Study Title: Functional Resistance Training to Improve Knee Function after ACL Reconstruction

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The *objective of this study is to perform a pilot* ***randomized clinical trial*** *that assesses whether progressive functional resistance training during gait will significantly improve quadriceps function, neural excitability, and knee mechanics after ACL reconstruction.* We anticipate that this approach will lead to symmetrical quadriceps strength and gait climbing biomechanics, complete voluntary activation, and improved neural excitability and patient-based outcomes.

Aim 1: Determine the effects of progressive functional resistance training during walking on knee outcomes after ACL reconstruction.

Hypothesis 1: Progressive functional resistance training while walking will result in greater improvements in knee extensor strength (primary outcome) than dose-matched treadmill walking. *Hypothesis 1B:* Voluntary activation, sagittal plane knee biomechanics and patient-reported outcomes will also be significantly better after progressive functional resistance training than after dose-matched treadmill training.

Aim 2: Determine the effects of progressive functional resistance training during gait on cortical and spinal reflex excitability of individuals with ACL reconstruction.

Hypothesis 2A: Progressive functional resistance training while walking will result in greater changes in corticospinal excitability than dose-matched treadmill walking. *Hypothesis 2B:* There will be a strong association between changes in knee extensor strength, voluntary activation and corticospinal plasticity.

APPROACH

Study Design for ACLR subjects: This is a single-center randomized controlled pilot trial of functional resistance training during treadmill walking. Patients with ACLR will be randomized using permuted blocks into one of three groups: 1) functional resistance training with a custom brace during treadmill walking, 2) functional resistance training with elastic bands during treadmill walking, and 3) treadmill walking (sham/control arm). Isometric quadriceps strength symmetry index will be our primary outcome measure. Our secondary outcome measures are: 1) % voluntary activation, 2) knee flexion angle symmetry, 3) knee moment symmetry. Our tertiary outcomes are: 1) patient-reported outcomes via Knee Injury and Osteoarthritis Outcome Score, 2) cortical excitability, and 3) spinal reflex excitability. All outcome measures will be examined at 3 study time points: 1) *Pre-intervention*: about 6 weeks after ACLR (a time-point when adequate quadriceps control is usually achieved), 2) *Post-intervention*: immediately after the intervention, and 3) *Follow-up*: 6-12 months post-ACLR (±2 weeks) (when patients are typically cleared for return to activity) (Fig. 1).

Subject Characteristics: To be eligible for inclusion in the study, ACL subjects must meet the following criteria:1) aged 14-40 years; 2) suffered an acute, complete ACL rupture; 3) scheduled to undergo ACL reconstruction with an autograft, 4)willingness to participate in testing and follow-up as outlined in the protocol; and 5) English-speaking. Exclusion criteria for the trial are: 1) inability to provide written informed consent; 2) female subjects who are pregnant or are planning to become pregnant (determined via self report); 3) previous ACL injury; 4) previous surgery to either knee; 5) recent significant knee injury; 6) history of uncontrolled diabetes or hypertension, and 7) patients who are contraindicated for TMS (e.g., metal implants in head, unexplained recurrent headaches, history of seizures, epileptogenic drugs, active psychiatric illness, etc.). To be eligible for inclusion in the study, healthy subjects must meet the following criteria: 1) aged 14-40 years; 2) have no history of of major kee injury, 3) willingness to participate in testing and follow-up as outlined in the protocol; and 4) English-speaking. Exclusion criteria for healthys subjects are: 1) inability to provide written informed consent; 2) female subjects who are pregnant or are planning to become pregnant (determined via self report); 3) previous ACL injury; 4) previous surgery to either knee; 5) previous history of significant knee injury; 6) history of uncontrolled diabetes or hypertension, and 7) patients who are contraindicated for TMS (e.g., metal implants in head, unexplained recurrent headaches, history of seizures, epileptogenic drugs, active psychiatric illness, etc.).

ACL Standard of Care Rehabilitation: Participants in all groups will undergo standard ACL rehabilitation (e.g., standard of care). Total standardization of the ACL rehabilitation program will not be possible given that the various concomitant injuries accompanying the ACL rupture may dictate a slower progression through exercises (e.g., patients with a meniscal repair will be progressed through rehabilitation slower than those with a meniscectomy). We have shown previously that meniscal treatment does not influence quadriceps function at the time of return to activity.[1] Further, the intervention of interest, functional resistance training, is being studied as an adjunct to the standard of care and is meant to supplement current practices. To ensure similar practices between therapists, we will have basic guidelines that therapists will follow.[2-4] Further, to help ensure fidelity of the standard of care across patients, only 2 physical therapists, with a minimum of 5 years of experience, will deliver the rehabilitation. Additionally, guidelines will be discussed prior to the study initiation and a manual of operating procedures will be provided.

Study Interventions – ACL subjects

Functional Resistance Training: Patients randomized into this group will receive progressive functional resistance training while walking on a treadmill using a resistive device applied to the leg (resistance during walking could be applied via a resistive brace (using eddy current braking) or elastic tubing or cuff that is attached to the subject's leg). Subjects will exercise 2-3 ×/week for 8 weeks, beginning at ~6 weeks post-ACLR. To perform the exercise, patients will wear a brace/cuff/band that is capable of providing scalable resistive torques with their ACLR knee with range of motion limited to 10° to 70° of knee flexion. Patients will warm-up for 2 minutes by wearing the brace/cuff/band on the ACLR limb and walk on a treadmill at their comfortable walking speed with resistance set at zero level. Following the warm-up trial, each participant will perform six blocks of treadmill walking at their self-selected pace, with each block of training lasting for 5 minutes. Two minutes of rest will be provided after each block of training. Real-time kinematic feedback will be provided to ensure that subjects maintain proper kinematic patterns during the training.[5-8] During resisted walking trials, subjects will cyclically engage their quadriceps and their hamstring muscles with the ACLR limb. The patients will train at an intensity equal to corresponding to a difficulty level between 5-7 on the OMNI scale.

Treadmill Walking (sham condition): Participants randomized to the treadmill walking group will receive treadmill training 3x/week for 8-12 weeks beginning at 6 weeks post-ACLR. The treadmill walking group will utilize the same equipment and follow the same protocol as in the functional resistance training intervention, with the exception that the intensity of the resistive brace/cuff/band will be set with no resistance throughout the training.

Objective 1: Determine the effects of progressive functional resistance training during walking on knee outcomes after ACL reconstruction. The goal of Aim 1 is to test the hypothesis that functional resistance training during walking will improve knee outcomes to a greater extent than dose-matched treadmill walking in individuals with ACLR. Subjects with ACLR will participate in an 8-week training program. Knee outcomes will be assessed before, immediately after the intervention, and at 6 months after ACLR.

Knee Strength and Voluntary Activation: Quadriceps strength and voluntary activation will be measured at 60° of knee flexion with the interpolated triplet technique as we have done previously.[1,9-12] This method provides detailed information about strength as well as the level to which a subject can activate the quadriceps muscle.[11,13-15] Quadriceps strength symmetry index will be computed by normalizing peak torque of the reconstructed leg to that of the non-reconstructed leg. Voluntary activation will be computed as in Fig. 3. Intra- and Inter-session reliability for recording isometric quadriceps strength and voluntary activation are high (ICC range ≥ .92).[16-22] Isokinetic knee strength will also be assessed at the second post-intervention testing session (measurement 3, figure 1).

Biomechanics: Three-dimensional biomechanical data will be collected for the knee during walking (along a 4 m walkway) using a 12 camera motion capture system sampling at 240 Hz and synchronized with analog data (force) sampling at 1200 Hz. Subjects will walk at a standardized speed 1.1 m/sec (± 5%) as speed during level walking is known to influence lower extremity biomechanics. Five trials will be collected for each task and data will be analyzed for both limbs. Lower limb joint rotations will be defined based on the 3D coordinates of 32 retroreflective markers, as we have done previously. A static trial of each participant aligned within the laboratory coordinate system will be recorded, allowing for a kinematic model composed of 7 skeletal segments. Rotations will be calculated using the Cardan rotation sequence[23] and will be expressed relative to each subject's neutral static position. Filtered kinematic data and ground reaction force data will then be submitted to a standard inverse dynamics approach. Joint moments will be normalized to subject's body height and mass. All biomechanical data will be time normalized to 100% of the stance phase for walking and stair descent, with initial contact and toe-off being defined using a vertical ground reaction force threshold of 10 N.[24,25] We will use the symmetry values (i.e. (involved limb/uninvolved)×100) for the sagittal plane peak knee angles and moments recorded during weight-acceptance phase (initial contact to peak knee flexion) for walking and for stance during stair descent for analyses. The same, trained investigator will apply markers for all testing to minimize error. Good intra- (ICC > .80) and inter-session (ICC > .90) reliability has been established for sagittal plane biomechanics using 3D motion capture.

Patient-Reported Outcomes Measure: The Knee Injury and Osteoarthritis Outcome Score (KOOS) survey[26] will be used to obtain the subject's opinion about their knee and associated problems. KOOS is valid and reliable measure (ICC = .75-.93) for assessing the functional status and quality of life of athletes after ACLR.[27] We will also use the PROMIS, MARX scale, Tegner, and Tampa Scale for Kinesiophobia to quantify physical function, activity level (MARX and Tegner), and their fear of movement/activity, respectively.

Aim 2: Determine the effects of progressive functional resistance training during gait on cortical and spinal reflex excitability of individuals with ACL reconstruction. The goal of Aim 2 is to test the effects of progressive functional resistance training during walking on cortical and spinal reflex excitability in individuals with ACLR. Cortical and spinal excitability will be assessed before, immediately after the intervention, and at 6 months after ACLR. The assessor will be blinded to patients' group assignment.

Motor Cortical Excitability: Motor cortical excitabiltiy changes due to functional resistance training will be evaluated using reliable (ICC ≥ .82) single- and paired-pulse TMS protocols similar to our prior studies. First, the optimal site for eliciting quadriceps MEP (i.e., hotspot) will be determined using a double cone TMS coil, which is specifically designed for stimulating the leg motor cortex. The hotspot will be identified by determining the stimulation location that produces largest and most consistent MEPs. A frameless stereotaxic coil tracking system will be used to assure consistent placement of the coil during the experiment.[42,43] Active motor threshold will then be established during a slight background contraction (~5% MVIC) by determining the lowest stimulus intensity that elicits an MEP > 100μV in at least 5 of 10 consecutive trials.[40] Recruitment curves will be created by measuring motor evoked potentials (MEPs) and evoked torque responses of the quadriceps muscle over a range of TMS intensities (70% to 140% AMT). The intervention-mediated changes in cortical excitability will be assessed by examining the changes in MEP/torque amplitudes and slopes of recruitment curves obtained using Boltzmann equation. In cases where sigmoidal relationship is not appropriate (R^2 < 0.80), other fits (e.g., linear) will be used as appropriate.

H-Reflex Testing: Spinal reflex excitability will be measured with H-reflex testing using a reliable intra- and inter-session protocol (ICCs > 0.90)[51] that we have employed previously.[52,53] Briefly, patients will be positioned supine with the knee supported in flexion and hands at their sides. Factors such as head position, hand movement, etc. may affect the H-reflex so care will be taken to minimize movement. H and M recruitment curves will be mapped for the ACLR limb by applying a 1ms square-wave stimulus to the femoral nerve and recorded using EMG. Stimuli will be delivered by increasing the intensity in 0.2V increments, with a 10-second rest interval after each stimulus until the maximum H-reflex and maximum M-wave are obtained. Three peak-to-peak amplitudes of the maximum H-reflex and M-wave will be recorded and used to create the H-reflex to M-wave ratio.

Analytic Plan: Descriptive statistics will be used to explore the distribution, central tendency, and variation of each measurement, with an emphasis on graphical methods. Normality for each variable will be checked using a Shapiro-Wilks test, and appropriate transformations (e.g., log) will be made when necessary. Linear mixed models will be used to compare the continuous primary and secondary endpoints between the experimental and control arm of the randomized group. Fixed-effects terms will include group, time, group × time interaction, gender, group × gender interaction, and other potential covariates such as, age, activity level, and meniscal repair. Patients will be included as random effects in the intercept. A significant main or interaction effect at $\alpha = 0.05$ will be followed by appropriate post-hoc analysis with adjustments for multiple comparisons.