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Haddock, Bryan; Fan, Audrey P; Jørgensen, Niklas R; Suetta, Charlotte; Gold, Garry Evan; Kogan, Feliks

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Kinetic $[^{18}F]$-Fluoride of the Knee in Normal Volunteers

Bryan Haddock, MSc, * Audrey P. Fan, PhD, † Niklas R. Jørgensen, DrMed, § Charlotte Suetta, DrMed, ¶** and Feliks Kogan, PhD †

Purpose: $[^{18}F]$-sodium fluoride ($[^{18}F]$NaF) is a well-established bone-seeking agent that has shown promise to assess bone turnover in a variety of disorders, but its distribution in healthy knee joints has not been explored. This study aimed to investigate parametric values for $[^{18}F]$NaF uptake in various bone tissues types of the knee and their spatial distributions.

Methods: Twelve healthy subjects were hand-injected with 92.5 MBq of $[^{18}F]$NaF and scanned on a 3-T PET/MRI system. Listmode PET data for both knees were acquired for 50 minutes from injection simultaneously with MRI Dixon and angiography data. The image-derived input function was determined from the popliteal artery. Using the Hawkins model, Patlak analysis was performed to obtain $K_i$ $(K_i^*)$ values and nonlinear regression analysis to obtain $K_{NLR}$, $K_i$, $k_3(k_2 + k_3)$, and blood volume. Comparisons for the measured kinetic parameters, SUV, and SUVmax were made between tissue types (subchondral, cortical, and trabecular bone) and between regional subsections of subchondral bone.

Results: Cortical bone had the highest $[^{18}F]$NaF uptake differing significantly in all measured parameters when compared with trabecular bone and significantly higher SUVmax and $K_i$ than subchondral bone. Subchondral bone also had significantly higher SUV, SUVmax, and $K_i$ than trabecular bone tissue. Regional differences were observed in $K_i$ and $K_{NLR}$ as well as $k_3(k_2 + k_3)$ values.

Conclusions: Quantitative $[^{18}F]$NaF PET is sensitive to variations in bone vascularization and metabolism in the knee joint.

Key Words: bone, fluoride, hybrid imaging, kinetics, knee, MRI, NaF, PET, PET/MRI


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Authors ORCID: B.H. (0000-0002-9721-4712), A.F. (0000-0001-5850-6117), N.R.J. (0000-0001-9624-5210), C.S. (0000-0001-8063-6508), and F.K. (0000-0003-0580-7308).

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Correspondence to: Bryan Haddock, MSc, Department of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet Glostrup, Copenhagen University Hospital, Ndr. Ringvej 57, 2600-Glostrup Denmark. E-mail: bryan.haddock@regionh.dk.

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[18F]sodium fluoride ($[^{18}F]$NaF) is a well-established bone-seeking agent that has shown promise as a marker to study bone turnover in a variety of bone and joint disorders, including the knee. Although most often used in oncological examinations, elevated $[^{18}F]$NaF SUV has been reported to coincide with early disease changes in osteoarthritis, rheumatoid arthritis, and pain. However, SUV only provides a semiquantitative measure of tracer uptake and is unable to differentiate underlying physiological mechanisms of clinical importance. Fluoride uptake in bone tissue is dependent on a number of factors including perfusion, capillary permeability, and transit times between blood plasma and extracellular fluid. After reaching the bone matrix, fluoride ions either bind by exchanging with hydroxyl groups in the hydroxyapatite-like mineral of bone to form fluorapatite at sites of remodeling and turnover or reenter the bloodstream. Using the Hawkins kinetic model of $[^{18}F]$NaF uptake (Fig. 1), these underlying processes can be quantified by the rate of transit of the $^{18}$F concentration from plasma to the extravascular bone compartment ($K_i$), the fraction of extravascular $^{18}$F ions binding to the bone matrix ($k_3(k_2 + k_3)$), and the total rate of fluoride clearance from plasma to the bone matrix ($K_i$). The parameter $K_i$ has been found to have higher sensitivity to treatment response than SUV and similar precision in terms of repeatability. Further, $K_i$ has been applied by several groups as a marker for bone vasculature, whereas the parameter describing the tracer extraction fraction ($k_3(k_2 + k_3)$) has been used as a marker for bone turnover.

Although $[^{18}F]$NaF kinetic modeling has been studied for bone turnover in the upper body, there are few data for parametric values in the healthy knee. Further, integrated PET/MRI systems have the potential to improve the clinical feasibility of kinetic modeling. Not only is MRI already widely utilized for imaging of joint disorders, but also high-resolution MR angiograms can also help obtain the necessary input function of PET tracer delivery without invasive arterial blood sampling. Furthermore, quantitative MRI metrics such as T1rho and T2 relaxation times are able to assess biochemical and structural properties in cartilage, tendons, and muscle. PET/MRI systems provide a unique opportunity to leverage the extended MRI scanning time for a simultaneous kinetic PET examination and lower radiation dose, combining the advantages of conventional MRI, quantitative MRI, and molecular information from PET. The purpose of this study was to investigate key parametric and semiparametric values for $[^{18}F]$NaF uptake in the healthy knee, including $K_i$, $K_1$, $k_3(k_2 + k_3)$, SUV, and SUVmax, using PET/MRI. The bone tissues investigated included trabecular bone and subchondral bone of the distal end of the femoral bone and tibial head, as well as the cortical bone of the femoral and tibial shafts.

METHODS

Study Population

Twelve healthy subjects with no history of musculoskeletal complications (7 women, aged 22–44 years, body mass index 23 ± 3.3 kg/m$^2$) and having abstained from exercise for 24 hours were hand-injected via an intravenous catheter with 92.5 MBq of...
The coils were used because of their lower attenuation effect on PET photons. Both knees were scanned using a PET-MR hybrid system (GE Healthcare, Milwaukee, Wis). Each subject was positioned feet first with a 16-channel flexible phased-array receive-only coil (NeoCoil, Pewaukee, Wis) around each knee. The coils were used because of their lower attenuation effect on PET photons. Both knees were scanned using 1 PET bed (field of view = 25 cm) in list mode starting with the injection of NaF for 50 minutes, and all MRI data were acquired simultaneously with PET imaging.

Magnetic resonance angiography data were acquired using a 3-dimensional gradient echo sequence with imaging parameters: repetition time/echo time (TE) = 21/2.1 milliseconds, slices = 18, slice thickness = 1.2 mm, and flip angle = 15°. A 2-point Dixon fat-water T1-weighted spoiled gradient echo MR sequence was acquired for MR-based attenuation correction of PET data with acquisition parameters: repetition time/TE1/TE2 = 4.1/1.1/2.2 milliseconds, field of view = 50 x 37.5 cm, matrix = 256 x 128, slice thickness/overlap = 5.2/2.6 mm, 120 images/slab, scan time = 18 seconds.

For calculation of the image-derived input function (IDIF), dynamic PET frame times of 40 x 1 seconds, 13 x 10 seconds, and 23 x 2 minutes were reconstructed using time of flight-ordered subset expectation maximization with 3 iterations and 21 subsets with corrections for decay, attenuation, scatter, random, and dead time. Time activity curves of bone PET uptake were determined using dynamic PET time frames of 8 x 2 seconds and 24 x 2 minutes with the same corrections. A 3-mL venous blood sample was taken 50 minutes after injection when arterial and venous blood concentrations have equilibrated and measured in a well counter.

### IDIF Calculation

The IDIF was determined from $[^{18}\text{F}]\text{NaF}$ activity (kBq/mL) within the popliteal artery of each knee. The artery was segmented automatically from MR angiography images and a short time-frame PET angiogram during the arterial phase (0–16 seconds after injection) when the tracer is predominantly in the arteries. In order to minimize spillover artifacts, the voxels centered in the middle of the artery were determined for each dynamic PET frame and used for the IDIF. Central voxels were defined by including the voxels in each axial slice within the highest 10% of arterial NaF activity.

### Bone Segmentation and Regions of Interest

Using the in-phase, out-of-phase, and water images from the Dixon scans, masks covering the femur, patella, and tibia were first created by manually drawing regions of interest (ROIs) (Fig. 2). The bone tissue was then segmented further to create subchondral/cortical bone masks using k-means clustering (4 cluster groups minimized to squared Euclidean distance repeated 4 times with different initial centroids). The long bone of the femur and tibia was identified as the cortical bone 6 to 8 cm from the center of the joint space. Trabecular bone ROIs in the tibia and distal end of the femoral bone were drawn for both legs maintaining a minimum of 3-mm distance from the edge of the bone to avoid partial voluming. Thereafter, the subchondral bone of the femur was manually subdivided into 5 regions: trochlea and central and posterior regions of the medial and lateral compartments. Similarly, tibial subchondral bone was further separated into lateral and medial regions. Lastly, cortical bone at the site of a patellar tendon insertion (tibial tuberosity) was identified and excluded from the analysis of cortical bone.

### SUV and Kinetic Modeling

The time activity curves and IDIF data were fitted to the 2-tissue compartment model using the Patlak method and again using the non-linear regression (NLR) method. Patlak analysis is a graphical technique for estimating $K_T$, the total rate of plasma clearance of NaF to the bone matrix, which assumes that $^{18}\text{F}$ is irreversibly bound to bone mineral ($k_4 = 0$). Data from 10 to 50 minutes were fit to allow for equilibration between tracer in plasma and the bone extracellular...
fluid. Nonlinear regression fitting included estimation of 3 rate parameters ($K_1$, $k_2$, and $k_3$) along with a partial volume fraction, a blood fraction, and an input dispersion estimate and was computed using COMKAT software. The rate constant $k_d$ was predefined as 0. For both blood fraction and $K_1$, a parameter range from 0 to 1 was applied, whereas a range of 0.015 to 0.8 was used for $k_2$ and $k_3$, and 0 to 2 seconds for the dispersion constant $\tau_d$. To avoid local minima, fits were repeated with 3 starting conditions, and results with the lowest residuals were used. The rate of total plasma clearance using the NLR method ($K_{NLR}^{11}$) was calculated from the $K_1$, $k_2$, and $k_3$ values obtained by using the following formula:

$$K_{NLR}^{11} = k_1' \left( k_3 / (k_2 + k_3) \right)$$  \hspace{1cm} (1)

$K_{NLR}^{11}$, like $K_1$, has units of mL·min$^{-1}$·mL$^{-1}$, whereas $k_2 - k_3$ have units of min$^{-1}$. The $K_{NLR}^{11}$ parameter can be separated into 2 parameters of physiological interest. One parameter is $K_1$, the rate of transit of the $^{18}$F plasma concentration into the extravascular compartment, and reflects flow delivery of the tracer. Perfusion ($P$) estimates for each ROI were derived from $K_1$ values using least squares regression to the Renkin-Crone formula:

$$K_1 = P \cdot (1 - \exp(-PS/F))$$  \hspace{1cm} (2)

where the product of permeability and surface area (PS) was assumed to be 0.24, as reported by Pier et al.$^{21}$ The second physiological parameter is the extraction fraction, $k_3/(k_2 + k_3)$, which represents the fraction of $^{18}$F entering the tissue that binds to the bone matrix as opposed to reentering the bloodstream.

Images for mean SUV and SUVmax were calculated from images obtained by averaging the last 2 frames of the dynamic study (46–50 minutes).

**Statistical Analysis**

Values across the entire patient cohort are reported as median with interquartile range, and $P$ values are from paired Student 2-tailed $t$ tests using a threshold for significance of $P < 0.05$ after Bonferroni correction for multiple comparisons. Correlations between obtained parameters were analyzed using least products linear regression where goodness of fit was evaluated with a Pearson adjusted $R^2$ value. Reproducibility between IDIF blood activity and venous blood samples was analyzed by calculating the coefficient of variation, reported in percent. Image coregistration, ROI analysis, calculations, and statistical analysis were performed with software created in MATLAB 2013b (MathWorks, Natick, Mass).

**RESULTS**

Median parametric values along with interquartile range across all subjects are presented in Table 1. Variations in global $^{18}$FNaF uptake were observed between subjects (Fig. 3) with consequently higher or lower SUV values across all 3 types of bone tissue. Comparisons between the 3 bone tissue types are shown in Figure 4. Cortical bone had highest $^{18}$FNaF uptake for all measured parameters compared with trabecular bone ($P < 0.01$), which had the lowest uptake. SUV and $K_1$ values for subchondral bone were lower than that of cortical bone, but these differences were not significant after correction for multiple comparisons. Subjects had significantly higher SUVmax and $K_1$ values and a significantly lower extraction fraction in cortical bone compared with subchondral bone. Subchondral bone had significantly higher $^{18}$FNaF uptake (SUV, SUVmax, and $K_{NLR}^{11}$; $P < 0.01$) than trabecular bone tissue.

There was a regional variance in distribution of $K_1$ and extraction fraction values. The distribution ranged from cortical bone.
of the shaft, which had the highest vascularization where $K_1 > K_i$ and $k_3/(k_3 + k_2) < 1$, to the trochlea and patella region of subchondral bone, where $k_3/(k_3 + k_2) \approx 1$ and $K_1 \approx K_i$ (Fig. 5). By visual analysis of $K_1$ and $k_3/(k_3 + k_2)$ maps, a negative gradient of $K_1$ values can be seen from the femoral and tibial shafts decreasing toward the joint space. A second gradient can be seen as $K_1$ is higher in subchondral bone and declines toward the center of the trabecular bone of the femur and tibial head (Fig. 6). In the subchondral bone of the femur, $K_1$ and blood volume values were higher in the posterior section, decreasing to the lowest in the trochlea ($P < 0.01$).

FIGURE 4. Parametric values of $[^{18}\text{F}]\text{NaF}$ uptake for different bone tissue types of the knee. Cortical bone had the highest $[^{18}\text{F}]\text{NaF}$ uptake in all measured parameters when compared with trabecular bone, which had the lowest uptake. Subchondral bone also had higher uptake than trabecular bone with significantly higher SUVmean, SUVmax, and $K_i^{\text{NLR}}$ values, yet only slightly elevated $K_1$ and $k_3/(k_3 + k_2)$ values. The relative distribution of $K_i^{\text{NLR}}$ values between bone tissues was almost identical to that of SUV. Note that despite having the highest uptake as expressed by SUV and $K_i^{\text{NLR}}$, cortical bone has the lowest extraction fraction. $P$ values were corrected for 18 comparisons using a Bonferroni correction ($^\dagger P < 0.01$ difference compared with cortical bone, $^\ddagger P < 0.01$ difference between trabecular bone and subchondral bone).
opposite gradient was observed in the extraction fraction maps, resulting in total metabolism $K_i^{\text{NLR}}$ and SUV images that were more spatially uniform.

There were no other significant differences in $[^{18}\text{F}]\text{NaF}$ uptake parameters between the 3 bone tissue types or between subregions of subchondral bone. The sites of tendon insertion had elevated SUV values and significantly higher $K_i^{\text{NLR}}$ ($P < 0.05$) than remaining cortical bone tissue. The vascularization was lower ($K_1$ 33% less, blood volume 84% lower [both $P > 0.01$]), and the extraction fraction higher ($k_i/(k_3 + k_2)$ 88% higher, $P < 0.01$).

$K_i^{\text{NLR}}$ values correlated highly with SUV values ($R^2 = 0.90$). $K_i^{\text{Pat}}$ values from the Patlak method had a slightly poorer correlation to SUV ($R^2 = 0.87$) and were 17% lower than those obtained by NLR (Fig. 7). The correlation of $K_i^{\text{Pat}}$ values to $K_i^{\text{NLR}}$ values was high ($R^2 = 0.97$) despite the 17% bias (Fig. 7). Using $K_1$ values from the NLR fit, flow values were obtained and found to be within a few percentage points of $K_1$ values (Table 1). The $K_1$ values were in the range where $K_1 < \ll PS$, and thereby the condition $F \approx K_1$ applies.

Group average IDIF values at 1, 5, 10, and 50 minutes were 10.2, 6.0, 4.2, and 2 kBq/mL when normalized to a 100-MBq injection. At 50 minutes, mean IDIF values were 6% higher than mean venous blood sample values. Coefficient of variation values between venous blood samples and IDIF values measured at 50 minutes were 8.3%. Repeated injections in 1 subject had mean coefficient of variation values of 9% across time points observed between 1 and 50 minutes (Fig. 8).

FIGURE 5. Components of $K_i$ for different bone tissue type. The SUV/$K_i^{\text{NLR}}$ relationship did not vary significantly between tissue types or between subjects. Linear regression analysis of SUV and $K_i^{\text{NLR}}$ gave SUV $\simeq 89 \times K_i^{\text{NLR}}$. The first column compares different ROI values from all subjects to this regression. Given that $K_i = K_1 \times k_i/(k_3 + k_2)$, $K_i$ can be broken into a flow-related component, $k_i/(k_3 + k_2)$, which is the fraction of the tracer having entered the tissue that binds to the bone matrix. SUV of the cortical bone (shaft) is correlated to both $K_1$ and $k_i/(k_3 + k_2)$ values, whereas in trabecular bone and the patella, SUV is primarily determined by $K_1$ where $K_i = K_1$ and $k_i/(k_3 + k_2) = 1$ in all subjects.

DISCUSSION

Semiquantitative and quantitative values for $[^{18}\text{F}]\text{NaF}$ uptake in the knee were obtained from healthy subjects using PET/MRI. A large intersubject variation in NaF uptake was observed as there were significant differences in uptake parameters between cortical bone and the subchondral/trabecular bone tissues. Trabecular bone was found to have significantly lower SUV, $K_1$, $K_i$, and blood volume values yet a significantly higher extraction fraction than the cortical bone tissue in the shaft of the femur and tibia. Blood volume was the parameter with the largest discrepancy between bone tissues being significantly higher in the shaft compared with subchondral or trabecular bone of the knee. Subjects had higher vascularization (larger blood volume and higher $K_1$ values) in the shaft of the femur and tibia declining with a negative gradient toward the joint space reaching the lowest values at the center of the trabecular bone near the distal end. This $K_1$ gradient was partially offset by a gradient of increasing extraction efficiency that was significantly lower in the shaft. A similar regional discrepancy was also evident in SUV, SUVmax, and $K_i^{\text{NLR}}$, although to a lesser degree. These parameters, like $K_1$, were significantly higher in the shaft decreasing in the subchondral bone and trabecular bone of the knee joint in these healthy individuals. Likewise, the sites of tendon insertion of the cortical bone had much lower vascularization ($K_1$ and blood volume), yet a net uptake than regular cortical bone due to a high extraction fraction. A similar observation has been
made between the spine and humeral bone tissues where low $K_1$ values in the humeral bone were partially compensated by a higher $k_3/(k_2 + k_3)$ to give a more comparable, yet still significantly lower, $K_1$ value. Aside from the $K_1$ and $k_3/(k_2 + k_3)$ gradients, all other parametric values within the subchondral bone tissue ROIs of subjects were quite homogenous with no significant differences when comparing subchondral subregions across the patella, femur, and tibia.

$K_i^{\text{NLR}}$ values from the Patlak method were 17% lower than those obtained by NLR, which is a larger bias than previously reported by Siddique et al., where $K_i^{\text{Pat}}$ was 10% lower than $K_i^{\text{NLR}}$ in the lumbar vertebrae. Still, $K_i^{\text{NLR}}$ values correlated highly with both $K_i^{\text{Pat}}$ values ($R^2 = 0.97$) and SUV ($R^2 = 0.90$) with no regional variations in their correlation. Ultimately, this study gives no evidence of meaningful differences in using Patlak or NLR methods to determine $K_i$ as they could be interchanged with a conversion factor. Studies including mean SUV, $K_i^{\text{Pat}}$, and $K_i^{\text{NLR}}$ have found these parameters to have similar reproducibility with coefficients of variation ranging between 9% and 15% and $K_i^{\text{NLR}}$ values have lower reproducibility when $k_3$ is not limited to 0 when fitting. In this study, SUV, $K_i^{\text{Pat}}$, and $K_i^{\text{NLR}}$ have comparable variance where intersubject SDs are between 43% and 46% of mean values. Despite similar reproducibility, $K_1$ values have been reported to be a more sensitive measure of regional bone metabolism than SUV. In the limbs, where $F^*$ uptake is low, Brenner et al. and Apostolova and Brenner concluded the minimal change of SUV in a patient must be greater than 50% to reliably detect disease or treatment-related changes, whereas the same diagnosis could be made from a change in $K_1$ of 25%. $K_1$ values have also shown to be more sensitive when analyzing alterations in subchondral bone of the femur adjacent to cartilage defects. SUVmax values in this study are similar to previously reported mean SUVmax values of 2.44 for the tibia and 2.22 in the femur shaft. SUVmax has been found to correlate well with adjacent cartilage alterations and although it had the largest intrasubject variation in this study, it had a relatively lower variance between subjects and greater differentiation between bone tissues (Fig. 4). In this study, using NLR was advantageous as obtaining $K_1$ and extraction fraction parameters provided useful information that could not be extracted from $K_1$ alone.

The $K_1$ values obtained in this study were within a flow-dominant regimen where it has, theoretically, a linear correlation to blood flow ($K_1 << PS$). The flow values obtained in this study compare well with measured blood flow in the femoral shaft, but lack a criterion-standard measure to investigate $K_1$ as a surrogate flow measure. To date, the most convincing studies to confirm the relationship between blood flow in bone tissue and $K_1$ for $[^{18}F]$NaF kinetics have been performed in swine vertebrae. Since then, authors have reported a poor correlation between $K_1$ and bone perfusion in studies of the hip of human surgery patients and the forelimbs of healthy rats. Obtaining an estimate of flow would be of great clinical value. Bone perfusion is usually linked to metabolic activity and varies greatly between different bones and bone regions in the skeleton where the extremities are among the lowest.
Perfusion studies using microspheres have shown a reduction of blood flow in bones related to age, osteoporosis, and reduced endothelium-dependent vasodilation.

With regard to this study’s aim to report key parametric values for $^{18}$FNaF uptake in the healthy knee, there are several limitations to be considered when interpreting the results. First, the number of subjects is small where results can be skewed by relatively few abnormalities. The range of ages (22–44 years) is a period of rather stable bone density in human adults, but factors such as body mass index, varus/valgus alignment, disease, or activity level could alter the kinetics in bone tissue. Second, despite the numerous advantages from combining PET imaging with MRI in knee examinations, there are disadvantages in foregoing the superior information on bone density, which CT provides. This information is valuable in both the attenuation correction of PET data and the segmentation of bone tissue. Dixon-based methods, as used by the scanner in this study, have been shown to underestimate bone $^{18}$FNaF mean SUV by 10%, ranging between 0% and 20% depending on location. The subchondral bone would be least affected being close to the bone surface, whereas the trabecular bone could have a more pronounced underestimation of SUV due to improper attenuation correction. Likewise, a similar underestimation of $K_i$ and $K_i^{\text{NLR}}$ would be expected, although it would be partially offset by a similar underestimation of activity in input function obtained from the popliteal artery. Lastly, the use of an IDIF would best be confirmed by using arterial sampling as a criterion standard. In this study, venous samples confirmed the activity of the later phase of the IDIF but not the earlier phase of high activity.

PET/MRI is an optimal dual-imaging combination offering the advantages of the high soft tissue contrast and resolution of MRI and the sensitivity of PET. In this study, MR angiography added the advantage of segmenting the popliteal artery, making an automated process to obtain the IDIF possible. The input functions obtained correspond well with literature values for $^{18}$FNaF from arterial sampling, and visual inspection of generated ROIs confirmed successful automated segmentation of the popliteal artery. Mean IDIF values 50 minutes after injection were 6% higher than venous blood samples taken on an equilibrium time point, whereas Cook et al. found arterial blood samples to be 2% higher than venous blood samples after 24 minutes. With the increased use of NaF in nononcological studies of the skeleton, it has become even more relevant as moderate differences in NaF uptake may be an early indication of bone degradation in diseases such as osteoarthritis.

The combination of PET/MRI reduces the radiation dose significantly in 2 ways. First by eliminating CT and, second, because the PET data are acquired for the duration of the MRI protocol (which can be up...
Quantitative MRI techniques have been widely studied to develop robust
and still retain the same signal-to-noise ratio in PET SUV maps.

The effective dose of this study is estimated to be 2.16 mSv.

a standard clinical dose of 200 MBq to 90 MBq (used in this study)
and monitoring of patients having had an anterior cruciate ligament injury.

CONCLUSIONS

This study showed significant variations in regional bone perfusion and metabolism between skeletal tissue types in the knee joint. We have shown the feasibility of using PET/MRI to create an accurate IDIF from the popliteal artery and to conduct a quantitative and semiquantitative evaluation of bone metabolism in the knee at a low radiation dosage. \(^{18}\)F-fluoride PET/MRI techniques have been widely studied to develop robust biomarkers for the early detection and monitoring of osteoarthritis and monitoring of patients having had an anterior cruciate ligament injury.

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