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

Bryan Haddock, MSc, * Audrey P. Fan, PhD, † Niklas R. Jørgensen, DrMed, ‡ § Charlotte Suetta, DrMed, *†‡‖ Garry Evan Gold, MD, †¶** and Feliks Kogan, PhD†‡

Purpose: $^{[18F]}$-sodium fluoride ($^{[18F]}$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 $^{[18F]}$NaF uptake in various bone tissue types of the knee and their spatial distributions.

Methods: Twelve healthy subjects were hand-injected with 92.5 MBq of $^{[18F]}$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 $K_i$ ($K_i^{NL}$) values and nonlinear regression analysis to obtain $K_i^{NL}$, $k_2(k_3 + k_4)$, and blood volume. Comparisons for the measured kinetic parameters, SUV, and SVUVMAX were made between tissue types (subchondral, cortical, and trabecular bone) and between regional subsections of subchondral bone.

Results: Cortical bone had the highest $^{[18F]}$NaF uptake differing significantly in all measured parameters when compared with trabecular bone and significantly higher SVUVMAX and $K_i$ than subchondral bone. Subchondral bone also had significantly higher SUV, SVUVMAX, and $K_i$ than trabecular bone tissue. Regional differences were observed in $K_i$ and $k_2(k_3 + k_4)$ values.

Conclusions: Quantitative $^{[18F]}$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. Ringgøjd 57, 2600-Glostrup Denmark. E-mail: bryan.haddock@regionh.dk.

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The coils were used because of their lower attenuation compared to MRI coils. The matrix = 256 × 256 × 128 images/slab, scan time = 18 seconds. PET time frames of 8 seconds, field of view = 50 cm. The time of transit of the tracer to the extravascular compartment was determined from the time activity curves and IDIF data. 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 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 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 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 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 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 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 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 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 bone tissue was then segmented further to create subchondal/cortical bone masks using k-means clustering (4 cluster groups minimized to squared Euclidean distance repeated 4 times with different initial centroids). The bone tissue was then segmented further to create subchondal/cortical bone masks using k-means clustering (4 cluster groups minimized to squared Euclidean distance repeated 4 times with different initial centroids). The bone tissue was then segmented further to create subchondal/cortical bone masks using k-means clustering (4 cluster groups minimized to squared Euclidean distance repeated 4 times with different initial centroids). The bone tissue was then segmented further to create subchondal/cortical bone masks using k-means clustering (4 cluster groups minimized to squared Euclidean distance repeated 4 times with different initial centroids). The bone tissue was then segmented further to create subchondal/cortical bone masks using k-means clustering (4 cluster groups.
Nonlinear regression fitting included estimation of 3 rate parameters ($K_1$, $K_2$, and $K_3$) along with a partial volume factor, a blood fraction, and an input dispersion estimate and was computed using COMKAT software.20 The rate constant $k_0$ 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 $\tau$. 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 ($K_{NLR}^{NL}$) was calculated from the $K_1$, $K_2$, and $K_3$ values obtained by using the following formula:

$$K_{NLR}^{NL} = K_1 \left( \frac{k_3}{k_2 + k_3} \right)$$

($K_{NLR}^{NL}$, like $K_1$, has units of mL·min$^{-1}$·mL$^{-1}$, whereas $k_2 - k_3$ have units of min$^{-1}$).

The $K_{NLR}^{NL}$ 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 $^{21}$:

$$K_1 = F^* \left( 1 - \exp \left( -\frac{PS}{F} \right) \right)$$

where the product of permeability and surface area (PS) was assumed to be 0.24, as reported by Pierp 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 lower $^{18}$FNaF uptake (SUV, SUVmax, and $K_{NLR}^{NL}$; $P < 0.01$) than trabecular bone tissue.

There was a regional variation 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 ($P < 0.01$). The

FIGURE 3. SUV of representative slice from 2 subjects. There was a wide intersubject range of $[^{18}\text{F}]$NaF uptake across the joint. The left image is a subject with low uptake in knee, whereas the right image is a subject with high uptake in all bone tissues. In addition to global variations in tracer uptake between subjects, some individual variations in the relative distribution of $[^{18}\text{F}]$NaF uptake across bone tissues regions were observed. In this example, the subject on the right has relatively low uptake in the subchondral bone of the femur compared with the subchondral bone of the patella and tibial head, whereas the subject on the left has equally low uptake in all subchondral regions.

FIGURE 4. Parametric values of $[^{18}\text{F}]$NaF uptake for different bone tissue types of the knee. Cortical bone had the highest $[^{18}\text{F}]$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 $K_i^{NLR}$ values, yet only slightly elevated $K_1$ and $k_3/(k_3 + k_2)$ values. The relative distribution of $K_i^{NLR}$ values between bone tissues was almost identical to that of SUV. Note that despite having the highest uptake as expressed by SUV and $K_i^{NLR}$, 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).
and SUV images that were more ≃ (0.87) and were 17% lower than those obtained by values (Table 1). The > 0.01), and the extraction fraction values was ≃ 0.97) despite the 17% bias (Fig. 7). Using for different bone tissue type. The SUV/K\text{trabecular} values were in the range where K\text{trabecular} < < PS, and thereby the condition F≈K\text{trabecular} 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\text{trabecular} for different bone tissue type. The SUV/K\text{NLR} relationship did not vary significantly between tissue types or between subjects. Linear regression analysis of SUV and K\text{NLR} gave SUV = 89 x K\text{NLR}. The first column compares different ROI values from all subjects to this regression. Given that K\text{trabecular} = K\text{1} x K\text{3}/(K\text{3} + K\text{2}), K\text{1} can be broken into a flow-related K\text{1} component, which is the rate of tracer entering the tissue, and an extraction fraction component, K\text{3}/(K\text{3} + K\text{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\text{1} and K\text{3}/(K\text{3} + K\text{2}) values, whereas in trabecular bone and the patella, SUV is primarily determined by K\text{1} where K\text{trabecular} = K\text{1} and K\text{3}/(K\text{3} + K\text{2}) = 1 in all subjects.

DISCUSSION

Semiquantitative and quantitative values for [18F]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\text{trabecular}, 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\text{NLR}) 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\text{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\text{NLR}, although to a lesser degree. These parameters, like K\text{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\text{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.

$K_{\text{NLR}}$ 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% in the spine where $K_i^{\text{NLR}}$ had lower reproducibility when $k_1$ 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, $K_i$ 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%. $K_i$ 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 intraindividual 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 $K_i$ and extraction fraction parameters provided useful information that could not be extracted from $K_i$ alone.

FIGURE 6. Example of the distribution of $K_1$, $K_i^{\text{NLR}}$, and SUV from 1 subject. Subjects had a negative gradient of $K_1$ values from the shaft toward the joint space and from the subchondral bone toward the center of the distal end of the femoral bone and tibial head. In the sagittal plane, $K_1$ values were highest in the posterior section of subchondral bone and decreased in the anterior direction toward the trochlea and patella. However, the opposite gradient was observed in extraction fraction $k_3/(k_2 + k_3)$ maps, resulting in $K_i^{\text{NLR}}$ and SUV images with more localized heterogeneity.

The $K_1$ values obtained in this study were within a flow-dominant regimen where it has, theoretically, a linear correlation to blood flow ($K_1 << \text{PS}$). 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 $^{18}$F-NaF 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 $^{18}$F-NaF 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 $K_i$ 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 $^{18}$F-NaF 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

**FIGURE 7.** Comparison of $K_{\text{NLR}}$ with SUV values and $K_{\text{Pat}}$. A, Scatterplot of $K_{\text{NLR}}$ results from all ROIs of all subjects plotted against ROI mean SUV ($R^2 = 0.90$). The Bland-Altman plot compares SUV values and $K_{\text{NLR}}$ values multiplied by the slope determined from the regression (slope = 0.90). B, A scatterplot with regression fit and Bland-Altman plot of the same ROIs comparing $K_{\text{NLR}}$ vs $K_{\text{Pat}}$ values ($R^2 = 0.97$). The Patlak method produced $K_i$ values that were 17% lower than those obtained by NLR and had a slightly poorer correlation to SUV ($R^2 = 0.87$).
to an hour), the injected dose of $^{18}$F-fluoride can be decreased from a standard clinical dose of 200 MBq to 90 MBq (used in this study) 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. Quantitative 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.

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/MR 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-NaF PET/MRI is a noninvasive technique that offers an attractive tool to simultaneously estimate bone perfusion and metabolism at clinically relevant sites of the knee.

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