Study Title: Molecular and Magnetic Resonance Imaging Biomarkers of Facet Joint Pain of the Lumbar Spine with PET/MRI

Version: 1; 5/17/2017

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Investigators:

The investigators collectively have extensive expertise in all the relevant areas including spine intervention, clinical spinal pain evaluation, neuroradiology, nuclear medicine, and biostatistics.

Vance Lehman, MD	PI, Spine interventionalist, neuroradiologist
Bradley Kemp, PhD	Co-PI, Nuclear medicine physicist
Timothy Maus, MD	Spine interventionalist, neuro/MSK radiologist
Randy Shelerud, MD	PMR clinician
Jeffrey Brault, MD	PMR clinician
Michael Halasy, PA	PMR clinician
Felix Diehn, MD	Spine interventionalist, neuroradiologist
Mark Nathan, MD	Nuclear Medicine Physician
Stephen Broski, MD	Nuclear Medicine Physician
Rickey Carter, PhD	Biostatistician

1. Background/Significance

Low back pain (LBP), often due to facet joint pain, is a very prevalent and costly condition. Percutaneous facet joint intervention is expensive on a per patient session and per facet joint basis. This is typically prescribed to all 4 lowest lumbar facet joints in a given patient since both conventional imaging findings and clinical exam reliably identify specific painful facet joints. Identification of reliable biomarkers to predict facet joint pain and response to percutaneous treatment is needed. We have retrospective data demonstrating that bone agents such as Tc99m MDP may not be specific for location of patients' facet joint pain (1) and seems to have low effectiveness for predicting response to steroid injection in clinical practice in other spinal locations (2). FDG PET may be more specific for inflammatory change than a bone radiotracer. Although there are some prior retrospective studies assessing both signal change on fat suppressed MRI (3) and bone radiotracers (4-5), *there is no proven or widely used imaging biomarker*. Specifically, these prior studies all retrospective, unblinded, have unclear methods of evaluation of facet joint abnormality, have unclear methods of joint enumeration, and none confirmed facet joint pain with the gold standard test, comparative medial branch blocks.
A prospective randomized blinded study using comparative medial branch blocks will ultimately be needed. However, it is now clear that initial exploratory study is necessary to ensure appropriate study design prior to committing to prospective study. Our currently unpublished data (6) indicate that we need to develop sound imaging parameters allowing for low interobserver variability of interpretation, need to establish prevalence of potential imaging biomarkers in the relevant population, and need to select the best biomarker(s) as initial steps.

Combined MR/PET has number advantages: 1. This allows near-simultaneous assessment of 2 imaging biomarkers to avert criticism of discordance due to biomarker fluctuation, 2. MRI data is probably much more useful than CT data, 3. MRI may be preferred over CT if FDG PET activity proves a promising biomarker for this purpose, and 4. this will allow minimization of radiation dose.

2. Specific Aims

1. Determine the value of FDG PET and MRI imaging biomarker status in clinical decision making and concordance with initial clinical impression.
2. Determine the approximate frequency of each independently studied imaging biomarker to facilitate power calculations.
3. Determine if FDG PET activity and MR biomarkers are highly correlated and thus potential surrogates, or if these are discrepant and possibly complementary.
4. Perform an exploratory evaluation of DWI for assessment of fact joints.
5. Assess the concordance of findings on gadolinium enhanced MRI with T2 fat-suppressed MRI using both axial and sagittal images to determine if gadolinium administration will be necessary for future clinical investigation.

We plan to screen up to 40 patients to ensure we enroll 10 subjects.

3. Hypothesis/Study Category:

This is an exploratory study investigating the utility of FDG PET activity and MRI signal change around facet joints in the clinical management of low back pain. This study will help determine if such imaging biomarkers could change clinical management. Additionally, this will provide data that will be vital to planning a larger prospective study evaluating the ability of imaging biomarkers to predict response to comparison medial branch blocks and RF ablation for treatment of facet joint pain. Such a prospective study could not be adequately designed without this initial exploratory component.

4. Methodology

4.1. Patient Enrollment

Eligibility criteria - inclusion:

1. Male and female patients over the age of 50-100 years with clinically suspected facetogenic low back pain.
2. Patients must be considered to have at least a 60% chance of having facet joints as the major source of low back pain based on overall clinical impression.
3. All patients will undergo a standardized clinical exam by an experienced physical medicine and rehabilitation clinician to confirm clinical suspicion of axial low back pain.
4. Patients with either unilateral or bilateral axial low back pain may be enrolled.

Eligibility criteria - exclusion:

1. Pregnancy
2. Prior lumbar back surgery
3. History of endovascular repair of abdominal aortic aneurysm or other postoperative change likely to introduce imaging artifact to the lumbar spine
4. Suspected spine infection
5. Known osseous metastatic or other osseous malignancy
6. Facet joint percutaneous treatment within the past 2 months
7. History of major lumbar spine trauma
8. Inability to provide own consent
9. Claustrophobia, cardiac pacemaker/wires in place, any absolute contraindication to MRI
10. Impaired renal function indicated by a GFR less than 30
11. Gadolinium allergy
12. Highly radiosensitive medical conditions
13. Patients who are unable to lay quietly for 60 minutes of imaging

4.2 Patient Preparation

A Review Preparatory to Research will be conducted by the study coordinators to determine if the patient meets inclusion criteria including a pre-screen for MRI safety and body habitus and whether the patient's schedule will allow for study participation.

4.3 Patient Scanning Protocol

The PET/MR study consists of an injection of 12 mCi (+/-10%) fluorodeoxyglucose (FDG) and an uptake period of 60 minutes followed by a PET/MRI on the Signa PET/MR system. Patients will need to fast for 18 hours prior to the injection. The patients may require a creatinine check per routine MRI clinical protocol. Patients may request sedation to make the scan more comfortable. They will be given Ativan by mouth to relax by the MR/PET nurse. As per Radiology Departmental policy, the additional MR images obtained during the study will also be given a full clinical read by the staff radiologists to ensure no unexpected findings.
Patients will undergo one scan for this study.

MRI Sequences

1. Sagittal and axial T2 images with fat saturation Lumbar spine
2. Sagittal and axial T1 images with gadolinium and fat saturation lumbar spine
3. A T1 series without fat saturation (volumetric) lumbar spine
4. Axial DWI images lumbar spine

PET images

1. 18F-FDG PET images of the lumbar spine, reformatted in axial and sagittal planes

4.4 Dosimetry

Each patient will receive 12 mCi (+/-10%) F18 FDG

5. Initial Clinical Assessment

1. Patients will undergo a standardized clinical exam by Jeffrey Brault, MD, Randy Shelerud, MD or Michael Halasy, PA from the physical medicine rehabilitation department.
2. The clinician will score the likelihood of the lumbar facet joint(s) as a structural source of pain in each patient using a standardized checklist of clinical and physical exam features and overall clinical impression. The patient must have at least 1 clinical and 1 physical exam feature consistent with facet joint pain.
3. The clinician will qualitatively score his/her confidence that the axial low back pain is derived from facet joints using a percentile (i.e. 60-100%).
4. Determination of the likelihood of facet joint pain on the basis of results from prior imaging with fat saturated sequences will not be permitted to avoid selection bias. However, it is not practical to keep clinicians blinded from prior clinical imaging tests.
5. Indicate the treatment plan (including specific facet joints to be treated percutaneously by either steroid injection or medial branch blocks/radiofrequency ablation).
6. The severity (0-10 scale) and duration of pain (months) on each side will be recorded.
7. Patients will undergo the PET/MR examination as soon as both patient and scanner availability allows; the imaging study must be within 3 months of this clinical assessment.

6. Image Analysis

Lumbar facet joint levels (e.g. L4/L5) will be enumerated by the PI prior to scoring for consistency.

MRI Images

1. Two readers will view images independently. The MRI readers will be blinded to the PET images/results.
2. Peri-facet signal change for every lumbar facet joint on MRI will be determined by 2 neuroradiologists using an established 0-4 grading scale for T2 fat-suppressed images first (blinded to the gadolinium enhanced images).
3. Peri-facet signal change for every lumbar facet joint on MRI will be determined by 2 neuroradiologists using an established 0-4 grading scale for gadolinium enhanced T1 fat-suppressed images.
4. Dichotomous qualitative assessment of presence of pure synovial enhancement will be scored separately.

5. Dichotomous qualitative assessment of facet joint effusion will be scored separately.
6. DWI/ADC images will be examined as an exploratory component, each joint rated as normal, increased DWI signal, or true restricted diffusion by visual inspection.
7. After each group of up to 5 studies (or fewer), the 2 readers will re-review the studies together to establish consensus and document reasons for interobserver variability.
8. The consensus facet joint scores will then be grouped into 3 categories for comparison to PET data and clinical translation: 1 = normal (0/4), 2= mild peri-facet signal change (1-2/4), 3 = high grade peri-facet signal change (3-4/4).
9. After each group of 5 studies, the 2 readers will re-review the studies together to establish consensus and identify/document reasons for interobserver variability (if any).
10. The overall score for each lumbar facet joint (L1/L2 through L5/S1) will represent the highest of the 2 consensus grades (of T2 fatsat and T1 fatsat with gad).

PET Images

1. Patients will receive a routine clinical dose of F18 FDG and undergo PET imaging at a standard recorded interval.
2. Every lumbar facet joint will be rated as either normal or having increased activity on qualitative visual inspection independently by 2 nuclear medicine physicians on a scale of normal, mildly increased, or markedly increased (high grade).
3. Maximum standard uptake value (SUV-max) will also be determined and will be compared to the SUV-max of the adjacent normal vertebral body (avoiding areas increased in association with degenerative disc disease).
4. The PET readers can view anatomic T1 images for coregistration, but will be blinded to the fat-suppressed MR images/results.
5. After each group of up to 5 studies (or fewer), the 2 readers will re-review the studies together to establish consensus and identify/document reasons for interobserver variability (if any).
6. The consensus rating by visual inspection will establish the qualitative score.

6.1 Clinical Evaluation after Imaging

The clinician will be serially unblinded to MRI and PET data *in the following sequence* for each patient; this need not be done during an actual patient recheck. The clinician shall remain blinded to the QREADS radiology report. Qualitative scores are used for PET since the MRI scale is qualitative and since quantitative cut-off values for SUV-max do not currently exist:

1. Unblinded to facet joints positive for high-grade MRI change based on overall scores
2. Unblinded to all positive facet joints on MRI based on overall scores (low grade and high grade)
3. Unblinded to facet joints positive for marked FDG PET activity based on qualitative scores
4. Unblinded to all positive facet joints on FDG PET based on qualitative scores (low grade and high grade)

For each of these 4 iterations, the clinician will score if:

1. The data is concordant or discordant with the clinical impression (dichotomous yes/no)
2. The data would change clinical management (dichotomous yes/no)

These 2 scores will be performed with the assumption the biomarker is an accurate predictor of facet joint pain and/or response to percutaneous treatment. Without this assumption, the results would have no impact on management. This will be done independently on each side per patient.

Note that the results could be concordant with clinical impression, but still alter management (for example clinically suspected left L5/S1 facet joint pain with a positive biomarker at only the left L4/L5 facet joint).

Finally, the clinician will indicate which facet joint(s) he/she would specifically prescribe percutaneous treatment for using both clinical and all available PET/MRI data. Note that the PET/MRI data is not an absolute determinant here. The clinician may believe strongly that a facet joint should undergo percutaneous treatment based on clinical data alone.

The actual clinical management is left to the discretion of the clinician for this phase of evaluation. He/she may choose to treat the patient based on clinical information alone or clinical and PET/MRI information. The clinical course including level of pain, response to injections, etc. of the patients may be followed up to 1 year after the PET/MR by chart review for descriptive purposes/analysis, but the patients will not be formally contacted.

6.2 Primary Data Analysis

1. The concordance of qualitative scores of FDG activity with clinical impression will be determined (high grade and all grades).
2. The concordance of overall scores of MR findings with clinical impression will be determined (high grade and all grades).
3. The frequency with which the qualitative scores of FDG activity altered clinical management will be scored (high grade and all grades).
4. The frequency with which the overall scores of MR findings altered clinical management will be scored (high grade and all grades).
5. For each patient, the number (and level) of facet joints prescribed percutaneous treatment will be determined in these 3 categories:
    a. Number of facet joints with unchanged treatment recommendation
    b. Number of new facet joints that would be treated with PET/MR data
    c. Number of facet joints initially prescribed treatment based on clinical exam that would not undergo percutaneous treatment with PET/MR data.
6. The degree of concordance of FDG PET activity and MRI findings will be scored.
7. The frequency of upgrading the overall score with gadolinium images versus T2 images alone will be determined.
8. The frequency of pure facet joint synovial enhancement or effusion without peri-facet signal change will be determined.

9. Qualitative FDG PET scores will be compared to SUV-max scores (absolute and as a ratio to normal vertebral body activity) to determine if quantitative thresholds can be established for future investigation.
10. The concordance of DWI results with other imaging findings and clinical data will be assessed for exploratory purposes.
11. Interobserver variability for both FDG PET scores and MRI scores will be examined.

6.3 Data Archival

All reconstructed image data will be transferred to a DICOM archive system for long-term storage. The clinical patient images will be sent to QREADS and MIDIA.

6.4 Patient Confidentiality

All patient image data will be anonymized prior to the image analysis and blinded review. Image data will be sent directly from the scanners to a Mayo Clinic DICOM receiver (a PACS for researchers called Notion, supported by Radiology Informatics) that will anonymize the patient data using predefined rules. In this manner the same patient will have the same anonymization rules applied, independent of when or what system they were scanned on. Both the original and anonymized data are archived in MIDIA and a log that patients that have been anonymized are maintained.

7. Data Safety Monitoring Board (DSMB)

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis. Monitoring participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

The PI will be informed of serious adverse events as soon as they occur and will notify the NIA and (e.g. DSMB) within 24 hours of notification. The (e.g. DSMB) will meet twice annually, either in-person or by teleconference call to review study progress, data quality, and participants safety

7.1 Human Studies Aspects

Both male and female adult patients will be screened and enrolled in this study.
For women of childbearing potential, both pregnancy and breast feeding will be addressed. If a patient has childbearing potential, a pregnancy test will be performed. If the pregnancy test is negative, the scan may proceed. If the pregnancy test is positive, the scan will not proceed and the patient is documented as a screening failure. If a patient is breastfeeding, they are given written instructions to pump and discard their milk or pump and store it for a minimum of 8 hours per the MRI scanning technologist. It is safe for a mother to continue breastfeeding after administration of gadolinium (again instructed to discard for at least 8 hours due to FDG activity as stated above). However, if the mother

desires, she can abstain from breastfeeding for 24 hours with active expression and discarding of breastmilk (7). Sedation will be administered.

No monetary compensation will be provided. All research costs related to this protocol will be paid for by the Department of Radiology.

The MRI results will be recorded in the participant's electronic health record. Because the PET scan portion of the PET/MRI scan is being evaluated, no results will be included in their electronic health record.

8. Budget

All research costs related to this protocol will be paid for by the Department of Radiology. See attached letter from Dr. Kent Thielen in Appendix 3.

Because this is a novel imaging modality, clinical PET/MR procedure codes that will support FDA and CMS approved indications have yet to be developed and will be based on the results of developmental studies. Radiology RIMS codes specific to this development initiative will be utilized and indicate the study is a development project and there are no patient charges associated with the release of a clinical report. Additionally, Study Coordinator effort will be paid by the Department of Radiology

9. References

1. Lehman VT, Murphy RC, Kaufmann TJ, Diehn FE, Murthy NS, Wald JT, et al. Frequency of discordance between facet joint activity on technetium Tc99m methylene diphosphonate SPECT/CT and selection for percutaneous treatment at a large multispecialty institution AJNR Am J Neuroradiol 2014;35(3):609-614.
2. Verdoorn JA, Lehman VT, Diehn FE, Maus TP. – Increased ^{99m}Tc MDP Activity in the Costovertebral and Costotransverse Joints on SPECT-CT: Is It Predictive of Associated Pain or Response to Percutaneous Treatment? Diagnost Interv Radiol (In Press)
3. Czervionke LF, Fenton DS. Fat-saturated MR imaging in the detection of inflammatory facet arthropathy (facet synovitis) in the lumbar spine Pain Med. 2000;9(4):400-406.
4. Pneumaticos SG, Chatziioannou SN, Hipp JA, Moore WH, Esses SI. Low back pain: prediction of short-term outcome of facet joint injection with bone scintigraphy. Radiology 2006;238(2):693-698.
5. Dolan AL, Ryan PJ, Arden NK, Stratton R, Wedley JR, Hamann W, et al. The value of SPECT scans in identifying back pain likely to benefit from facet joint injection. Br J Rheumatol 1996;35(12):1269-1273.
6. Lehman VT, Murphy RC, Schenck LA, et al. Comparison of facet joint activity on ^{99m}Tc-MDP SPECT/CT with facet joint signal change on MRI with fat suppression (submitted).
7. https://www.infantrisk.com/sites/default/files/files/Radiocontrast%20Breastfeeding.pdf

Appendix 1: Radiology Funding Letter

MAYO CLINIC

PET/MR Research Committee
Department of Radiology
Mayo Clinic Rochester

To: Vance Lehman, MD: PI
Barbara Foreman: Study Coordinator

The following is an excerpt from the minutes of the PET/MR Research Committee meeting dated 8/13/15:

With regard to developmental funding for the proposal entitled "molecular and MRI biomarkers of Facet Joint Pain" version #1 dated 5/14/15 from Dr. Lehman and colleagues. The Committee reviewed Dr. Lehman's responses to the committee's requested proposal modifications and also reviewed the IRB protocol version submitted on behalf of Dr. Lehman. These items have been recorded in the Committee's records. The committee approved developmental funding for this proposal.

The Committee approves 10 PET/MR slots to be paid for by Department of Radiology PET/MR Development Funds. These are internally funded through the department and no formal budget is required for the performance of the PET/MR scans. This approval serves as documentation of "Mayo Funding/No Funds" in Section 12 of the IRBe application. Slots are up to 1.5 hours with the ultimate goal of scanning for less than 1 hour. The proponent is reminded that funding of PET/MR scans will begin on 8/31/15 and sunset on 5/1/16, with the possibility of extension upon request.

Approval of additional PET/MR scans may be considered by the PET/MR Research Committee after completion of the specified scans and an interim review by the PET/MR Research Committee.

Please contact Rose Busta for details of how to claim 3 scholarship days the committee has approved for the PE or Co-Investigators to use in the development of this project.

The committee requests the proponent proceed with a formal protocol for IRBe submission which may include review by:

Nuclear Medicine Research Committee
Radiology Research Committee
Radiation Safety Clinical Trials Committee
Rose Busta, Secretary

cc: Geoffrey Johnson, MD, PhD

MAYO CLINIC

200 First Street SW
Rochester, Minnesota 55905
507-284-2511

March 12, 2015

To Whom It May Concern:

An important part of the Department of Radiology's 2015 Strategic Plan is the development of PET/MR technology. An important and necessary part of this development is supporting innovation/development scanning in the afternoons. The cost of these scans is being covered by the department. These will include phantom and volunteer studies, correlative studies with PET/CT, and in some instances initial PET/MR exams migrating from PET/CT to PET/MR. This resource will be utilized to meet the goal of developing a clinically reimbursable PET/MR practice that benefits our patients, our Radiology practice and the Mayo Clinic. The progress of this development effort will be reported regularly to department leadership. Department support for an individual project will stop once it is determined by the PET/MR research and development committee (approved by PET/MR executive committee) that the exam is ready for clinical use (usually after it has shown to be comparable or improved compared to PET/CT). After such decisions PET/MR scans for a given indication can be billed to the patient/insurance/CMS directly.

It is anticipated that scanning will begin 5/1/2015. Development codes for PET/MR are being developed, and exams performed under these codes will not be charged. This support will be re-evaluated in one year 5/1/2016. This support includes billing the cost of PET/MR imaging, associated diagnostic MRI imaging performed on the same scanner and related radiopharmaceuticals to the Department of Radiology.

Specifically included in this allocation of resources, is the promise to fund the imaging of patients in the "Clinical Evaluation of a PET/MR System", which amounts to pilot studies of FDG PET/CT correlated to same day FDG PET/MR plus focused diagnostic MRI for multiple FDA and CMS approved oncology indications. Scans performed on the SIGNA PET/MR scanner under this protocol can be billed to the Department of Radiology.

Sincerely,

Kent Thielen, MD
Chair, Department of Radiology