Protocol Title: Molecular Imaging Assessment of ACL Viability

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Principal Investigator: Michael V. Knopp, MD, PhD
Professor of Radiology and Novartis Chair of Imaging Research
Vice Chair of Research, Department of Radiology
395 West 12th Avenue, 4th Floor
Columbus, OH 43210

Knopp.16@osu.edu

Office: 614-293-9998
Fax: 614-293-9275

I. Objectives

Primary Research Question:

1. Does the appearance of the reconstructed anterior cruciate ligament (ACL) vary in appearance on PET/MRI depending on graft type and time after surgery?

Secondary Research Question:

1. What is the appearance of the native ACL on Positron Emission Tomography/Magnetic Resonance Imaging (PET/MRI)?

II. Background and Rationale

The ACL is commonly injured and is the most frequently reconstructed ligament of the knee. Reconstructive techniques have evolved over time with variable results.[11] Modern techniques allow clinically stable ligament reconstruction in the majority of cases; however, failed reconstruction continues to be a problem with failure rates for ACL reconstruction reported to be between 5 and 20%.

The use of allograft tissue in ACL reconstruction has been associated with increased graft failure rates.[3] While the etiology increased allograft failure rates is unclear and likely multifactorial, different patterns of revascularization and ligamentization may contribute. This process typically follows a regular pattern.[12] Vascular invasion of the graft is noted by three weeks, but the central portion remains poorly vascularized compared to the distal and proximal ends.[2] By about eight weeks post-operative, the entire graft is generally revascularized when autograft is used.[1] Numerous animal studies[5, 9, 14] have demonstrated slower revascularization and a magnetic resonance imaging (MRI) study[13] in humans has suggested slower ligamentization in allografts. Complete ligamentization of the central portion may never occur in some cases.[8] In addition, these studies demonstrate that the ligamentization process is quite variable among individuals.

The last thirty years have also witnessed a significant shift in the approach to rehabilitation following ACL reconstruction.[4] Protocols have moved away from immobilization and bracing in favor of early weight-bearing and restoration of range of motion and muscle control.[4, 17] These changes have resulted in decreased incidence of flexion contractures[6, 15] and earlier return of muscle strength and control.[16] These protocols have also decreased the time required for athletes' strength and function to return to levels required for return to sport. Returning injured athletes to play as quickly as is safely possible following ACL reconstruction has become an area of intense interest in recent years. While numerous studies have demonstrated the safety of early mobilization and strengthening activities, earlier return to unrestricted sports is supported by significantly less data. One retrospective study has shown no difference in objective knee stability or patient reported outcome with return to play between 2 and 6 months compared to return to play between 7 and 14 months.[7] However, in addition to being

small and underpowered to address the issue of graft failure, this study utilized older surgical and rehabilitation techniques that do not necessarily reflect current practice.

Given the different rates of ligamentization noted among individuals as well as graft types and the desire to return athletes to sport as early as possible, a tool that could quantify the revascularization and incorporation of an ACL graft would be highly useful. Positron emission tomography (PET) scans have the capacity to demonstrate revascularization as well as metabolic activity of tissues. Recent technologic advances have improved the resolution of PET scans and the imaging of structures such as the anterior cruciate ligament is now possible. In addition, advances in ACL imaging techniques such as chemical exchange saturation transfer (proteinCEST) have improved the ability of MRI to assess the intra-articular environment.[10] We propose to use PET/MRI to evaluate intact and reconstructed ACL tissue to assess the utility of this technique in ligament imaging.

III. Procedures

A. Research Design

This Phase I feasibility trial will evaluate knee injuries utilizing a standard of care non-contrast 3 Tesla (T) MRI. In addition, knee injuries will be assessed with a low dose (1/5 of the dose given for standard of care PET scans) fluorodeoxyglucose (FDG) PET research scan with CEST sequences. Patients enrolled in this study will include both those with and without a history of ACL repair; however, patients receiving the standard of care MRI will not be currently suspected of having an ACL injury based on physical examination and history.

Patients with and without a history of ACL reconstruction will undergo a low dose FDG PET scan in the same setting as their MRI. The PET examination will be performed such that the early phase of imaging is performed prior to the MRI and the delayed phase is completed immediately following the MRI. This dual-phase scanning will allow for both assessment of the vascularity of the graft as well as its metabolic activity.

Patients will be asked to provide study personnel with authorization to their medical records regarding the outcome of the knee graft. This authorization will be provided for 10 years from date of signed consent.

Comparisons of the finding in normal and reconstructed ligaments as well as between graft types based on time from reconstruction will demonstrate the feasibility of this imaging technique and allow for generation of an imaging based hypothesis that will provide metabolic activity of the graft in a post-operative knee.

B. Sample

The study population will include 100 evaluable patients between 18 and 60 years of age undergoing a standard of care MRI at OSU. All patients will have no current or suspected ACL injuries based on a physical examination and patient history. Five patients will not have a history of ACL injury or reconstruction and 95 patients will have a history of ACL reconstruction. The 100 patients will be selected to include a variety of graft types (autograft and allografts) at a variety of time points after surgery.

Inclusion Criteria:

- Male and female patients between 18 and 60 years of age.
- Patients scheduled for a standard of care MRI at OSU.

Exclusion Criteria:

- Patients with a suspected ACL injury.
- Patients who are pregnant or lactating.
- Patients who are prisoners.
- Patients who are unable to provide consent.
- Patient with significant renal insufficiency, i.e. an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m^2.
- Patients who exhibit noticeable anxiety and/or claustrophobia or who exhibit sever vertigo when they are moved into the MR.
- Subjects with any type of bioimplant activated by mechanical, electronic, or magnetic means (e.g., cochlear implants, pacemakers, neurostimulators, biostimulators, electronic infusion pumps, etc.).
- Subjects with any type of ferromagnetic bioimplant that could potentially be displaced or damaged.
- Subjects that have vascular or aneurysm clips, or metallic staples from a surgical procedure.
- Subjects with permanent tattoo eye liner (may contain metallic coloring).
- Subjects that may have shrapnel imbedded in their bodies, such as from war wounds, metal workers and machinists (metallic fragments in or near eyes), severe auto accident victims.

C. Detailed Study Procedures

For each participant, written informed consent will be obtained prior to any protocol related activities. As part of this procedure, the principal investigator or one of the study personnel will explain orally and in writing the nature, duration, and purpose of the study as well as all associated risks and benefits. They will inform the patient that he/she may withdraw from the study at any time. At the time of consent, patients will complete an MRI Subject Screening that will assess the patient's compatibility with the MR scanner.

Patients interested in taking part in the study will undergo a complete standardized knee examination by one of the orthopaedic surgeons on the research team. Patients will also complete a patient-oriented knee evaluation form that captures prior knee history and allows calculation of patient reported knee scores including the subjective International Knee Documentation Committee (IKDC) score, the Knee injury Osteoarthritis Outcome Score (KOOS), and the Marx activity score.

All patients will undergo a low dose PET scan in the same setting as their MRI. The MRI will include standard diagnostic sequences as well as a protein/CEST sequence. This additional sequence will add about 15 minutes to the study and carries no additional risk. The PET examination will be performed such that the early phase of imaging is performed prior to the MRI and the delayed phase immediately following the MRI. This dual-phase scanning will allow for both assessment of the vascularity of the graft as well as its metabolic activity.

Patients will be asked to lie about 90 minutes in the PET system. The imaging maybe interrupted to allow the patient to void the bladder.

Risks:
Patients will have an intravenous injection of FDG. There is slight risk of inflammation, infection, or hematoma from the i.v. and there is some associated discomfort. This is a standard procedure for many diagnostic tests. The i.v. will be removed prior to the positioning of the patient within the PET scanner. There is a remote possibility of an allergic reaction to FDG, though we are unaware of any reported incidents.

Patients will receive radiation exposure as a result of this research project. It is estimated that patients will be exposed to an effective dose equivalent of 550 millirem related to the F-18 FDG radiotracer (based on 5 mCi estimated dose) per scan, and an effective dose equivalent of 20 millirem related to a low dose CT of the knee, for a total effective dose equivalent of 570 millirem.

The MRI will include standard diagnostic sequences as well as a protein/CEST sequence. This additional sequence will add about 15 minutes to the study and carries no additional risk.

Benefits:
Possible benefits for some participants include insight into the status of their ACL graft as determined by the PET results. All scans will contribute to improvements in our understanding of graft incorporation and failure mechanisms in ACL reconstruction.

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