STUDY PROTOCOL Open Access

Blood flow Restriction training After patellar INStability (BRAINS Trial)

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Abstract

Background: Patellar instability is a common and understudied condition that disproportionately affects athletes and military personnel. The rate of post-traumatic osteoarthritis that develops following a patellar dislocation can be up to 50% of individuals 5–15 years after injury. Conservative treatment is the standard of care for patellar instability however, there are no evidence-informed rehabilitation guidelines in the scientific literature. The purpose of this study is to assess the effectiveness of blood-flow restriction training (BFRT) for patellar instability. Our hypotheses are that this strategy will improve patient-reported outcomes and accelerate restoration of symmetric strength and knee biomechanics necessary to safely return to activity.

Methods/design: This is a parallel-group, superiority, randomized, double-blinded, placebo-controlled clinical trial at the University of Kentucky, sports medicine clinic that aims to recruit 78 patients with acute patellar dislocations randomly allocated into two groups: (1) sham BFRT and (2) BFRT. Both groups will receive the current standard of care physical therapy 3 times per week for up to 9 weeks. Physical therapy sessions will consist of typical standard of care treatment followed by BFRT or sham BFRT. Primary outcomes include the Norwich Patellar Instability Scale, quadriceps strength, and imaging and biochemical biomarkers of cartilage degradation.

Discussion: The current standard of care for non-operative treatment of patellar instability is highly variable does not adequately address the mechanisms necessary to restore lower extremity function and protect the long-term health of articular cartilage following injury. This proposed novel intervention strategy uses an easily implementable therapy to evaluate if BFRT significantly improves patient-reported outcomes, function, and joint health over the first year of recovery.

Trial registration: Blood Flow Restriction Training, Aspiration, and Intraarticular Normal Saline (BRAINS) NCT04554212. Registered on 18 September 2020.

Keywords: Patellar instability, Blood-flow restriction training, Rehabilitation, Randomized controlled trial

Background

Patellar dislocations are a common and understudied condition that disproportionately affects athletes and military personnel [1]. The rate of having a patellar dislocation is greater than having an anterior cruciate ligament (ACL) tear in this population [1]. Regardless of intervention, 30% to 50% of those who sustain a primary dislocation experience continued pain and the sensation of instability [2]. A significant long-term concern is the rate of post-traumatic osteoarthritis that develops following a patellar dislocation which can be up to 50% of individuals within 5–15 years after injury [3]. Nonoperative treatment is currently the standard of care following most first-time dislocations; however, 31% of patellar...
instability patients treated conservatively suffer a re-
dislocation [4]. A single patellar dislocation increases the
lifetime risk of post-traumatic osteoarthritis (PTOA) and
recurrent dislocations markedly increase this risk [3, 5].
Therefore, there is an urgent need to minimize the inci-
dents of recurrent patellar dislocations and PTOA se-
quela which safely allows an earlier return to sport or
work while also limiting long-term functional impair-
ments and reduced quality of life.

While nonoperative treatment is most commonly
employed for patellar instability, specific evidence-
informed rehabilitation guidelines are sparse [4]. One
modality that could potentially improve treatment for
those with patellar instability is blood flow restriction
training (BFRT). BFRT involves the use of an inflatable
cuff applied to the thigh to slow arterial blood flow and
eliminate venous return as subjects exercise with a rela-
tively low resistance. It is thought that the increased
metabolic stress and mechanical tension during BFRT
act to stimulate various metabolic pathways leading to
muscle hypertrophy [6–8]. There is evidence supporting
the premise that BFRT will result in improved quadri-
ceps and hip strength without the need for high-
hintensity resistance exercise [9–11]. Due to the nature
of patellar instability, patients may not tolerate high-
hintensity quadriceps exercises early in the rehabilita-
ion process thus delaying the recovery of strength. BFRT
may allow them to receive the same training benefits as
if they were training under high loads. Achieving greater
muscle strength earlier after injury may result in im-
proved lower extremity biomechanics, improved func-
tional capacity, and an accelerated recovery.

The purpose of this double-blind randomized clinical
trial is to assess whether BFRT in addition to standard
physical therapy will improve patient-reported outcomes
and accelerate return to work or sport through the ear-
lier restoration of symmetric strength and knee biome-
chanics, and reduce early cartilage degradation for those
with patellar instability.

Methods/design

Aims

The overarching rationale is that BFRT will expedite the
return to work or sports, minimize muscle impairment,
and ultimately slow cartilage degradation over the first
year following patellar dislocation. This strategy will im-
prove patient-reported outcomes and accelerate restor-
ation of symmetric strength and knee biomechanics
necessary to safely return to activity. We will test the fol-
lowing specific aims:

AIM 1: Determine if BFRT improves patient-reported
outcomes and lessens the time to return to work or
sport following patellar instability.

Hypothesis: BFRT will result in significantly improved
responses on the patient-reported Norwich Patella In-
stability, visual analog scale (VAS) for Pain, Cincinnati
Occupational Rating Scale, Tegner activity scores, and
an earlier return to work and/or sport.

AIM 2: Assess whether BFRT results in more symmet-
ric quadriceps strength and knee biomechanics following
patellar instability.

Hypothesis: BFRT will result in improved quadriceps
strength and knee biomechanics (knee moments and
excursions).

AIM 3: Compare progressive changes in cartilage deg-
radation, muscle architecture, and inflammatory profiles
between those treated with or without BFRT over the first
2 years.

Hypothesis: BFRT will reduce degradative changes on
Magnetic Resonance Imaging (MRI) as well as serum
and urinary biomarkers of inflammation and cartilage
degradation.

Participants

Participants will be males and females recruited from
the University of Kentucky Sports Medicine Clinic. A
sample of 78 patients with patellar instability will be re-
cruited. Potential study participants will be identified by
members of the research team during regularly sched-
uled office visits with 6 physicians at the UK Ortho-
paedic and Sports Medicine Center. After being
identified as a potential study participant, the patient will
meet with a research assistant. Provided that the patient
meets all inclusion and exclusion criteria, a clinical re-
search coordinator will begin the process to obtain in-
formed consent. Before enrollment, each subject will
provide written informed consent. An American Board
of Family Medicine-certified physician with a Certificate
of Added Qualifications in Sports Medicine, board-
certified orthopedic surgeon, or a licensed physical ther-
apist will make the diagnosis of patellar instability utiliz-
ing the following criteria: patients’ report of at least one
episodic of patellar instability within the past 3 months, a
positive patellar apprehension test during clinical exam-
ination, and no evidence on MRI or x-ray of loose body
formation or osteochondral defects, avulsion, or osteo-
chondral defect that would require the need for surgical
intervention (Table 1).

Design

This is a parallel-group, superiority, randomized,
double-blinded, placebo-controlled clinical trial that be-
gins in the winter of 2022 and will continue for 4 years.
This study will take place at the University of Kentucky,
and has been approved by the University of Kentucky
IRB (IRB #56541, ClinicalTrials.gov Identifier:
NCT04554212). Any changes to the protocol will be first
Table 1 Inclusion and exclusion criteria for the BRAINS clinical trial for patients with patellar instability

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| Diagnosis of traumatic patellar dislocation (either primary or recurrent) determined by an American Board of Family Medicine-certified physician with a Certificate of Added Qualifications in Sports Medicine, a board-certified orthopedic surgeon, or a licensed physical therapist utilizing clinical examination, radiographic imaging, and patients’ reports of instability | Concomitant osteochondral lesion requiring surgical fixation |
| Age 14 to 40 years | Radiographic evidence of osteoarthritis (≥ Kellgren-Lawrence Grade 2) |
| Skeletally mature with closed growth plates visualized by radiograph | Previous ipsilateral or contralateral knee surgery |
| A score of 80 or more on the Sports Activity Scale, which corresponds to participating in "running, twisting, turning (tennis, racquetball, handball, ice hockey, field hockey, skiing, wrestling)" at least 1–3 times per week | Most recent instability event more than 3 months before enrollment |
| Desire to resume pre-injury activity level | History of intra-articular injection into either knee within 3 months |

Inclusion criteria

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- Desire to resume pre-injury activity level

Exclusion criteria

- Concomitant osteochondral lesion requiring surgical fixation
- Radiographic evidence of osteoarthritis (≥ Kellgren-Lawrence Grade 2)
- Previous ipsilateral or contralateral knee surgery
- Most recent instability event more than 3 months before enrollment
- History of intra-articular injection into either knee within 3 months
- History of any inflammatory disorder
- Body mass index > 35 kg/m²
- Diabetes or uncontrolled hypertension
- Varicose veins or a history of personal or immediate family history (parental or sibling) of deep vein thrombosis

randomization schedule will meet with the pre-specified needs at the time of screening based on the severity of the injury and with the goal of adequately preparing them to return to their sport of choice.

Readership: The team member that prepared the randomization schedule will meet with the pre-specified unblinded study personnel prior to the site initiation visit. The unblinded personnel will then prepare sealed envelopes that contain each subject’s group assignment. All assessments and data analyses will be performed by a separate individual to the person applying the BFRT unit to ensure blinding. The study statistician will generate a randomization plan using SAS or R to assign subjects to groups. Randomization will occur by sex and be in sets of 2 subjects to ensure adequate distribution of all groups across the collection period. Patients will be randomized into one of the two following treatment groups:

1) Standard of care physical therapy + sham BFRT
2) Standard of care physical therapy + BFRT

Should an investigator become inadvertently unblinded, the medical officer and principal investigator will determine the extent of the unblinding and potential ramifications. If necessary, the investigator’s role may need to be altered to only include tasks affiliated with unblinded personnel. Should a patient become inadvertently unblinded, that patient’s data will continue to be collected for safety purposes; however, the data will not be used for the final analyses and a replacement subject will be enrolled. Unblinding of a subject(s) group assignment will be documented and will include an explanation of why the study intervention was unblinded. Following data lock, group assignment can be unblinded and the unblinded information can be sent to the study participants at the discretion of the principal investigator.

Interventions

All groups will receive current standard of care physical therapy from a licensed physical therapist. Physical therapy sessions will consist of typical standard of care treatment followed by BFRT or sham BFRT. The standard of care portion of the session will consist of brief subjective and objective screening followed by a structured treatment paradigm consisting of pain modulation, neuromuscular re-education, dynamic warm-up, range of motion and mobility, progressive strengthening, and power training with an emphasis on the lower extremities and trunk musculature. The standard physical therapy portion of the treatment session will last approximately 40 min. Interventions for pain modulation, range of motion, and neuromuscular re-education, balance, and gait training will be utilized as needed to address individual subjects’ specific needs at the time of screening based on the severity of the injury and with the goal of adequately preparing them to return to their sport of choice.
Blood flow restriction training

Two brands of blood flow restriction units will be used (brand names not included in this text to avoid the potential for subjects to become unblinded). Subjects will be split into groups as previously described where brand 1 will be used as sham BFRT and the intervention group will use brand 2. All quadriceps-focused exercises will be performed with the bands inflated. As directed by the manufacturer’s instructions, the bands will be placed on the proximal thigh as close to the femoroacetabular joint as possible (Fig. 1). Limb arterial occlusion pressure will be constantly monitored and adjusted by the unit to maintain the desired occlusion pressure throughout the duration of exercise. Consistent with our current trial assessing the efficacy of BFRT for ACL reconstruction patients (NCT03364647), participants in all groups will perform the same exercises with an emphasis on quadriceps and hip strengthening, and for those randomized to the active BFRT groups, each BFRT session will last approximately 20 min [12]. All subjects will attend 3 visits per week for 8 weeks divided into 4 phases.

The active BFRT group will have the arterial blood flow occlusion pressure set per manufacturer instructions to achieve the desired limb occlusion pressure (LOP), whereas the sham BFRT group will have restriction pressure set at a sub-clinical level of occlusion. Occlusion personalized tourniquet pressure (PTP) will be reassessed each visit by rechecking the LOP. Each subject will perform a block of 4–5 quadriceps and hip-focused exercises each lasting approximately 5 min for a total of 20 min (exercises: seated single leg press, seated single leg knee extension, single leg forward step-ups progressed to forward step downs when tolerated, and resisted double leg squats). Exercise intensity will be adjusted between groups to accommodate the achievement of volitional fatigue and an acceptable sensation of discomfort during exercise. Cuffs will be deflated for a minimum of 1 min between exercises. The quadriceps and hip strengthening exercises with the cuff donned will be performed at the end of the rehabilitation session with the intention of reducing the impact of fatiguing the muscles for the standard physical therapy portion of the treatment session.

For all subjects, rating of perceived discomfort and rating of perceived effort will be recorded from separate 11-point Likert-type scale (0 no discomfort or effort to 10 maximal discomfort or effort) for each BFRT exercise. Emphasis will be placed on distinguishing between effort (the amount of physical energy being given to the exercise) and discomfort (the physiological and unpleasant sensations associated with the exercise), with the goal of maximizing effort. All exercises should be challenging and/or hard to perform; however, subjects need to maintain proper form, as determined by the treating physical therapist, to ensure appropriate quadriceps engagement.

Criteria for progression of resistance or exercises include (1) no excessively aberrant movement causing pain due to fatigue of desired muscle group(s), (2) no excessive form deviation where the desired muscle group is no longer the primary mover completing the desired task, (3) no concordant pain > 4/10, (4) ability to complete delineated sets and repetitions without pausing within a set, and (5) able to complete 2 or more repetitions than delineated during the last set of the exercise.

Criteria for clearance to return to sport include (1) negative moving patellar apprehension test, (2) a score of 0 indicating no effusion with the stroke test, (3) at least 0 degrees of knee extension active range of motion of the involved knee, (4) knee flexion active range of motion within 5 degrees of the uninvolved knee, (5) < 4/10 numeric pain rating with activity, and (6) 90% limb symmetry index as measured with isometric knee extension peak torque and the 60-s step down test.

Treatment adherence

Treatment adherence is the extent to which a therapist uses interventions prescribed by a protocol. To maximize adherence and treatment fidelity, electronic logs of all the exercises per session will be kept on a custom Microsoft Access database. Adherence to the treatment protocol will be audited by an external physical therapist regularly throughout the duration of the study. We will monitor session attendance using a diary log with participant ID numbers and session dates to track the percentage of attendance and to account for absenteeism and reasons for missed sessions. We will make every effort to deliver the full treatment, but we expect...
some variation in treatment delivery dose as well as treatment drop-out. Reasons for attrition will be assessed with an open-ended question for enrolled participants who withdraw.

**Outcome measures**

Primary outcomes include the Norwich Patellar Instability Scale [13] collected at the time of enrollment, 4 weeks, 9 weeks, 6 months, and 12 months after enrollment, isometric and isokinetic quadriceps strength at 1 week, 4 weeks, 9 weeks, 6 months, and 12 months after enrollment, MRI T₁ρ and T₂ relaxation times 1 week, and 12 months enrollment, and biochemical biomarkers which will include urinary C-terminal cross-linked telopeptide type II collagen (CTXII) and a neoepitope of type I and type II collagen cleavage (C1,2C) at the time of enrollment, 4 weeks, 9 weeks, 6 months, and 12 months after enrollment. Secondary outcomes include the VAS for pain [14], Cincinnati Occupational Rating Scale [15], Tegner Activity Scale [16], and the time to returning to work and/or sporting activities, hip muscle strength (hip abduction, hip external rotation), and knee biomechanics (knee extensor moment, knee flexion excursion, knee adduction moment, knee adduction excursion) during walking, running, and anterior step-downs 1 week, 9 weeks, 6 months, and 12 months after enrollment. Data will be captured using REDCap and will be reviewed on a quarterly basis by an unblinded member of the study team to ensure data quality and completeness (Table 2).

**Statistical methods**

The primary outcome variable for Aim 1 is the Norwich Patellar Instability Scale. Utilizing the standard deviation of 18.6 points from our pilot results, a sample size of 34 subjects per group will be adequately powered (80%) to detect a moderate effect size between groups difference (13 points difference, effect size = 0.7). To protect against up to 15% of subjects being lost to follow-up, an additional 5 subjects will be enrolled per group (39 subjects per group; 78 total). Based on our previous pilot work, a sample size of 34 patients per group will also be more than 80% powered to detect group differences in the primary outcome variables for both Aim 2 (quadriceps strength and knee biomechanics) and Aim 3 (T₁ρ relaxation time).

Since all endpoints are quantitative and longitudinal data is collected, repeated measures analysis of covariance (ANCOVAs) will be used to assess differences in scales across the two treatment groups (BFRT vs. sham BFRT). The repeated measures ANCOVAs will adjust for demographic covariates (e.g., age, sex, and race) as well as look for differences across any other potential confounders (such as first-time vs. repeated instability events). Assumptions such as normality and constant variance will be assessed, and remedial measures will be employed as needed. In addition, interaction effects and/or variable transformations will be explored appropriately. In the case that endpoints are related, multivariate analysis of covariance (MANCOVAs) may be used to consider those that naturally group themselves.

All analyses will be performed with a significance level of 0.05, and appropriate multiple comparisons adjustments will be performed as needed. Categorical variables will be described with counts and percentages and analyzed using appropriate statistical methods, such as hypothesis tests or logistic regression models.

For both primary and secondary analyses, in the case of participants that violate group allocation or do not attend a minimum of 80% of the prescribed physical therapy sessions, we will perform intention-to-treat and per protocol analyses. We will not employ imputation methods in the case of missing data. No interim or other subgroup analyses will be performed.
Participant information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. Participants will not be personally identified in these written materials. We may publish the results of this study; however, we will keep participant names and other identifying information private. The study information collected from participation in the study may be entered into a secure computer system. The study physician is committed to maintaining the privacy of every study participant and any personal information submitted and follows the principles of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. All data are stored at a secure site behind a firewall, which monitors and protects against unauthorized access. Participant charts and any other items containing confidential items will be stored in a safe place overnight and not left on the desk. Charts will not be left in an area where others might have access to them. Participants should know, however, that there are some circumstances in which we may have to show their information to other people. For example, the law may require us to show their information to a court or to tell authorities if they report information about a child being abused or if they pose a danger to themselves or someone else. Officials of the University of Kentucky, the Department of Defense, members of an independent Data Safety Monitor Board, the Center for Clinical and Translational Science, and Bluegrass Research Consultants may look at or copy pertinent portions of records that identify participants. Participants withdraw from the study or are withdrawn; data collected to that point will be kept.

Monitoring
We will utilize the standing independent Data Safety Monitoring Board (DSMB) as chartered by the Center for Clinical and Translational Science (CCTS). The DSMB will meet three times per year or as needed and will review participant recruitment, AE’s, side effects, laboratory results, dropouts, protocol violations, and inclusion/exclusion criteria. More frequent meetings will take place if side effects or other problems are prevalent. Should an adverse or serious adverse event occur, the research participant will be followed by physicians, registered nurses, and other research staff members for the duration of the participant’s hospitalization. Routine care will be provided by hospital staff. Emergency medical equipment, medications, and supplies will be at the physician’s disposal should the participants have an acute untoward reaction.

Discussion
Currently, scientific evidence regarding the medical management and treatment of patellar instability is sparse. As such, the standard of care for non-operative treatment is highly variable does not adequately address the mechanisms necessary to restore lower extremity function and protect the long-term health of articular cartilage and surrounding musculature following injury. A significant need remains to identify novel therapies that successfully restore function and preserve joint integrity. The goal of this trial is to evaluate if augmenting standard physical therapy with BFRT significantly improves patient-reported outcomes, function, and joint health over the first 2 years of recovery.

Blood-flow restriction training is a promising modality for patients who suffer from patellar instability. We have previously shown that these individuals have clinically important impairments in quadriceps and hip strength as well as altered knee biomechanics compared to healthy volunteers [17]. Increased quadriceps strength has been shown to be protective against patellofemoral cartilage loss as well as improved pain and function [18]. Hip weakness and increased knee abduction angles may place the patient at greater risk for repeated lateral patellar dislocation or subluxation and increase the compressive and shear forces born by the articular cartilage [18, 19]. BFRT allows the subject to exercise with light resistance to derive similar training benefits seen with higher-intensity resistance exercises (Fig. 1) [6–10, 20–23]. Potentially, with BFRT the negative morphological adaptations of hip and thigh musculature that result in abnormal lower extremity biomechanics can be addressed, while compressive and shear forces born by the patellofemoral articular cartilage are minimized thereby promoting recovery [11, 19].

We seek to address the shortcomings of the current treatment strategies by specifically addressing progressive cartilage degradation, muscle weakness, and functional impairment for those with patellar instability. Current physical therapy protocols do not adequately restore quadriceps or hip muscle strength resulting in altered knee biomechanics. The combination of a pro-inflammatory intra-articular environment and persistent biomechanical deficits undoubtedly contribute to the high rate of PTOA for those with patellar instability. By potentially addressing both biologic and biomechanical mechanisms of PTOA, the proposed interventions may alter the progression of PTOA in this high-risk patient population. The long-term impact of this study is that the progression of PTOA may be delayed or potentially even avoided. These results may then impact the treatment paradigms for other acute conditions such as anterior cruciate ligament injuries, shoulder dislocation, and/or ankle sprains.
Trial status
This is protocol version 2.0 (December 15, 2021). Patient recruitment will begin in January 2022 with recruitment ending December 2023.

Abbreviations
BRAINS: Blood flow Restriction training, Aspiration, and Intra-articular Normal Saline; BFRT: Blood-flow restriction training; ACL: Anterior cruciate ligament; PTOA: Post-traumatic osteoarthritis; IL-1α: Interleukin-1α; MMP-3: Matrix metalloproteinase-3; VAS: Visual analog scale; MRI: Magnetic resonance imaging; LOP: Limb occlusion pressure; PTP: Personalized tourniquet pressure; ANCOVAs: Analysis of covariance; MANCOVAs: Multivariate analysis of covariance

Acknowledgements
Not applicable.

Biological specimens
Laboratory analyses of biologic samples outcomes: Data sheets will record descriptive information on the biopsy when collected (number of tubes, etc.). Samples will be labeled according to the visit the study participant attended. The sample tubes will be labeled with the participant’s study ID number first. For example, when collecting data subject 05 on visit 2, the images will be labeled as PI05_V2 followed by the type of fluid. For biologic samples, similar identifiers will be used with _urine or _serum used to identify the type of fluid (example: PI05_V2 urine).

Blood samples: Standard venipuncture will be used to collect 10 mL blood samples at each of the five study visits. The PI and research coordinator have both completed the UK Phlebotomy Class and completed the “Phlebotomy Clinical Training and Competency Validation” form to allow drawing blood samples from study subjects. In addition, the 4 other research coordinators in the Department of Orthopaedic Surgery and Sports Medicine have also been trained and certified in phlebotomy. While not key personnel in the current study, they will be added to the study personnel list to act as backups should both the study coordinator and PI not be available to perform the study blood draws.

Urine samples: Similarly, urine samples will be collected at all 5 study visits. The Functional Orthopedics Assessment Laboratory (FOAL) is located within the clinical space at the UK Orthopaedic and Sports Medicine Center. There is a dedicated, lockable restroom located next to door to the FOAL which allows participants a private area to provide a urine sample, and the sample can then be discreetly transferred from the restroom to the FOAL.

Sample processing: Blood and urine samples will be collected at all study time points. Serum and urine samples will be initially processed in the FOAL. Blood and urine samples will be spun in a refrigerated centrifuge at 3500 RPM for 10 min. Serum and urine will then be aliquoted into separate pre-labeled cryovials. Samples will be initially stored on site at ~80°C in a freezer, and subsequently transferred from the clinical facility to the University of Kentucky Orthopaedic Biomarker Repository for analysis (UK’s Charles T. Wethington Building, Room 443) on a monthly basis.

Acquisitions of biological specimens will be obtained in accordance with the principles expressed in the Declaration of Helsinki. Participants will be informed about the scope and procedures of the study and will be asked to sign an informed consent form by a member of the research staff before starting the initial evaluation.

Funding
The project is funded by the Department of Defense (Award number: W81XWH2010449) with additional support by the NIH National Center for Advancing Translational Sciences through grant number UL1TR001998. The Department of Defense contact person for this trial is Robin Walker, PhD, Science Officer, Peer Review Medical Research Program (PRMRP). The Departmentally Directed Medical Research Programs (DDMRP), Phone: 301.619.7177, Email: robin.k.walker5.cbr@email.mil. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Defense or NIH. The Department of Defense and the NIH did not have a role in the design of the study, collection, analysis, or interpretation of data, or writing the manuscript.

Availability of data and materials
Data will be collected in a protected database with an unidentified ID number provided for each participant. All authors of the current manuscript will have access to the final dataset. Participant-level data are available on request by sending an email to Cale Jacobs. All data will be available for 5 years after the relevant publication.

Declarations
Ethics approval and consent to participate
All materials and methods regarding this study have been analyzed and approved by the Institutional Review Board at the University of Kentucky (IRB#: 56541). All procedures are in agreement with the principles expressed in the Declaration of Helsinki. Participants will be informed about the scope and procedures of the study and will be asked to sign an informed consent form to allow drawing blood samples from study subjects. In addition, the 4 other research coordinators in the Department of Orthopaedic Surgery and Sports Medicine have also been trained and certified in phlebotomy. While not key personnel in the current study, they will be added to the study personnel list to act as backups should both the study coordinator and PI not be available to perform the study blood draws.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 26 March 2021 Accepted: 10 January 2022
Published online: 28 January 2022

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