Project Title: An imaging framework for clinically testing new treatments to prevent post-traumatic Osteoarthritis

Protocol Version June 16, 2025

Background:
Post-traumatic osteoarthritis (PTOA) is a common disabling condition following intra-articular fractures (IAFs), despite best treatment efforts (1,2). Between 23% and 44% of patients develop PTOA after tibial plateau fractures (3-5) and >50% of patients after tibial pilon fractures (6-11). In one study, 30% of ankles had PTOA within 2-4 years after a pilon fracture (11). PTOA brings substantial pain, disability, lost work capacity, and decreased general health status. In the ankle, where the vast majority of OA is post-traumatic, the associated impairment is comparable to that caused by end-stage kidney disease or congestive heart failure (12,13). The societal cost of PTOA is high; ~$12 billion/year in the United States (13) since pain and lost function frequently leads to lost work capacity. Recent findings indicate that IAFs, by virtue of both acute and chronic mechanical factors, initiate a sequence of biologic events leading to PTOA (14). Clinical trials of agents aimed at interrupting this sequence of events face barriers of limited capability to predict PTOA risk and poor early indicators of PTOA development. We have established methods to quantify PTOA risk from mechanical factors, a critical step in overcoming these barriers. There remains an urgent need for better PTOA imaging biomarkers. Diagnosis and prognosis, as well as evaluation of therapeutic efficacy, require biomarkers sufficiently sensitive to detect development and progression of disease (15). Clinical monitoring for PTOA following IAF presently involves the serial acquisition of weight-bearing radiographs to check for joint degeneration (16). However, radiographs capture an obscured 2D projection of a complex 3D structure and pathology. Our working hypothesis is that a low-dose standing CT (SCT) scanner for the foot and ankle will provide more sensitive and responsive measures of joint degeneration, without an increase in cost or time and without a significant increase in radiation (17). SCT would provide much greater diagnostic value, not only because of its 3D nature, but also because patients are imaged in a functional weight-bearing position. The SCT scanner will also simplify articular contact stress computation and could guide earlier preventive therapies.

Specific Aims:
Aim 1. Determine the extent to which OA findings on SCT correlate earlier and more strongly with joint symptoms than findings on plain radiographs.
Aim 2. Measure the incidence of PTOA following surgical fracture reduction in patients with tibial pilon fractures and quantify the extent to which post-reduction contact stress predicts risk and correlates with changes in 3D joint space width.
Aim 3: Identify post-injury inflammatory cytokine synovial biomarkers that correspond with worse PROMIS-29 scores.

Hypothesis: Acute IL-1b concentration in synovial fluid is associated with worse PROMIS-29 score at 12 months post-injury

Methods:

Subjects

Inclusion criteria:

- Age 18-70 years
- Intra-articular tibial plafond fracture
- Enrollment within 4 weeks of injury

Exclusion criteria:

- Pregnant or planning to become pregnant

Procedures

Individuals who present to hospital with an IAF of the tibial plafond and meet eligibility criteria will be consented to participate in this study. The only procedures that will be outside of their standard clinical care will be the WBCT scans obtained at 6, 12, and 18 months post-injury, and annually at 2-6 years post-injury, as well as several questionnaires that will be administered during the clinical visits. Questionnaires will be administered via RedCap, either with an iPad or a clinic computer. The scan will take place at their scheduled clinical visit at these time points. The scan itself takes about 5 minutes; this is the only research-related procedure. There is no follow-up beyond standard clinical care for this type of injury. Women who are capable of becoming pregnant will undergo a urine pregnancy test prior to having the WBCT scan.

Additionally, information on the timing and mechanism of injury, time from injury to surgery, length of hospital stay, any complications and/or subsequent ankle surgeries, as well as any clinic notes, imaging, and/or outcomes scores related to the calcaneus fracture will be collected from the electronic medical record. There is also an optional collection of synovial fluid sample at the time of surgery for subjects consented within the first 72 hours of injury.

Subjects are able to decide whether or not they wish to consent for the aspirate portion of this study and this decision does not interfere with their ability to participate in the other study procedures. The surgeon performing the ankle procedure will collect a small (between 2-10cc) aspirate of synovial fluid intraoperatively. If subjects participate in the synovial fluid collection portion of this study there will be additional WBCTs conducted at 3 weeks and 3 months post-injury during regularly scheduled follow ups. This aspirate would normally be considered

surgical discard, and poses minimal risk to the subject. Samples will be tested at the Central Laboratory at the University of Utah.

Questionnaires that will be administered at each clinic visit include the Foot and Ankle Ability Measure, PROMIS Pain Interference, and PROMIS Physical Function. Each of these questionnaires will take approximately 10-15 minutes to complete. The total time allocated to these questionnaires will be approximately 30-45 minutes. Starting at the 6-month follow-up visit, the Rand 36 item SF Health Survey will be included in the batch of questionnaires administered. All of these questionnaires are study-specific and not standard of care.

Statistical Methods:

To address Aim 1, associations between continuous baseline pain and function scores and ordinal a) osteophyte and b) joint space width on pedCAT and radiographs will be assessed by calculating Spearman correlation coefficients. We will then test for the equality of dependent correlations from radiographs and pedCAT. For Aim 2, we will fit a logistic regression model with PTOA status as the dependent variable and injury severity and contact stress as independent variables. We will test null whether the coefficient for contact stress differs from zero at the 0.05 type-I error level. For power calculation, we made the following assumptions: (1) the correlation between fracture severity and contact stress is 0.5 and (2) the incidence of PTOA by 18 months at the mean value of contact stress is 20%. We will also employ descriptive statistic measures, using a statistics software program such as SAS or SPSS, to analyze subjects' validated outcomes questionnaire scores (baseline and post-operative). We will look for any significant associations between these scores and other outcomes, including joint space width and contact stress, and biomarkers present in the synovial fluid samples

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