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[¹⁸F]-Sodium Fluoride PET MR–Based Localization and Quantification of Bone Turnover as a Biomarker for Facet Joint–Induced Disability

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ABSTRACT

SUMMARY: Our aim was to prospectively evaluate the relationship between low back pain–related disability and quantitative measures from [¹⁸F]-sodium fluoride ([¹⁸F]-NaF) MR imaging. Six patients with facetogenic low back pain underwent dynamic [¹⁸F]-NaF PET/MR imaging. PET metrics were correlated with clinical measures and MR imaging grading of lumbar facet arthropathy. A significant positive correlation was observed between maximum facet joint uptake rate and clinical disability ($P < .05$). These data suggest that dynamic [¹⁸F]-NaF PET may serve as a useful biomarker for facetogenic disability.

ABBREVIATIONS: FJ = facet joint; IPAQ = International Physical Activity Questionnaire; max = maximum; min = minimum; mL/ccm/min = milliliters/cubic centimeter/minute; ODI = Oswestry Disability Index; SUV = standard uptake value

Clinical assessment for facetogenic low back pain is often hampered by overlapping and nonspecific symptoms and physical examination findings.¹ Conventional imaging techniques limited to evaluation of structural changes in the spine may identify morphologic abnormalities in asymptomatic spinal structures that are indistinguishable from degenerative structural alterations that produce severe pain and disability.² Objective and quantitative biomarkers that are more specific for active generators of low back pain would greatly aid in the effective, targeted treatment of patients with low back pain.

[¹⁸F]-sodium fluoride ([¹⁸F]-NaF) is a positron-emission tomography radiotracer, which is chemically absorbed into hydroxyapatite in the bone matrix by osteoblasts and can noninvasively detect osteoblastic activity. [¹⁸F]-NaF has been increasingly used for evaluating bone diseases, particularly for identification of bone metastases and primary tumors.^{3–5} The utility of [¹⁸F]-NaF PET for evaluating degenerative disease of the lumbar spine remains largely unexplored.⁶

The goal of this prospective pilot study was to examine the potential correlation between facetogenic low back pain measures of disability with quantitative and semiquantitative [¹⁸F]-NaF PET/MR imaging measures of bone turnover and structural MR imaging changes in lumbar facet joints.

MATERIALS AND METHODS

Patient Population

This prospective feasibility study recruited patients after obtaining human study institutional review board approval and complying with Health Insurance Portability and Accountability Act regulations. Patients served as internal controls with diseased and healthy subregions. Patients with a history of suspected lower lumbar facetogenic syndrome were recruited from UCSF Radiology Spine Clinic. Written informed consent was acquired before entry into the study. The study began in November 2014 and concluded in August 2015.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: 1) at least 18 years of age with the capacity for informed consent, 2) a reported history of axial nonradicular low back pain, and 3) recommended by the spine interventional radiologists. Exclusion criteria were as follows: 1) a history of fracture or tumor of the spine, including osteoblastic metastases, 2) women who were pregnant or breastfeeding, 3) contraindications to MR imaging or administration of tracer or contrast, and 4) prior lumbar surgery or instrumentation.


Immediately before PET/MR imaging, subjects completed questionnaires measuring pain (numeric rating scale, from 0 to 10 with 0 equal to no pain and 10, the most severe intensity of pain),


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quality of life (Oswestry Disability Index Low Back Pain Disability Questionnaire [ODI]), and activity (International Physical Activity Questionnaire [IPAQ]).^{7,8}

PET/MR Protocol and Image Review

A 3T Signa PET/MR imaging scanner (GE Healthcare, Milwaukee, Wisconsin) was used for a simultaneous PET and MR image acquisition. Dynamic PET was initiated as 0.08 mCi/Kg of [¹⁸F]-NaF (mean dose, 4.6 ± 0.8 mCi) injected intravenously.

Acquisition Parameters

Clinical MR imaging sequences included the following: sagittal T1 (TR/TE = 510/8.6 ms), sagittal T2 fat-saturated (TR/TE = 4208/86.2 ms), axial T2 fast recovery fast spin-echo with and without fat saturation (TR/TE = 750/9.2 ms), axial T1 fast spin-echo (TR/TE = 575/8.9 ms), and axial T1 fast spin-echo postgadolinium (TR/TE = 562/8.6 ms) imaging. The MR imaging attenuation correction for the lumbar spine region was calculated with the accepted standard 2-point Dixon method.⁹ Sixty minutes of dynamic PET data were acquired across 3 temporal phases (phase 1 = 12 frames of 10 seconds each, phase 2 = 4 frames of 30 seconds each, phase 3 = 14 frames of 4 minutes each). PET reconstruction included postprocessing to correct for decay, attenuation, scatter, and dead time.

MR Imaging Facet Joint Grading

Two board-certified neuroradiologists with 3 (J.F.T.) and >30 (W.P.D.) years' postfellowship experience were blinded to the clinical data and interpreted clinical MR imaging sequences on a reprocessing workstation. Facet synovitis was graded as previously described by Czervionke and Fenton (On-line Fig 1).¹⁰

Data Analysis

Quantitative and semiquantitative PET analysis included all facet joints from the L1–L2 to L5–S1 levels. Volumes of interest were selected using anatomic T2 MR images. A spheric VOI (7.5-mm diameter) was constructed around the center of each facet joint. A 5-mm-diameter VOI was placed in the right iliac crest in the central marrow cavity as a reference region. All PET analysis was performed with PMOD licensed software (PMOD Technologies, Zurich, Switzerland). This software facilitates model-based analysis of dynamic PET data. PMOD allows only validated kinetic models that have been extensively studied, and the output of the results is highly reproducible.

Standard Uptake Value Calculations and Kinetic Data

Placement of facet joint (FJ) VOIs is shown in On-line Fig 2A. A cylindrical VOI covering 2 axial sections was placed on the abdominal aorta, and the partial volume correction coefficient was calculated. Maximum standard uptake value (SUV_{max}) and SUV_{mean} values (Equation 1) for each subsite were calculated using the 60-minute time point.

The 3-compartment model used for kinetic modeling is shown in On-line Fig 2B. In Equation 2, C_i represents the bone tissue activity concentration and is the sum of C_e (extravascular compartment) and C_t (target tissue bound compartment); C_p is the concentration of tracer in the blood; V is the effective distribution

Profile of patients with facetogenic low back pain

| Profile | |
|-------------------------|-------------|
| No. of patients | 6 |
| Age (mean) (range) (yr) | 68 (45–80) |
| Sex (M/F) | 5:1 |
| ODI score (mean) (SD) | 18 (5.5) |
| Pain score (mean) (SD) | 5.2 (1.5) |
| IPAQ (mean) | |
| Vigorous MET (SD) | 1728 (1721) |
| Moderate MET (SD) | 1872 (2310) |
| Walking MET (SD) | 2376 (1454) |
| Categoric score (SD) | 0.8 (1.09) |

Note.—MET indicates metabolic equivalent task.

volume of the tracer.¹¹ A 3-compartment irreversible linear model was used for the Patlak linear model.¹¹ The 2-tissue irreversible compartment model was used to calculate the region-specific influx rate constants (in minute⁻¹) for [¹⁸F]-NaF.¹² Uptake was normalized by using the iliac crest as the reference region. The tracer influx rate from the blood pool to the bone matrix was calculated with Equation 2 for K_{i_Patlak}. K_{i_Patlak} represents the rate at which [¹⁸F]-NaF leaves the arterial blood pool and irreversibly binds to a subsite bone matrix. The kinetic analysis was performed by using PMOD. For each subject, FJs with maximum uptake were identified, henceforth referred to as FJ_{max}.

$$1) \text{ SUV} = \frac{\text{Radioactivity Concentration} \left[\frac{\text{kBq}}{\text{mL}} \right]}{\text{Decay-Corrected Amount of Injected Tracer [kBq]} \times \text{Lean Body Mass (g)}}$$

Equation 2 is the Patlak graphical kinetic model:

$$2) \frac{C_i(T)}{C_p(T)} = K_{PL} \frac{\int_0^T C_p(t) dt}{C_p(T)} + \text{Intercept.}$$

Statistical Analyses

The statistical significance of the correlations between PET/MR imaging and clinical disability metrics was tested with the Pearson correlation. A 2-samples *t* test was used (*P* < .05) to assess the significance of differences in the K_{i_Patlak} influx rate between the mean FJ_{max} and mean FJ_{minimum (min)} K_{i_Patlak} and among FJ MR imaging grades.

RESULTS

Patient Profile

Patient demographic and clinical disability scores are summarized in the Table.

[¹⁸F]-NaF Uptake Measurements and MR Imaging Grading

Uptake values were measured in bilateral facet joints across 5 levels in all subjects for a total of 60 measurements. For all 60 sampled regions, the relationship between semiquantitative SUV_{max} and K_{i_Patlak} produced a linear correlation (*r* = 0.58, *P* < .001; On-line Fig 3A). A similar statistically significant linear correlation was observed between K_{i_Patlak} and SUV_{mean} (*r* = 0.7, *P* < .001; On-line Fig 3B).

For each patient, the single facet joint with the highest K_{i_Patlak} (FJ_{max} K_{i_Patlak}) was identified. When FJ_{max} K_{i_Patlak} was plotted

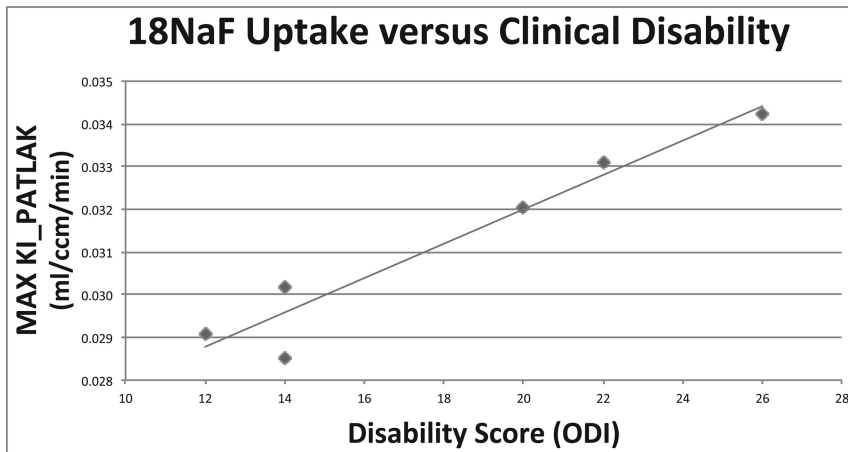


FIG 1. Maximum K_{i_Patlak} significantly correlates with clinical disability as measured by the Oswestry Disability Index. Facet joints with maximum K_{i_Patlak} ($FJ_{max} K_{i_Patlak}$) plotted against the corresponding patient ODI scores reveal a strong, statistically significant linear correlation ($r = 0.96$, $P = .0013$).

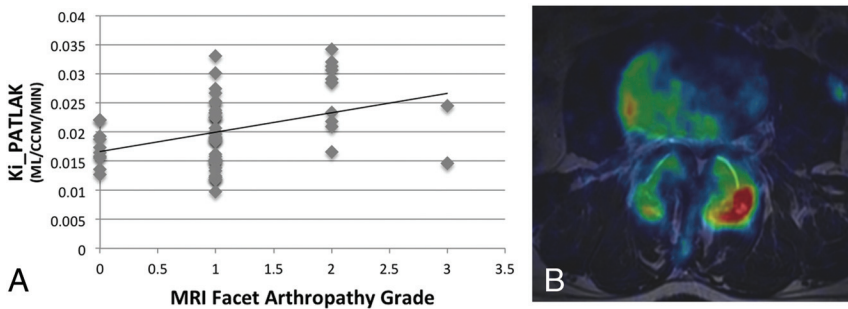


FIG 2. $[^{18}F]$ -NaF PET uptake and MR imaging arthropathy grade are weakly correlated. **A**, $[^{18}F]$ -NaF uptake (K_{i_Patlak}) plotted against the facet arthropathy grade on MR imaging shows a weak-to-moderate but statistically significant ($r = 0.37$, $P = .03$) correlation. **B**, Sample PET/MR imaging-fused axial image at the L3–L4 level in a 61-year-old man with suspected facetogenic pain shows differential FJ uptake with noticeably higher uptake on the left. On MR imaging, both facets were grade 2 facet synovitis.

against the ODI score, a strong, statistically significant positive correlation was observed ($r = 0.96$, $P = .0013$; Fig 1).

The FJ SUV_{max} and SUV_{mean} for each subject ($n = 6$) were plotted against the ODI score, and no significant correlations were observed ($r = -0.55$, $P = .35$, and $r = -0.47$, $P = .35$). The correlation between the maximum MR imaging grade and ODI ($n = 6$) was not significant ($r = 0.38$, $P = .44$). $FJ_{max} K_{i_Patlak}$ plotted against corresponding patient maximum pain scores showed no correlation ($r = 0.06$, $P = .91$). $FJ_{max} K_{i_Patlak}$ plotted against corresponding patient IPAQ categoric scores showed no correlation ($r = 0.15$, $P = .77$).

A weak-to-moderate, but statistically significant, correlation was observed between the MR imaging grade of facet arthropathy and K_{i_Patlak} ($r = 0.37$, $P = .03$; Fig 2A). The average uptake rate as measured by K_{i_Patlak} for FJ_{min} (0.019 milliliter/cubic centimeter/min [mL/ccm/min]) and FJ_{max} (0.032 mL/ccm/min) showed that FJ_{max} was significantly higher with close to twice the uptake rate ($P < .001$).

DISCUSSION

In this prospective pilot study of patients with suspected facetogenic low back pain, we show a strong positive linear correlation

between a kinetic measure of dynamic NaF uptake by the FJ with maximum uptake ($FJ_{max} K_{i_Patlak}$) and disability as measured with ODI. These data suggest that $FJ_{max} K_{i_Patlak}$ may be a useful metric for quantifying and localizing lumbar facetogenic-related disability. Thus, $[^{18}F]$ -NaF PET may aid in treatment planning and longitudinal monitoring of degenerative lumbar facet disease. With our small sample size of 6 subjects with relatively mild disability and the lack of a healthy control cohort, these data are preliminary. However, our observed strong correlation between $[^{18}F]$ -NaF uptake as measured with $FJ_{max} K_{i_Patlak}$ and clinical disability, even in this small cohort of patients with facet syndrome, is reassuring that $FJ_{max} K_{i_Patlak}$ may serve as a useful biomarker for facet joint-related disability. Further larger scale studies are warranted to validate these preliminary data, and a cost-benefit analysis will need to be performed. Most important, our average measurement for $FJ_{max} K_{i_Patlak}$ across all subjects (0.32 ± 0.003 , $n = 6$) is like that of Brenner et al¹³ in areas of high bone turnover, including bone grafts, supporting the validity of our quantitative PET measurements.

Neither SUV_{max} nor SUV_{mean} showed a statistically significant correlation with the ODI score or any other clinical measure of low back pain and disability. While larger studies are needed to confirm this result, the primary finding of this study is that the kinetic variable K_{i_Patlak} may be useful for evaluating facetogenic pathology by providing a quantitative value that more accurately reflects the dynamic process of bone turnover and osteoblastic activity. SUV values assume that radiotracer is evenly distributed throughout the entire body and base the measurement off a lean body mass coefficient. K_{i_Patlak} measures specific concentrations of radiotracer reaching the target via the arterial system during the scan. This added information may reveal subtle changes in the flow of the tracer to ROIs that would otherwise be missed.

It is also of interest that a weak, but statistically significant, correlation was observed between the MR imaging morphologic grade of facet arthropathy and quantitative PET measures or ODI. This finding is consistent with a previous study in which a similarly weak correlation was found between NaF-PET uptake and CT measures of facet arthropathy, further supporting the hypothesis that physiologic information afforded by NaF uptake may supplement conventional structural imaging for identifying symptomatic facet joints.⁶

As a pilot study, the small number of patients and relatively

mild disability represent a primary limitation of this study. Despite this limitation, the observed strong and statistically significant correlation between $FJ_{\max} K_{i_Patlak}$ and ODI in this small, inclusive cohort suggests that [^{18}F]-NaF may serve as a robust biomarker for facet syndrome, and future larger studies are warranted to confirm these data. Also, we provide only correlative evidence that $FJ_{\max} K_{i_Patlak}$ and clinical disability are related. Future studies involving targeted facet joint injections based on dynamic PET/MR imaging data are planned and will be needed to validate the present results.

CONCLUSIONS

In the lumbar spine, [^{18}F]-NaF uptake rates in facet joints as measured with K_{i_Patlak} strongly correlate with patient-reported ODI scores. These pilot data suggest that kinetic measurements of [^{18}F]-NaF facet joint uptake may serve as sensitive, quantitative, and noninvasive biomarkers of facetogenic low back pain.

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