statistical significance of difference in T₂ values between knees is noted by nominal p-value [significant p-values with Bonferroni adjustment in bold with asterisks]

	Median T ₂ - All Cartilage (Inter-Quartile Range)			Median T ₂ - Deep Layer Cartilage (Inter-Quartile Range)			Median T ₂ - Superficial Cartilage (Inter-Quartile Range)	
	ACL Injured Knee	Contra-lateral Knee	p-Value	ACL Injured Knee	Contra-lateral Knee	p-Value	ACL Injured Knee	Contra-lateral Knee
Patella	33.4 (3.1)	33.2 (2.3)	<i>0.735</i>	28.1 (3.4)	27.4 (3.0)	<i>0.195</i>	37.8 (5.0)	37.8 (5.0)
Trochlear Femur	36.7 (4.3)	35.5 (2.5)	<i>0.042</i>	32.2 (4.3)	30.6 (3.2)	<i>0.093</i>	41.7 (4.6)	41.7 (4.6)
Lateral Central Femur	37.6 (8.7)	33.8 (4.3)	<i>0.011</i>	28.8 (5.1)	25.4 (3.3)	<i>0.001*</i>	45.0 (9.6)	45.0 (9.6)
Lateral Posterior Femur	38.7 (7.0)	35.2 (6.1)	<i>0.001*</i>	31.6 (6.2)	28.4 (5.1)	<i>0.001*</i>	43.4 (5.8)	43.4 (5.8)
Lateral Tibia	34.7 (8.2)	31.6 (6.0)	<i>0.006</i>	29.4 (7.9)	26.7 (5.5)	<i>0.001*</i>	39.3 (6.1)	39.3 (6.1)
Medial Central Femur	36.1 (4.4)	34.0 (4.3)	<i>0.022</i>	28.9 (3.6)	25.5 (4.5)	<i>0.001*</i>	41.8 (5.8)	41.8 (5.8)
Medial Posterior Femur	39.1 (4.8)	37.4 (5.8)	<i>0.107</i>	33.5 (4.5)	28.4 (4.8)	<i>0.002*</i>	43.9 (6.9)	43.9 (6.9)
Medial Tibia	35.3 (2.7)	33.4 (2.0)	<i>0.149</i>	30.4 (6.4)	28.4 (5.1)	<i>0.010</i>	42.0 (1.9)	42.0 (1.9)