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Section: Original Research Report

Article Title: MRI-Based Assessment of Lower Extremity Muscle Volumes in Patients Before and After ACL Reconstruction

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Running Head: Muscle Volume Before and After ACL Reconstruction

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ABSTRACT

Context: Study of muscle volumes in patients after anterior cruciate ligament (ACL) injury and reconstruction (ACL-R) is largely limited to cross-sectional assessment of the thigh musculature, which may inadequately describe post-traumatic and post-surgical muscle function. No studies have prospectively examined the influence of ACL injury and reconstruction on lower extremity muscle volumes. **Objective:** Assess magnetic resonance imaging (MRI) derived lower extremity muscle volumes, and quantify quadriceps strength and activation in patients following ACL injury and reconstruction. **Design:** Prospective case series. **Setting:** Research laboratory and MRI facility. **Patients (or Other Participants):** Four patients (2 males, 2 females, age=27.4±7.4, height=169.2±8.1cm, mass=74.3±18.5kg) scheduled for ACL-R. **Intervention(s):** 35 muscle volumes were obtained from a bilateral lower extremity MRI before and after ACL-R. **Main Outcome Measures:** Muscle volumes expressed relative to (1) a normative database pre-and-post-surgery, (2) limb symmetry pre-and-post-surgery, and (3) percentage change pre-to-post-surgery. Quadriceps function was quantified by normalized knee extension maximal voluntary isometric contraction (MVIC) torque and central activation ratio (CAR). **Results:** Involved vastus lateralis and tibialis anterior were consistently smaller than healthy individuals (Z< -1SD) pre-and-post-surgery in all patients. Involved rectus femoris and vastus lateralis were more than 15% smaller than the contralateral limb pre-surgery, whereas the involved rectus femoris, gracilis, vastus medialis, vastus intermedius, and vastus lateralis muscle volumes exceeded 20% asymmetry post-operatively. Involved gracilis and semitendinosus atrophied more than 30% from pre-to-post-surgery. Involved MVIC torque and CAR increased by 12.7% and 12.5% respectively, yet strength remained 33.2% asymmetric post-surgery. **Conclusions:** Adaptations in lower extremity muscle volumes are present following ACL injury and reconstruction. Anterior thigh and shank muscles were smaller than healthy individuals, and large asymmetries in quadriceps volumes were observed pre- and post-surgery. Selective atrophy of the semitendinosus and gracilis occurred following surgery. Volumetric deficits of the quadriceps musculature may exist despite improvements in muscle strength and activation.

Word Count: 300

INTRODUCTION

Anterior cruciate ligament (ACL) injuries continue to constitute a common major joint injury among active individuals, often resulting in high economic costs,[1] reduced physical activity,[2] and decreased quality of life.[2] An estimated range of 80,000 to more than 250,000 ACL injuries are reported to occur annually within the United States,[3] with 127,446 ACL reconstructions (ACL-R) performed according to a 2006 national survey.[4] Despite preventative efforts, ACL injury rates remain high and have continued to rise in recent decades. Unfortunately, an array of sub-optimal functional and patient-reported outcomes related to decreased muscular function and return to activity persist following ACL-R, specifically among highly active populations. In a recent systematic review of 7,556 patients, 81% of individuals reported returning to sport, while only 65% returned to pre-injury sporting activity, and 55% to competitive sport.[5] To maximize the potential for success following ACL-R, sensitive patient specific assessment tools are needed to identify early impairments and guide targeted treatment approaches.

Post-operative rehabilitation is an integral aspect of therapeutic management, and may strongly influence clinical outcomes following ACL-R. Common therapeutic goals include the restoration of pre-injury muscle function, as measured by strength, girth, and limb symmetry at the time of physician clearance.[6] Muscle dysfunction secondary to ACL injury is well-described[7] and poses a specific threat to long-term joint health,[8] making early detection and intervention a hallmark of prevention. Although much attention has been given to the thigh musculature in response to ACL injury, hip abduction and external rotation strength are reported to predict future noncontact ACL injury in competitive athletes,[9] and reductions in ipsilateral hip extensor torque have been identified prior to reconstruction.[10] From an injury prevention perspective, hip extensor, abductor, and external rotator strength are reported to have a strong inverse relationship with knee valgus angle during a single-leg landing task,[11] highlighting the clinical significance of studying proximal musculature following ACL injury. Distally, the soleus has been suggested to protect the ACL in a closed chain position, and an increase in electromyographic activity of the soleus has been observed in ACL deficient and reconstructed individuals.[12] Reduced summated extension moments (hip, knee, and ankle) during a single-leg vertical jump have been identified in patients after ACL-R,[13] suggesting that a pattern of movement compensation may occur at the hip or ankle to maintain function following reconstruction. Sports medicine providers are uniquely positioned to intervene early on modifiable manifestations of joint injury that play a role is disease pathogenesis, such as muscle function.

Post-traumatic muscle dysfunction may manifest clinically as muscle weakness,[14] activation failure,[7] and atrophy,[15] resulting in meaningful asymmetries. Limb symmetry indices (LSI) ranging 80-90% are commonly recommended prior to return to unrestricted physical activity.[6] Independent of surgical procedure, deficits in muscle function have been reported to persist beyond the time of physician clearance,[16] suggesting incomplete recovery, which may place individuals at a greater risk for re-injury upon resumption of pre-injury activities. Although objective measures of muscle function are advocated when determining readiness for return to activity, current techniques used to assess muscle strength are largely limited to gross estimates of force production, and may be insufficient to detect subtle changes among individual muscle properties. For example, the individual muscles of the quadriceps femoris are reported to contribute differently to maximum knee extension torque in patients following ACL-R.[17] Timing from surgery may also prohibit the use of force-based measurement techniques such as isometric knee extension torque and muscle activation, or confound the accuracy of strength estimates during early phases of recovery. MRI-based volumetric assessment of skeletal muscle, on the other hand, can provide unique information about the individual muscle that is challenging with traditional force-based techniques alone.

Persistent muscle atrophy has been observed following ACL injury,[18,19] which may limit the ongoing restoration of pre-injury muscle function during terminal stages of rehabilitation. Peripheral changes in skeletal muscle morphology and neural mechanisms within the central nervous system are reported to contribute to persistent muscle weakness.[19] Clinically based techniques used to assess muscle atrophy, such as thigh circumference and real-time ultrasound may provide meaningful information, but rely on the extrapolation of findings to estimate total muscle volumes, which may be inaccurate for understanding patient-specific muscle size. Similarly, more sophisticated estimates of muscle cross-sectional area (CSA) using computed tomography or magnetic resonance imaging (MRI) are limited in the ability to generalize to an entire muscle, and may depend on the anatomical level studied.[20] A differential response (i.e. non-uniform atrophy or hypertrophy) of the individual heads of the quadriceps femoris has been described,[20] suggesting the need for a more comprehensive assessment when characterizing post-traumatic muscle properties. In contrast, MRI-based 3-Dimensional (3-D) muscle volumes have been assessed in patients after ACL injury[19,21-27] and reconstruction,[28-35] which may provide a more comprehensive insight in post-traumatic muscular response. While much attention has been directed towards knee extensor muscular impairments associated with bone-patellar tendon-bone autograft, morphological changes related to long-term outcomes have been observed in the knee flexors of patients with semitendinosus-gracilis tendon autograft.[22] However, these studies are nearly exclusively limited to the thigh musculature, and thereby fail to describe complete lower extremity function in these cohorts. Altered loading patterns are well described after ACL injury,[36] which inherently influence skeletal muscle function away from the knee. Understanding changes in muscle after ACL injury and reconstruction would provide insight to the therapeutic impact of current rehabilitation programs in this regard, which may benefit clinicians in designing evidence-based treatments to optimize patient care. To our knowledge, only one study[37] has assessed longitudinal changes in hamstrings muscle volume prior to and following ACL-R, yet none have examined in vivo volumetric changes throughout the entire lower extremity.

Therefore, the purpose of this study was to assess lower extremity muscle volumes in patients prior to and following ACL-R. We aimed to quantify the volumetric change for 35 muscles by comparing (1) normalized muscle volumes to a healthy population, (2) limb symmetry pre- and post-surgery, and (3) percentage change pre- to post-surgery. Given the known impairments in quadriceps function (e.g. torque and central activation) that often accompany ACL-R, and the observed relationships between individual quadriceps muscle CSA and knee extensor torque, the secondary purposes of this paper were to (4) quantify quadriceps muscle function using traditional force-based measures, and to (5) assess the relationship between quadriceps muscle function and volume. We hypothesized that muscle volumes would be smaller than healthy individuals prior to surgery, and remain smaller at the time of physician clearance. We anticipated observing asymmetries in muscle volumes early after ACL injury, and that symmetry would be improved, but not restored to recommended thresholds for return to activity following reconstruction. As a result of graft harvesting, we hypothesized that the semitendinosus and gracilis muscles would atrophy most. Specifically, we hypothesized that the gluteus maximus, gluteus medius, and soleus would remain similar to healthy controls, symmetric, and would hypertrophy to compensate for decreased quadriceps femoris and semitendinosus volumes respectively. Given that muscle volume is reported to be an important determinant of muscle function, we hypothesized that knee extensor torque and activation would increase following surgery, but that asymmetries in quadriceps function and muscle volume would persist. Lastly, we hypothesized that quadriceps muscle volume would be positively related to knee extensor torque.

METHODS

This was a prospective case series designed to quantify changes in lower extremity muscle volumes and quadriceps function following ACL reconstruction. Independent variables included time (pre-surgery, post-surgery), and limb (involved, uninvolved). The primary outcome measures for muscle volume were (1) comparison of normalized muscle volumes to healthy control subjects[38] pre- and post-surgery, (2) limb symmetry pre- and post-surgery, and (3) percent change pre- to post-surgery. Secondary outcome measures of quadriceps function included knee extension maximal voluntary isometric contraction torque (T_{MVIC}), quadriceps central activation ratio (CAR), and superimposed burst torque (T_{SIB}).

Participants

Four patients with a history of ACL rupture were recruited from our orthopaedic clinic prior to surgical reconstruction, and volunteered to participate in this study (table 1). Participants must have sustained a unilateral ACL rupture confirmed by MRI, and be scheduled for reconstructive surgery. Patients with a multiligament knee injury, contralateral lower extremity joint injury within 6 months, prior contralateral lower extremity joint surgery, radiographic evidence of fracture or osteoarthritis, tumor or infection, metal implants, cardiac devices, or those who were pregnant were excluded from participation. A previously collected sample of 24 healthy individuals (8 female/16 male, age = 25.5 ± 11.1 years, height = 171.4 ± 9.6 cm, mass = 71.8 ± 14.6 kg) was used for comparison.[38] The University Institutional Review Board for Health

Sciences Research approved this study, and all participants provided informed consent prior to enrollment

Procedures

Measurements were obtained in a University laboratory and research MRI facility. Patients participated in two sessions to assess lower extremity muscle volumes and quadriceps muscle function pre- and post-surgery. During each visit, muscle volumes were obtained prior to strength testing to minimize the influence of physical exertion on muscle girth. The mean interval from time of injury to scan date (pre-surgery) and time of surgery to scan date (post-surgery) was 8.1 months (range, 2.1-24.3 months) and 7.4 months (range, 5.5-9.6 months) respectively. One patient, ACL 3, elected to attempt non-operative treatment initially, and underwent delayed ACL reconstruction after reporting continued instability that limited daily activities. Each patient underwent physical therapy between the time of ACL rupture and reconstruction. The pre-surgery visit occurred within 1 week of surgical reconstruction. The post-surgery evaluation occurred at a minimum of 5 months after ACL-R for each patient once cleared by his or her physician to return to unrestricted physical activity.

Muscle Volume

Bilateral muscle volumes of the lower extremity were measured as previously described[38-40] using a 3.0 Tesla MRI Scanner (Siemens Trio, Munich, Germany), and 2-D multi-slice gradient-echo pulse sequence with a spiral k-space trajectory for rapid data acquisition.[41] Continuous axial-plane images were collected from the twelfth thoracic vertebra to ankle mortise. Scanning parameters included: TE/TR/α 3.8 ms/800 ms/90°, field of view: 400 mm x 40 mm, slice thickness: 5 mm, in plane spatial resolution: 1.1 mm x 1.1 mm with a Chebyshev approximation for offresonance correction, and spectral-spatial excitation pulses for fat suppression to improve muscle contrast.[42]

For all patients, 35 muscles of both lower extremities were segmented by outlining the 2-D perimeter of the muscles in each axial slice using custom in-house image-processing software in Matlab (The Mathworks Inc., Natick, MA).[38] Muscle volume was computed by summing all of the slice-wise voxel volumes for each muscle structure.[38] Four trained individuals, who were each provided with a detailed slice-by-slice segmentation atlas based on a healthy control subject, completed segmentations. The inter-user variability of this process was determined to be acceptable (< 0.6% limb volume).[38] A single highly trained user vetted each dataset for consistency prior to further analysis.

Quadriceps Function

Isometric knee extensor torque was recorded using a calibrated Biodex System 3 isokinetic dynamometer (Biodex Medical Systems, Inc., Shirley, NY) with the hips and knees flexed to 85 and 90 degrees respectively. The tibial pad was secured to the shank, approximately 2 cm proximal to the lateral malleolus. Data was exported and digitized at 125 Hz (MP150 BIOPAC Systems, Inc., Goleta, CA). Participants were acclimated through a series of sub-maximal isometric knee extension contractions at 25%, 50%, and 75% of their perceived maximal effort prior to data collection. Three maximal contractions, with 60 seconds of rest in between, were then performed to determine participants' T_{MVIC}. Strong verbal encouragement along with visual feedback was provided to ensure maximal effort. Quadriceps activation was measured using the superimposed burst technique as previously described.[43] When the isometric torque plateaued, a square-wave stimulator (S88 GRASS TeleFactor, W. Warwick, RI) and stimulation isolation unit (SIU8T GRASS TeleFactor, W. Warwick, RI) were used to produce an electrical stimulus that was manually applied to the quadriceps musculature, causing an immediate and transient increase in torque production, termed the superimposed burst torque (T_{SIB}). Bilateral measurements were recorded for the uninvolved limb, followed by the involved limb.

Data Reduction

Torque data were filtered with a 10 Hz low-pass filter and normalized to body mass (Nm/kg). Quadriceps CAR was calculated as previously described[44] using a mean of three trials. T_{MVIC} was calculated by taking the mean of a 100-ms epoch immediately prior to the electrical stimulus.[43] Individual raw muscle volumes were normalized to patient mass and height (cm^3/(kg*m)) as previously described.[38]

Surgical Procedure

All surgical procedures were performed by 1 of 2 sports medicine fellowship-trained orthopaedic surgeons. Each patient received an autologous semitendinosus-gracilis (STG) 4-strand autograft. A primary anatomical reconstruction was performed in Patients 2-4, whereas, Patient 1 underwent revision reconstruction. The ipsilateral STG was harvested in Patients 3-4, and augmented using the contralateral STG per surgeon preference for Patients 1-2. Patient 2 underwent an isolated ACL reconstruction, while an arthroscopic partial meniscectomy was performed in Patients 3 and 4, and meniscus repair in Patient 1.

Statistical Analysis

Descriptive statistics were calculated for muscle volumes, knee extensor torque, and quadriceps activation in each limb pre- and post-surgery. Muscle volumes were normalized by the product of body height and mass, and compared to a normative database of healthy individuals;[38] the comparative muscle size was then quantified using Z-scores.[45] Z-scores were calculated for each muscle using the equation Z = (normalized ACL volume – mean of normalized healthy volumes)/ standard deviation of normalized healthy volumes). The Z-scores provide a statistically meaningful measurement of how many standard deviations a subject's muscle volume differs from the healthy subjects, and were interpreted as *extremely larger* ($Z \geq 3$ SD), *moderately larger* ($3 > Z \geq 2$ SD), *slightly larger* ($2 > Z \geq 1$ SD), *normal* ($1 > Z > -1$ SD), *slightly smaller* ($-1 \geq Z > -2$ SD), *moderately smaller* ($-2 \geq Z > -3$ SD), or *extremely smaller* ($Z \leq -3$ SD) than the healthy subjects' muscle volumes. Limb symmetry was expressed as the percent difference between limbs, and calculated using the equation: ((injured muscle volume – uninjured muscle volume)/ uninjured muscle volume)*100. Percent change in muscle volume was calculated using the equation: ((post-surgery muscle volume – pre-surgery muscle volume)/ pre-surgery muscle volume)*100. Percent difference and change were interpreted as *slight* (5-10%), *moderate* (11-15%), or *extreme* (>15%). Bivariate Pearson's *r* correlation coefficients were used to identify relationships between quadriceps muscle volumes, knee extensor torque, and quadriceps activation. Cohen's *d* effect sizes with 95% confidence intervals (CIs) were calculated to determine the magnitude of post-surgical changes in muscle volume, strength, and activation. The level of significance was set a priori at $p \leq .05$. All analyses were performed using custom Matlab software, SPSS (version 20.0; SPSS, Chicago, IL), and Microsoft Excel (v. 14.4.7).

RESULTS

Participant demographics and injury profiles are presented in table 1. A comprehensive list of average pre- and post-surgery normalized muscle volumes, percent change, limb symmetry, and Z-scores are presented for each muscle in table 2.

Healthy Comparison

Heat maps depicting Z-scores of individual muscle volumes compared to healthy individuals pre- and post-surgery are presented for each patient in figure 1. On average, 42.9% (95% CI 20.1, 65.6%) of muscles in the involved limb were smaller than healthy individuals pre-surgery, and 51.4% (95% CI 27.0, 75.8%) were smaller post-surgery. All of the involved vastii muscles were *slightly smaller* than the corresponding healthy muscle volumes pre-surgery, and all quadriceps muscles were *slightly smaller* post-surgery. This pattern was observed in 2/4 patients; however, each patient consistently demonstrated a *slightly smaller* vastus lateralis pre- and post-surgery. The involved gluteus maximus, gluteus medius, and soleus muscle volumes were each within normal limits pre- and post-surgery. On average, 27.1% (95% CI 13.1, 41.1%) of muscles in the uninvolved limb were smaller pre-surgery, and 26.4% (95% CI 14.7, 38.2%) were smaller post-surgery.

Limb Symmetry

Selective asymmetries in muscle volumes were observed pre- and post-surgery (Figure 2). On average, the involved rectus femoris (3/4 patients) and vastus lateralis (2/4 patients) were *extremely smaller* than the contralateral limb pre- surgery. Additionally, the vastus medialis and intermedius were extremely smaller in 2 of 4 patients. Following surgery, the involved rectus femoris (3/4 patients), gracilis (3/4 patients), vastus medialis (2/4 patients), vastus intermedius (2/4 patients), and vastus lateralis (3/4 patients) were *extremely smaller*. The gluteus maximus remained symmetric on average, while the gluteus medius was *moderately smaller* than the contralateral limb (2/4 patients) pre-surgery and *slightly smaller* (3/4 patients) post-surgery. The involved soleus was symmetric pre-surgery, and *slightly smaller* (3/4 patients) post-surgery.

Percent Change Pre- to Post-Surgery

Varying patterns of trophic changes were observed bilaterally from pre- to post-surgery (Figure 3). The involved gracilis (*d* = -2.2 [95% CI -0.4, -3.8]) and semitendinosus (*d* = -1.9 [95% CI -0.1, -1.6]) were *extremely atrophied* (< 15%) in all patients. Similarly, the uninvolved semitendinosus was *extremely atrophied* in 2/4 patients. The involved rectus femoris (3/4 patients), vastus lateralis (3/4 patients), and vastus medialis (4/4 patients) were *slightly atrophied*, whereas the vastus intermedius (2/4 patients) was *slightly hypertrophied*. The involved gluteus maximus (4/4 patients) and medius (3/4 patients) were *slightly hypertrophied*, and the soleus (3/4 patients) *slightly atrophied* post-surgery.

Quadriceps Function

Pre- and post-surgery normalized knee extensor MVIC torque (T_{MVIC}), superimposed burst torque (T_{SIB}), and quadriceps activation (CAR) are presented for each patient in table 3. Correlations between quadriceps muscle volumes, knee extensor MVIC torque, and CAR at pre- and post-surgery are presented in table 4. The relationships between percentage change in quadriceps function and muscle volume from pre- to post-surgery are depicted in figure 4.

DISCUSSION

This study identified more than a third of the muscles in the lower extremity that were smaller than healthy individuals following ACL injury, and more than half following ACL reconstruction. Our hypothesis that gluteal and soleus muscle volumes would remain within normal limits in the presence of reduced quadriceps volumes was confirmed. In partial agreement with our hypothesis regarding limb symmetry, large asymmetries (> 20%) in all quadriceps muscle volumes of the involved limb were observed post-operatively; however, mild asymmetries in gluteus medius and soleus volumes were also present. The involved gracilis and semitendinosus experienced the largest volumetric decline from pre- to post-surgery, confirming our hypothesis of selective atrophy related to graft harvesting. In further support of the adaptive response of peripheral musculature to persistent quadriceps atrophy, the involved gluteal muscles were slightly hypertrophied post-surgery, whereas the soleus was slightly atrophied. Although unilateral quadriceps strength and activation increased following surgery in the involved limb, large asymmetries (> 30%) in knee extensor torque persisted, whereas activation returned to normal. Owing to this finding, moderate to strong positive correlations between quadriceps muscle volumes and knee extensor torque were identified pre- and post-surgery. These data demonstrate the speed at which lower extremity muscle atrophy occurs following ACL injury, and highlight the incomplete recovery of muscle function with respect to volume and knee extensor torque 5-9 months post-operatively, unfortunately beyond the time of physician clearance. To our knowledge, this is the first study to prospectively demonstrate the existence of persistent lower extremity muscle atrophy measured in vivo in conjunction with impaired quadriceps function following ACL injury and reconstruction.

Healthy Comparison

The results of this study demonstrate reduced muscle volumes compared to previously established normative data,[38] which agrees with previous studies comparing post-traumatic thigh muscle volumes to control subjects. Interestingly, our data demonstrated an increased proportion of muscles of the involved limb were smaller than healthy counterparts post-surgery, which was also observed in the contralateral limb. The involved limb quadriceps muscles were most notably affected in this regard, specifically the vastus lateralis. In addition to the impairments observed for the quadriceps, gluteal and soleus muscle volumes remained within normal limits of healthy individuals pre- and post-surgery. Neuromuscular compensatory patterns have suggested a hip bias during a single limb hop for distance in patients after ACL-R who feel capable of performing pre-injury sporting activities.[46] Increased gluteus maximus and medius EMG activity have also been identified in ACL-R patients during stair descent.[47] The observations of increased hip activity during functional tasks have been theorized to shift the dependence of moment generation from the knee to the hip, thus preserving proximal muscle volumes. Likewise, the soleus remained within normal limits of healthy muscle volumes. The soleus is a reported agonist of the ACL, contributing a meaningful degree of posterior tibial force during a single-limb landing task in healthy individuals.[48] It may be possible that the soleus was relatively well preserved in an attempt to maintain protection of the injured ACL in this cohort. Interestingly, the involved tibialis anterior and phalangeal extensors were *slightly smaller* in each patient compared to healthy individuals with 95% CIs that did not cross zero, suggesting a clinically meaningful difference. Previous research[26] has reported an increase in tibialis anterior volume relative to the uninjured limb in non-coper compared to coper ACL deficient patients and healthy individuals, which is theorized to be the result of a lower extremity joint stiffening strategy. In contrast, it is possible that this cohort employed adaptive movement strategies that emphasized the hip musculature, and deemphasized the anterior shank musculature, although this remains speculative. Previous studies have identified atrophy as strong contributor of quadriceps strength.[15] Although restoration of muscle function is expected prior to return to sport, persistent lower extremity muscle weakness is well described beyond 6 months from ACL-R.[14,16] These data support the presence of persistent impairments in skeletal muscle volumes peripherally beyond the time of return to activity.

Limb Symmetry

Asymmetries were observed in muscles crossing the hip, knee, and ankle following initial injury of the ACL. Most notably, all quadriceps muscles were *moderately* to *extremely smaller* than the uninvolved limb on average. Previous studies have observed significant reductions in muscle volume of the involved vastus medialis and vastus intermedius compared to the contralateral limb in ACL deficient patients identified as non-copers.[21] While these muscles were smaller than the uninvolved limb prior to surgery, the greatest differences were observed in the rectus femoris and vastus lateralis in the current study. Patients were evaluated 2-24 months following ACL injury, which likely influenced the degree of asymmetry. Atrophy is reported to occur early after ACL injury, and consistent with previous research,[21] our results demonstrate meaningful asymmetries in quadriceps muscle volumes that occur as early as 2 months. Interestingly, *moderate* and *mild* gluteus medius asymmetry was observed pre- and post-surgery respectively, while the gluteus maximus remained symmetric. It is possible that movement preferentially occurred in the sagittal plane early after injury, which could preserve the gluteus maximus in the presence of gluteus medius atrophy.

Post-surgical asymmetries in lower extremity muscle volumes were observed, highlighting the clinical impact of ACL reconstruction on muscle properties away from the injured joint. Although standard guidelines are lacking, limb symmetry thresholds ranging 80-90% are commonly advocated prior to return to sport.[6] To better elucidate this criterion, recent authors[49] have considered limb dominance into symmetry recommendations, citing the need for a LSI > 90% in dominant limb injuries and LSI > 80% for non-dominant limb injuries. Although each patient suffered an injury to the non-dominant limb in this study, the involved gracilis, rectus femoris, and vastii musculature were more than 10% smaller (range, 10.7-37.3%) than the uninvolved limb in all patients up to 9 months following reconstruction. Additionally, our data demonstrate increased asymmetry in total quadriceps volume increased from 17% to 23%, and greater than 20% asymmetry of individual quadriceps muscle volume post-operatively. As a whole, the same degree of asymmetry was not observed for the hamstrings, although the involved semitendinosus was more than 10% smaller than the uninvolved limb, while the involved biceps femoris remained larger following ACL-R. The specific pattern of volumetric adaptations in lower extremity musculature is likely to vary based on factors such as time from injury, surgical procedure, and rehabilitation. Although the current ACL injured cohort was heterogeneous with regard to these factors, meaningful asymmetries were clearly observed prior to and following ACL-R.

Percent Change

Atrophic changes were observed in muscles crossing the hip, knee, and ankle for the involved and uninvolved limb from pre- to post-surgery. Of note, the involved gracilis and semitendinosus were extremely atrophied. Large effect sizes with 95% CIs not crossing zero were calculated for each, suggesting a clinically meaningful magnitude of change from pre-to post surgery. Hamstrings weakness has been reported to persist for two[50] to five[51] years following ACL-R in patients with STG graft. Although knee flexor strength was not assessed, hamstrings femoris muscle volumes were preserved, with the exception of the semitendinosus. The large change in semitendinosus volume observed despite a preservation of biceps femoris muscle volume appears to support the occurrence of selective atrophy. These findings are consistent with previous studies[32,35,52] demonstrating selective atrophy of the semitendinosus in patients with a STG graft. In contrast, the involved gluteal muscles *hypertrophied slightly* post-surgery. Additionally, the obturator externus was extremely hypertrophied post-surgery, which may further reflect a compensatory mechanism to indirectly minimize joint loading at the knee by stabilizing the hip proximally. Likewise, this pattern of proximal hypertrophy may be an attempt to compensate for decreased quadriceps strength and volume.[53] Future comparisons of movement biomechanics after ACL-R are likely warranted to determine whether functional aberrations or asymmetries are better combatted by proximal musculature rather than the quadriceps. Interestingly, the quadriceps musculature demonstrated a variable post-surgical response with changes ranging from 12.4% hypertrophy to 10.3% atrophy, suggesting a non-uniform response in this patient cohort. In contrast to the hypertrophic changes observed proximally, the involved soleus *atrophied slightly*, which followed the same trend as all other shank musculature.

The uninvolved limb demonstrated a similar pattern of muscle atrophy for muscles crossing each lower extremity joint. Most notably, the semitendinosus was *extremely atrophied* in 2/4 patients. In contrast, the vastus intermedius and obturator externus musculature had hypertrophied more than 10% following ACL-R. The semitendinosus demonstrated more post-surgical atrophy than any other muscle in each limb, however this finding varied considerably, with atrophy ranging 0-48%, where the two patients with an augmented contralateral STG graft experienced the greatest semitendinosus atrophy in the uninvolved limb. Additionally, the flexor digitorum longus and gracilis had also atrophied more than 10% in the uninvolved limb. Although these findings support the occurrence of selective atrophy as a result of the harvest site, it is clear that volumetric adaptations occur in a larger region of muscle, which may be an attempt to maintain a bilateral balance of muscle function to promote symmetric movement patterns. Bilateral muscular impairments are reported to occur following ACL injury,[54] highlighting the importance of addressing the contralateral limb during rehabilitation. Although functional deficits are commonly defined as a ratio of the ipsilateral to the contralateral limb, these results appear to indicate that the presence of symmetry in itself may not necessarily indicate complete recovery of skeletal muscle, as bilateral atrophy was observed.

Quadriceps Function

Bilateral impairments in knee extensor MVIC torque and voluntary quadriceps activation were observed pre- and post-surgery. Although each limb improved post-surgically, knee extensor torque symmetry declined from 71.4% to 66.8%. In a recent systematic review, average side-to-side deficits in quadriceps strength were 23% at 6 months following ACL-R, ranging 3-40%.[16] Similarly, our cohort experienced an average of 33.2% asymmetry (range, 14-47%) in knee extensor torque at an average of 7.4 months post-surgery. Large, clinically meaningful, asymmetries in quadriceps strength and volume are a major concern when considering these patients were each cleared for unrestricted physical activity. Persistent impairments at the time of return to activity following ACL-R may result in secondary injury, and likely contribute to poor outcomes in this patient population. Although persistent asymmetries are commonly reported at the time of return to sport, quadriceps strength asymmetry greater than 15% has been related to decreased functional performance.[14] As these characteristics may be associated with the acceleration of knee joint degeneration, achievement of limb symmetry with respect to quadriceps strength prior to return to sport may improve long-term clinical outcomes in ACL-R patients. Furthermore, asymmetry of quadriceps strength specifically is reported to influence self-reported function of the knee, where IKDC scores greater than 94.8 are indicative of acceptable quadriceps strength symmetry for return to sport.[55] Our data revealed a mean IKDC score of 70.1 and knee extensor torque symmetry index of 66.8% post-surgery. While these data are alarming, they are consistent with previous reports of persistent muscle weakness and reduced perception of knee function at the time of return to sport following ACL-R.[16] It is unknown whether exercise prescription aimed to hypertrophy lower extremity muscles prior to and following ACL-R would restore limb symmetry, and improve clinical outcomes.

Despite large asymmetries in quadriceps strength, activation remained greater in the involved limb pre- and post-surgery. A clinically meaningful increase in activation of the involved limb was observed, as represented by a large effect size in which the 95% CI did not cross zero. Consistent with previous literature, central activation failure of the quadriceps was present in the contralateral limb during each assessment,[56] which remained constant pre- to post-surgery. Previous authors[57] have observed a reduction in the decline of knee extensor strength and activation compared to healthy individuals, suggesting a preservation strategy in ACL reconstructed individuals to maintain function. Our data demonstrate a net reduction in quadriceps femoris volume despite a large magnitude increase in quadriceps activation, which may suggest that ACL injured patients must rely on using a larger portion of an already reduced motor neuron pool. In support of this theory, strong negative correlations were observed between quadriceps muscle volumes and CAR post-surgery, indicating that patients with smaller muscle volumes demonstrated higher quadriceps activation. Interestingly, our data demonstrated an inverse linear relationship between the change in quadriceps volume and voluntary activation, suggesting that patients with decreased post-operative muscle volumes achieved an increase in quadriceps activation. Alternatively, these data may suggest that peripheral changes in muscle (i.e. atrophy) contribute to muscle weakness more than those that are centrally mediated (i.e. quadriceps activation). Quadriceps activation is reportedly variable in ACL reconstructed patients at 6 months post-operatively, indicative of a non-homogenous neuromuscular response in this population. A unique finding of this study was the lack of consistency in the relationships between quadriceps muscle volumes and knee extension torque pre- and post-surgery. Prior to surgery, the vastus medialis and rectus femoris were most highly correlated with knee extensor torque, whereas the vastus lateralis and vastus intermedius were greatest following surgery. These data suggest that non-uniform patterns of atrophy likely occur, which may result in varying influence on quadriceps torque production. In support of this, we did not visualize a positive linear relationship between the change in quadriceps volume and MVIC torque from pre- to post-surgery among each patient. From these findings, we can theorize that the skeletal muscle consequences of joint injury may affect different muscles in different individuals, which may be an area for future study.

Clinical Implications

The findings of this study highlight persistent impairments in lower extremity muscle volumes and quadriceps strength in ACL-R patients beyond physician clearance. This is a major concern to sports medicine providers when making return to activity decisions, and to the patient with regard to risk for secondary injury. The restoration of quadriceps activation provides evidence for the impact of peripheral morphological adaptations in persistent muscle weakness. Furthermore, these data suggest that post-traumatic changes in muscle occur non-uniformly in musculature proximal and distal to the injured joint. Rehabilitation strategies may benefit by incorporating exercise regimes that aim to hypertrophy affected musculature of the entire lower extremity. Post-surgical outcomes related to quadriceps strength and central activation may be optimized by targeting each prior to surgery.[58] Since muscle volume is in part related to the torque-generating capacity of skeletal muscle, it is plausible that improvements in pre- and post-operative strength would yield larger muscle volumes.

Limitations

The sample size of this study was small, and limits the generalizability of these findings. In many cases, CIs were wide, suggesting clinical uncertainty in the direction and magnitude of change in muscle volumes following ACL-R. While this cohort was heterogeneous with respect to time from injury, concomitant pathology, and surgical procedure, variations in the response of muscular adaptations were expected, supporting the theory that muscle response and recovery following ACL injury is non-uniform by nature. It may be necessary for future studies to examine subgroupings of ACL injured patients based on these factors. Future studies may also benefit by investigating lower extremity strength and activation patterns in addition to functional tasks to better elucidate compensatory strategies after ACL injury. Furthermore, additional detail regarding the type, volume, and frequency of rehabilitation was not available, and the rehabilitation clinician differed between patients. Rehabilitation may be the most important determinant of post-surgical outcomes, making these data important for future study. The type and frequency of rehabilitation was not dictated by the research team, which may have influenced our findings. However, by not controlling post-surgical care (e.g. early weight-bearing status, rehabilitation protocol, clinician), we achieved a realistic representation of the type of care many patients experience after ACL-R. In an effort to understand the clinical implications of changes in post-traumatic muscle volumes, a larger sample is required to assess the relationships between muscle volumes and clinical measures of muscle function. Lastly, the minimal clinically important difference in lower extremity muscle volumes is not established, which will inherently improve the clinical interpretation of these findings.

CONCLUSIONS

Adaptations in lower extremity muscle volumes are present following ACL injury and persist after reconstruction. Most notably, the anterior thigh and shank muscle volumes were smaller than healthy individuals, and large asymmetries in quadriceps volumes were observed before and after ACL reconstruction. Selective atrophy of the semitendinosus and gracilis occurred following surgery. Unfortunately, volumetric deficits of the quadriceps musculature specifically may exist despite improvements in muscle strength and activation. Further study is warranted to determine whether exercise prescription designed to hypertrophy selective muscle impairments would improve clinical outcomes following ACL reconstruction.

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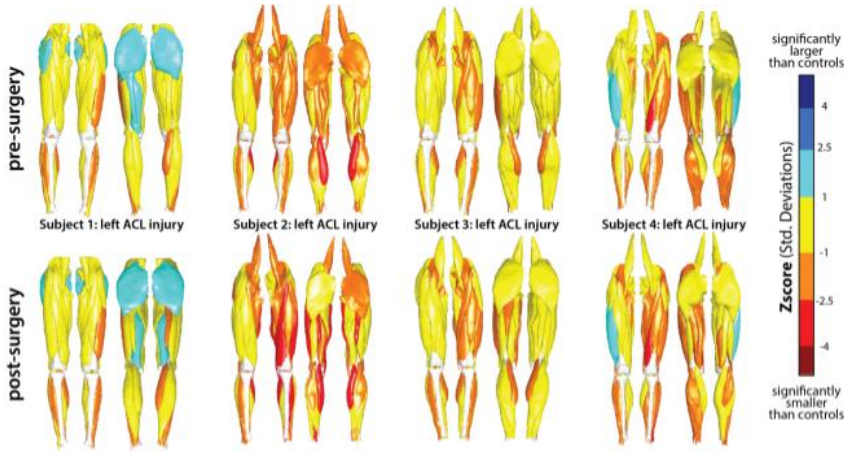

Figure 1. Z-scores of each subject's muscles compared to healthy control subjects at pre- and post-surgery is represented above. Individual muscle volumes were normalized to account for differences in body size by dividing by the product of each individual's height and mass, and compared to a previously published dataset of 24 healthy control subjects. The individual muscles of each subject are shown, colored by their Z-score, or the number of standard deviations away from the mean of the control dataset.

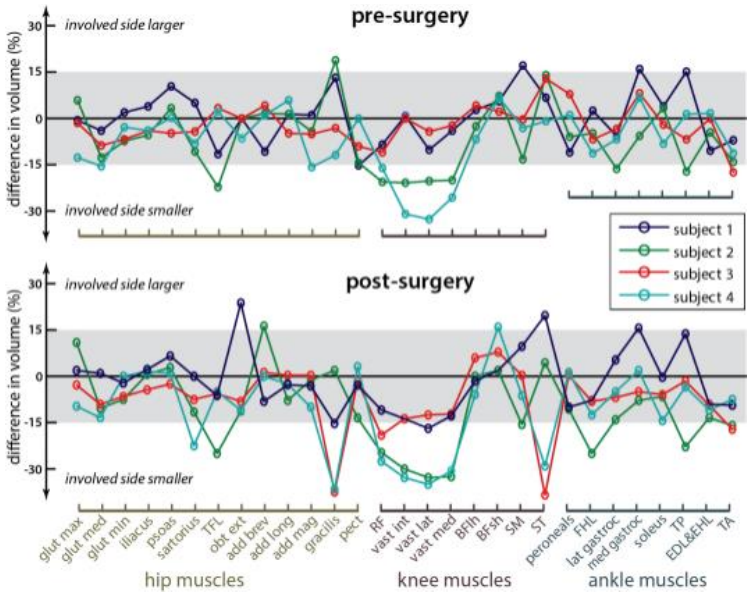

Figure 2. Limb symmetry of each subject's muscles at pre- and post-surgery is represented above. Symmetry was measured as the percent difference between the uninjured and injured muscle volume. Positive values indicate larger muscles on the involved limb, and negative values indicate smaller muscles on the involved limb. Differences greater than 15% in either direction were considered significant and are represented as any point located outside of the gray region.

"MRI-Based Assessment of Lower Extremity Muscle Volumes in Patients Before and After ACL Reconstruction"
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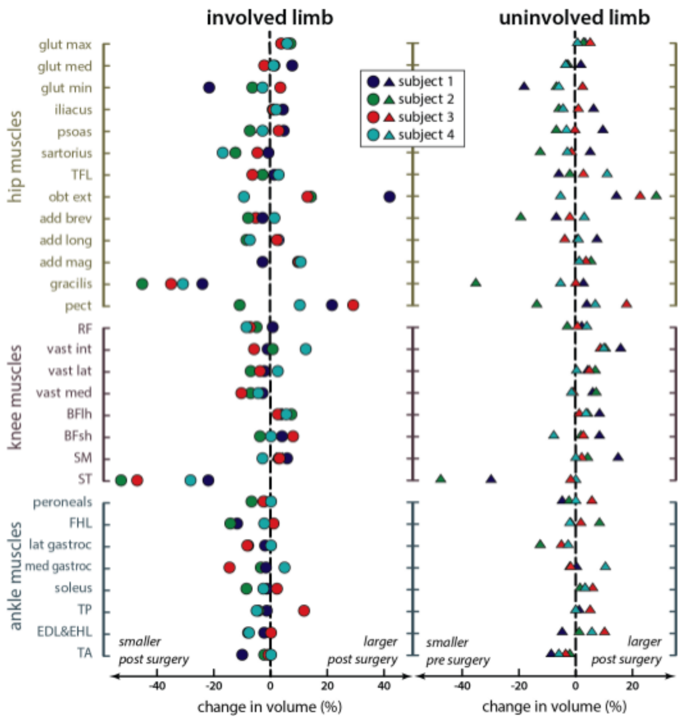

Figure 3. Percent change of each subject's muscles from pre- to post-surgery is represented above. Change in muscle volume was measured for each limb using the percent difference between the pre- and post-surgery muscle volumes. Positive values indicate that the muscle was larger post-surgery, and negative values indicate that the muscle was smaller post-surgery. The largest changes were measured in muscles whose tendons were harvested for graft tissue (semitendinosus and gracilis).

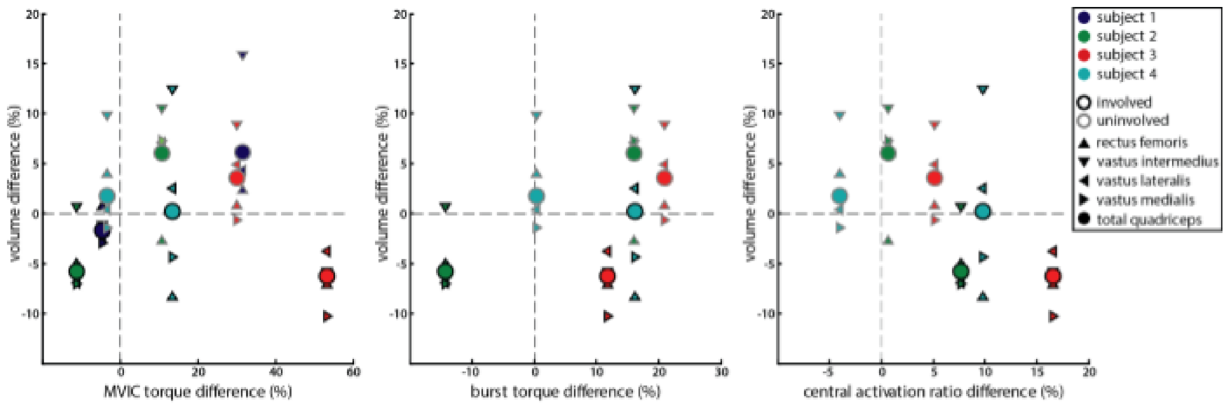

Figure 4: The relationship between change in quadriceps volume and function is represented above. The percent volume change from pre to post surgery in the four quadriceps is shown as well as the change in total quad volume with the percent change in the functional metrics of MVIC torque, burst torque, and central activation ratio.

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Table 1: Patient demographics and injury profiles.

	ACL 1	ACL 2	ACL 3	ACL 4	Mean
Sex	Male	Female	Male	Female	2 M, 2 F
Age (years)	29	23	36	19	27.4 ± 7.4
Height (cm)	172.7	167.6	177.8	158.8	169.2 ± 8.1
Mass (kg)	71.7	70.3	99.8	55.6	74.3 ± 18.5
BMI (kg/m^2)	24.0	25.0	31.6	22.1	25.7 ± 4.1
IKDC (%)	66.7 (Pre)	35.6 (Pre)	71.3 (Pre)	25.3 (Pre)	49.7 ± 22.7 (Pre)
	-	71.3 (Post)	-	69.0 (Post)	70.1 ± 1.6 (Post)
Tegner Activity: Pre-Injury	10	9	7	9	8.8 ± 1.3
Tegner Activity: Current	4 (Pre)	2 (Pre)	5 (Pre)	2 (Pre)	3.3 ± 1.5 (Pre)
	-	5 (Post)	-	5 (Post)	5.0 ± 0 (Post)
Godin Leisure-Time	39 (Pre)	81 (Pre)	18 (Pre)	46 (Pre)	46 ± 22.7 (Pre)
	-	70 (Post)	-	33 (Post)	51.5 ± 26.2 (Post)
VAS (cm)	0.5 (Pre)	6.5 (Pre)	1.0 (Pre)	7.0 (Pre)	3.8 ± 3.5 (Pre)
	-	0.2 (Post)	-	1.3 (Post)	0.8 ± 0.8 (Post)
Reconstruction	Revision	Primary	Primary	Primary	3/4 primary
Graft type	STG*	STG*	STG	STG	4/4 STG
Meniscus	Medial meniscus repair	N/A	Partial medial meniscectomy	Partial medial/ lateral meniscectomy	3/4 meniscal pathology
Rehabilitation (# visits)	-	36	36	144	72.0 ± 62.4
Pre-Surgery - Time to scan since injury (mo)	2.1	3.4	24.3	2.4	8.1 ± 10.9
Post-Surgery - Time to scan since surgery (mo)	9.6	5.5	7.9	6.8	7.4 ± 1.7
Time to physician clearance (mo)	6.1	5.2	6.1	6.0	5.9 ± 0.4

Abbreviations: Pre, pre-surgery; Post, post-surgery; M, male; F, female; BMI, body mass index; IKDC, international knee documentation committee subjective knee valuation form; VAS, visual analog scale; STG, semitendinosus-gracilis

- Indicates missing data point

* Indicates contralateral STG augmentation

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Table 2: Normalized muscle volumes, limb symmetry, Z-score, percent change, and effect size pre- and post-surgery.

Muscle Volume (cm^3/kg*m)	Pre-Surgery Mean ± SD	Pre-Surgery Limb Symmetry [95% CI]	Pre-Surgery Z-score [95% CI]	Post-Surgery Mean ± SD	Post-Surgery Limb Symmetry [95% CI]	Post-Surgery Z-score [95% CI]	% Change [95% CI]	Effect Size [95% CI]
Psoas Major	1.8 ± 0.4 (I)		-1.0 [-1.9, -0.1] (I)	1.8 ± 0.4 (I)		-1.0 [-1.9, -0.2] (I)	-0.6 [-6.0, 4.7] (I)	-0.1 [-1.4, 1.3] (I)
	1.7 ± 0.5 (U)	2.7 [-4.3, 9.8]	-1.0 [-2.1, 0.0] (U)	1.7 ± 0.4 (U)	2.2 [-1.5, 5.9]	-1.1 [-2.0, -0.2] (U)	-0.2 [-7.1, 6.7] (U)	-0.1 [-1.4, 1.3] (U)
Illiacus[a]	1.2 ± 0.1 (I)		-1.1 [-1.6, -0.6] (I)	1.2 ± 0.1 (I)		-1.0 [-1.6, -0.4] (I)	2.0 [0.5, 3.5] (I)	0.2 [-1.2, 1.6] (I)
	1.2 ± 0.1 (U)	-2.5 [-7.2, 2.1]	-1.0 [-1.3, -0.6] (U)	1.2 ± 0.1 (U)	0.2 [-2.8, 3.2]	-1.0 [-1.5, -0.5] (U)	-0.7 [-6.2, 4.7] (U)	-0.1 [-1.5, 1.3] (U)
Gluteus Maximus[c]	6.6 ± 0.9 (I)		-0.4 [-1.5, 0.7] (I)	6.9 ± 0.9 (I)		0.1 [-1.1, 1.3] (I)	5.7 [4.3, 7.1] (I)	0.4 [-1.0, 1.8] (I)
	6.8 ± 1.0 (U)	-2.3 [-10.7, 6.1]	-0.1 [-1.4, 1.2] (U)	7.0 ± 1.0 (U)	0.2 [-8.4, 8.7]	0.1 [-1.2, 1.5] (U)	3.1 [1.3, 4.9] (U)	0.2 [-1.2, 1.6] (U)
Gluteus Medius	2.4 ± 0.2 (I)		-0.6 [-1.0, -0.2] (I)	2.4 ± 0.2 (I)		-0.5 [-1.0, 0.0] (I)	2.0 [-2.1, 6.0] (I)	0.2 [-1.2, 1.6] (I)
	2.7 ± 0.1 (U)	-11.2 [-16.7, -5.7]	0.1 [-0.1, 0.2] (U)	2.6 ± 0.1 (U)	-7.8 [-13.9, -1.6]	0.0 [-0.2, 0.2] (U)	-1.8 [-4.3, 0.6] (U)	-0.6 [-2.0, 0.8] (U)
Gluteus Minimus	0.8 ± 0.1 (I)		-0.4 [-1.4, 0.6] (I)	0.7 ± 0.1 (I)		-0.8 [-1.1, -0.5] (I)	-6.9 [-17.4, 3.6] (I)	-0.6 [-2.0, 0.8] (I)
	0.8 ± 0.1 (U)	-3.9 [-8.6, 0.8]	-0.2 [-1.0, 0.6] (U)	0.8 ± 0.0 (U)	-3.9 [-7.4, -0.5]	-0.6 [-0.9, -0.3] (U)	-7.1 [-15.4, 1.2] (U)	-0.7 [-2.2, 0.7] (U)
Tensor Fascia Latae	0.5 ± 0.1 (I)		-0.2 [-1.1, 0.7] (I)	0.5 ± 0.1 (I)		-0.3 [-1.1, 0.6] (I)	-1.3 [-5.3, 2.8] (I)	-0.1 [-1.4, 1.3] (I)
	0.5 ± 0.1 (U)	-7.6 [-20.9, 5.6]	0.0 [-0.8, 0.9] (U)	0.5 ± 0.1 (U)	-10.4 [-20.0, -0.9]	0.0 [-0.7, 0.8] (U)	1.5 [-1.6, 7.2] (U)	0.0 [-1.4, 1.4] (U)
External Rotators	0.1 ± 0.0 (I)		-0.1 [-0.6, 0.4] (I)	0.1 ± 0.0 (I)		0.1 [-0.7, 1.0] (I)	6.6 [-8.5, 21.7] (I)	0.3 [-1.1, 1.7] (I)
	0.1 ± 0.2 (U)	-4.7 [-18.1, 8.6]	0.1 [-0.2, 0.3] (U)	0.1 ± 0.0 (U)	-2.9 [-19.9, 14.1]	0.2 [-0.2, 0.5] (U)	4.5 [-4.2, 13.3] (U)	0.4 [-1.0, 1.9] (U)
Piriformis	0.3 ± 0.1 (I)		-0.3 [-0.9, 0.4] (I)	0.3 ± 0.1 (I)		-0.0 [-1.0, 0.9] (I)	6.9 [-4.1, 17.9] (I)	0.3 [-1.1, 1.7] (I)
	0.4 ± 0.1 (U)	-8.6 [-24.2, 7.0]	0.0 [-0.8, 0.8] (U)	0.4 ± 0.1 (U)	-2.8 [-17.5, 11.8]	0.0 [-0.8, 0.9] (U)	0.0 [-4.3, 4.4] (U)	0.0 [-1.4, 1.4] (U)
Obturator Externus[b]	0.4 ± 0.1 (I)		-0.1 [-1.6, 1.5] (I)	0.5 ± 0.2 (I)		0.6 [-1.2, 2.4] (I)	15.0 [-5.5, 35.6] (I)	0.4 [-1.0, 1.8] (I)
	0.4 ± 0.2 (U)	-1.7 [-5.1, 1.7]	0.1 [-1.7, 1.8] (U)	0.5 ± 0.1 (U)	-1.5 [-18.2, 15.2]	0.6 [-0.6, 1.9] (U)	15.2 [0.7, 29.7] (U)	0.4 [-1.0, 1.8] (U)
Obturator Internus[a]	0.1 ± 0.0 (I)		-1.7 [-2.2, -1.1] (I)	0.2 ± 0.1 (I)		-0.7 [-1.8, 0.5] (I)	40.9 [20.6, 61.3] (I)	1.1 [-0.4, 2.6] (I)
	0.2 ± 0.0 (U)	-20.8 [-39.1, -2.4]	-1.0 [-1.7, -0.3] (U)	0.2 ± 0.1 (U)	-3.2 [-8.1, 1.7]	-0.5 [-1.8, -0.7] (U)	13.4 [-8.9, 35.8] (U)	0.4 [-1.0, 1.8] (U)
Quadratus Femoris	0.2 ± 0.1 (I)		-0.4 [-1.2, 0.5] (I)	0.2 ± 0.1 (I)		-0.5 [-1.4, 0.3] (I)	-4.1 [-11.8, 3.6] (I)	-0.2 [-1.6, 1.2] (I)
	0.2 ± 0.0 (U)	-0.2 [-15.1, 14.8]	-0.4 [-1.0, 0.3] (U)	0.2 ± 0.0 (U)	-6.5 [-25.8, 12.8]	-0.3 [-0.9, 0.4] (U)	3.5 [-8.0, 15.0] (U)	0.2 [-1.2, 1.6] (U)
Pectineus	0.4 ± 0.1 (I)		-1.4 [-2.0, -0.8] (I)	0.4 ± 0.1 (I)		-1.0 [-2.0, -0.0] (I)	12.6 [-4.5, 29.6] (I)	0.4 [-1.0, 1.8] (I)
	0.4 v 0.1 (U)	-10.6 [-18.2, -3.1]	-1.0 [-1.9, -0.1] (U)	0.4 ± 0.1 (U)	-3.5 [-10.2, 3.3]	-0.9 [-1.9, 0.0] (U)	3.9 [-9.0, 16.7] (U)	0.1 [-1.3, 1.5] (U)
Adductor Brevis	0.8 ± 0.0 (I)		-0.0 [-0.3, 0.3] (I)	0.8 ± 0.0 (I)		-0.3 [-0.4, -0.1] (I)	-3.6 [-7.5, 0.3] (I)	-0.9 [-2.3, 0.6] (I)
	0.8 ± 0.1 (U)	-0.8 [-8.0, 6.4]	0.0 [-0.5, 0.6] (U)	0.8 ± 0.1 (U)	2.4 [-7.5, 12.3]	-0.3 [-0.9, 0.3] (U)	-6.2 [-15.2, 3.1] (U)	-0.6 [-2.0, 0.8] (U)
Adductor Longus	1.2 ± 0.2 (I)		-0.5 [-1.3, 0.3] (I)	1.2 ± 0.3 (I)		-0.6 [-1.7, 0.5] (I)	-2.7 [-8.7, 3.2] (I)	-0.1 [-1.5, 1.3] (I)
	1.2 ± 0.2 (U)	1.3 [-3.5, 6.1]	-0.5 [-1.5, 0.5] (U)	1.2 ± 0.2 (U)	-3.1 [-6.4, 0.3]	-0.5 [-1.5, 0.6] (U)	1.5 [-3.0, 6.1] (U)	0.1 [-1.3, 1.5] (U)
Adductor Magnus[c]	4.1 ± 0.6 (I)		-0.7 [-1.6, 0.2] (I)	4.3 ± 0.4 (I)		-0.3 [-0.9, 0.3] (I)	6.8 [0.4, 13.2] (I)	0.5 [-0.9, 1.9] (I)
	4.3 ± 0.3 (U)	-6.5 [-14.3, 1.3]	-0.3 [-0.8, 0.2] (U)	4.5 ± 0.3 (U)	-3.3 [-7.9, 1.2]	-0.5 [-1.5, 0.6] (U)	3.0 [1.0, 5.0] (U)	0.4 [-1.0, 1.8] (U)
Sartorius	1.1 ± 0.2 (I)		-1.0 [-1.8, -0.2] (I)	1.0 ± 0.2 (I)		-1.4 [-2.5, -0.4] (I)	-8.6 [-15.8, -1.4] (I)	-0.5 [-1.9, 0.9] (I)
	1.2 ± 0.1 (U)	-4.8 [-12.4, 2.8]	-0.7 [-1.3, -0.2] (U)	1.1 ± 0.2 (U)	-10.3 [-19.4, -1.2]	-0.9 [-1.7, -0.0] (U)	-2.9 [-10.0, 4.3] (U)	-0.2 [-1.6, 1.2] (U)
Gracilis[a]	0.9 ± 0.1 (I)		-0.0 [-0.7, 0.6] (I)	0.6 ± 0.1 (I)		-1.6 [-2.3, -0.8] (I)	-33.8 [-42.6, -25] (I)	-2.2 [-4.0, -0.5] (I)

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Muscle Volume (cm^3/kg*m)	Pre-Surgery Mean ± SD	Pre-Surgery Limb Symmetry [95% CI]	Pre-Surgery Z-score [95% CI]	Post-Surgery Mean ± SD	Post-Surgery Limb Symmetry [95% CI]	Post-Surgery Z-score [95% CI]	% Change [95% CI]	Effect Size [95% CI]
	0.8 ± 0.2 (U)	4.9 [-10.5, 20.3]	-0.2 [-1.0, 0.7] (U)	0.8 ± 0.3 (U)	-21.7 [-40.2, -3.2]	-0.5 [-1.9, 0.9] (U)	-9.3 [-26.6, 7.9] (U)	-0.3 [-1.7, 1.1] (U)
Rectus Femoris[a]	1.9 ± 0.2 (I)		-0.7 [-1.3, -0.1] (I)	1.8 ± 0.3 (I)		-1.0 [-1.7, -0.2] (I)	-5.0 [-8.9, -1.0] (I)	-0.3 [-1.7, 1.1] (I)
	2.2 ± 0.2 (U)	-15.4 [-21.3, -9.6]	0.2 [-0.2, 0.6] (U)	2.3 ± 0.2 (U)	-20.4 [-27.7,-13.2]	0.3 [-0.3, 0.8] (U)	1.0 [-1.7, 3.9] (U)	0.1 [-1.2, 1.5] (U)
Vastus Intermedius[b]	1.8 ± 0.6 (I)		-1.3 [-2.9, 0.2] (I)	1.8 ± 0.5 (I)		-1.3 [-2.8, 0.3] (I)	1.5 [-6.0, 9.1] (I)	0.0 [-1.4, 1.4] (I)
	2.0 ± 0.3 (U)	-14.0 [-31.2, 3.1]	-0.4 [-1.3, 0.5] (U)	2.3 ± 0.3 (U)	-22.5 [-32.6,-12.3]	0.4 [-0.7, 1.4] (U)	11.3 [8.2, 14.3] (U)	0.8 [-0.7, 2.2] (U)
Vastus Lateralis[b]	5.4 ± 0.4 (I)		-1.5 [-2.0, -1.0] (I)	5.2 ± 0.4 (I)		-1.7 [-2.1, -1.2] (I)	-2.6 [-6.5, 1.3] (I)	-0.3 [-1.7, 1.0] (I)
	6.7 ± 0.8 (U)	-18.6 [-32.1, -5.0]	-0.0 [-0.8, 0.8] (U)	7.0 ± 0.6 (U)	-24.1 [-35.1,-13.1]	0.3 [-0.4, 1.0] (U)	4.3 [1.5, 6.9] (U)	0.4 [-1.0, 1.8] (U)
Vastus Medialis[a]	3.0 ± 0.6 (I)		-1.4 [-2.9, 0.2] (I)	2.8 ± 0.6 (I)		-1.8 [-3.3, -0.4] (I)	-6.2 [-9.4, -3.0] (I)	-0.3 [-1.7, 1.1] (I)
	3.4 ± 0.2 (U)	-14.3 [-26.8, -1.7]	-0.1 [-0.6, 0.4] (U)	3.5 ± 0.3 (U)	-21.8 [-32.7,-10.9]	0.2 [-0.7, 1.0] (U)	2.8 [-1.6, 7.2] (U)	0.4 [-1.0, 1.8] (U)
Biceps Femoris: LH[c]	1.6 ± 0.2 (I)		-0.3 [-0.9, 0.2] (I)	1.7 ± 0.1 (I)		-0.1 [-0.6, 0.4] (I)	4.8 [2.8, 6.9] (I)	0.5 [-0.9, 1.9] (I)
	1.6 ± 0.1 (U)	-0.5 [-6.0, 5.1]	-0.3 [-0.6, -0.0] (U)	1.7 ± 0.1 (U)	-0.2 [-5.0, 4.6]	-0.0 [-0.4, 0.4] (U)	4.5 [1.6, 7.5] (U)	0.8 [-0.7, 2.2] (U)
Biceps Femoris: SH[a]	0.6 ± 0.2 (I)		-1.1 [-1.9, -0.3] (I)	0.6 ± 0.2 (I)		-1.0 [-2.0, -0.0] (I)	2.0 [2.8, 6.9] (I)	0.1 [-1.3, 1.5] (I)
	0.6 ± 0.2 (U)	6.2 [3.8, 8.5]	-1.3 [-2.1, -0.4] (U)	0.6 ± 0.2 (U)	7.0 [0.4, 13.7]	-1.2 [-2.2, -0.2] (U)	1.4 [-5.0, 7.9] (U)	0.1 [-1.3, 1.5] (U)
Semimembranosus	1.9 ± 0.4 (I)		-0.5 [-1.8, 0.9] (I)	1.9 ± 0.5 (I)		-0.3 [-1.9, 1.3] (I)	2.2 [-1.3, 5.8] (I)	0.1 [-1.3, 1.5] (I)
	1.8 ± 0.2 (U)	0.3 [-13.5, 14.0]	-0.5 [-1.1, 0.0] (U)	1.9 ± 0.3 (U)	-2.8 [-13.4, 7.8]	-0.2 [-1.1, 0.8] (U)	5.3 [-1.2, 11.8] (U)	0.4 [-1.0, 1.8] (U)
Semitendinosus[a]	1.6 ± 0.3 (I)		0.2 [-0.7, 1.2] (I)	1.0 ± 0.3 (I)		-1.9 [-3.2, -0.7] (I)	-37.5 [-51.9, -23] (I)	-1.9 [-3.5, -0.2] (I)
	1.4 ± 0.3 (U)	9.4 [1.9, 16.8]	-0.2 [-1.2, 0.7] (U)	1.2 ± 0.4 (U)	-10.7 [-37.6, 16.2]	-1.2 [-2.9, 0.4] (U)	-19.7 [-42.4,2.9] (U)	-0.7 [-2.1, 0.7] (U)
Tibialis Anterior[b]	0.8 ± 0.1 (I)		-1.7 [-2.2, -1.3] (I)	0.8 ± 0.1 (I)		-1.9 [-2.3, -1.6] (I)	-3.2 [-7.8, 1.3] (I)	-0.4 [-1.8, 1.0] (I)
	1.0 ± 0.1 (U)	-13.7 [-18.5, -8.8]	-0.9 [-1.2, -0.6] (U)	0.9 ± 0.0 (U)	-12.3 [-17.0, -7.6]	-1.2 [-1.5, -0.9] (U)	-4.9 [-7.6, -2.1] (U)	-1.0 [-2.4, 0.5] (U)
Phalangeal Extensors[c]	0.7 ± 0.1 (I)		-1.5 [-2.0, -0.9] (I)	0.6 ± 0.1 (I)		-1.7 [-2.4, -1.1] (I)	-4.4 [-8.2, -0.5] (I)	-0.4 [-1.8, 1.0] (I)
	0.7 ± 0.1 (U)	-3.6 [-9.5, 2.2]	-1.2 [-2.2, -0.3] (U)	0.7 ± 0.1 (U)	-10.6 [-12.6, -8.6]	-1.1 [-1.7, -0.4] (U)	3.1 [-3.2, 9.4] (U)	0.2 [-1.2. 1.6] (U)
Peroneals[a]	0.9 ± 0.2 (I)		-0.7 [-1.8, 0.4] (I)	0.9 ± 0.2 (I)		-0.9 [-1.9, 0.1] (I)	-2.8 [-5.6, -0.1] (I)	-0.2 [-1.5, 1.2] (I)
	0.9 ± 0.2 (U)	-1.9 [-11.0, 7.1]	-0.6 [-1.5, 0.2] (U)	0.9 ± 0.2 (U)	-4.5 [-10.8, 1.8]	-0.7 [-1.7, 0.4] (U)	-0.3 [-4.7, 4.1] (U)	-0.0 [-1.4, 1.4] (U)
Popliteus[b]	0.1 ± 0.0 (I)		-1.5 [-2.4, -0.6] (I)	0.1 ± 0.0 (I)		-2.1 [-2.9, -1.2] (I)	-12.5 [-26.2, 1.2] (I)	-0.7 [-2.1, 0.7] (I)
	0.2 ± 0.0 (U)	-13.0 [-26.4, 0.4]	-0.8 [-1.3, -0.4] (U)	0.2 ± 0.0 (U)	-17.2 [-38.1, 3.8]	-1.2 [-1.6, -0.8] (U)	-7.5 [-12.1, -2.9] (U)	-0.9 [-2.4, 0.5] (U)
Tibialis Posterior	0.7 ± 0.1 (I)		-1.1 [-1.4, -0.7] (I)	0.7 ± 0.1 (I)		-1.1 [-1.6, -0.5] (I)	0.4 [-7.3, 8.1] (I)	0.1 [-1.3, 1.4] (I)
	0.7 ± 0.1 (U)	-2.0 [-16.8, 12.9]	-1.0 [-1.4, -0.5] (U)	0.7 ± 0.1 (U)	-3.4 [-18.0, 11.3]	-0.9 [-1.4, -0.4] (U)	1.6 [-0.7, 4.0] (U)	0.1 [-1.3, 1.5] (U)
Flexor Digitorum L.	0.2 ± 0.1 (I)		-0.8 [-2.0, 0.5] (I)	0.2 ± 0.1 (I)		-1.1 [-2.2, 0.0] (I)	-9.0 [-25.9, 7.8] (I)	-0.3 [-1.7, 1.1] (I)
	0.2 ± 0.1 (U)	-2.8 [-11.4, 5.9]	-0.7 [-1.7, 0.3] (U)	0.2 ± 0.1 (U)	-1.1 [-14.0, 11.8]	-1.1 [-2.0, -0.3] (U)	-10.8 [-22.1,0.5] (U)	-0.4 [-1.8, 1.0] (U)
Flexor Hallucis L.	0.5 ± 0.0 (I)		-1.0 [-1.4, -0.6] (I)	0.5 ± 0.1 (I)		-1.3 [-1.9, -0.7] (I)	-6.9 [-14.1, 0.3] (I)	-0.6 [-2.0, 0.9] (I)
	0.6 ± 0.1 (U)	-5.4 [-11.6, 0.9]	-0.8 [-1.2, -0.3] (U)	0.6 ± 0.1 (U)	-13.3 [-21.2, -5.4]	-0.7 [-1.1, -0.3] (U)	1.7 [-3.1, 6.4] (U)	0.2 [-1.2, 1.5] (U)
Soleus[b]	3.3 ± 0.5 (I)		-0.5 [-1.4, 0.4] (I)	3.2 ± 0.5 (I)		-0.6 [-1.5, 0.3] (I)	-2.5 [-6.9, 1.9] (I)	-0.2 [-1.6, 1.2] (I)
	3.3 ± 0.3 (U)	-0.7 [-6.9, 5.5]	-0.4 [-1.0, 0.1] (U)	3.4 ± 0.3 (U)	-6.7 [-12.3, -1.1]	-0.2 [-0.8, 0.3] (U)	3.6 [1.7, 5.5] (U)	0.4 [-1.0, 1.8] (U)
Gastrocnemius: LH[c]	1.0 ± 0.2 (I)		-0.8 [-1.8, 0.2] (I)	1.0 ± 0.2 (I)		-1.0 [-2.0, -0.0] (I)	-4.5 [-8.6, -0.4] (I)	-0.2 [-1.6, 1.2] (I)
	1.1 ± 0.2 (U)	-8.7 [-15.0, -2.4]	-0.3 [-1.2, 0.5] (U)	1.0 ± 0.2 (U)	-5.1 [-13.0, 2.8]	-0.8 [-1.5, -0.1] (U)	-8.1 [-13.1, -3.1] (U)	-0.6 [-2.0, 0.9] (U)

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	Pre-Surgery			Post-Surgery				
Muscle Volume (cm^3/kg*m)	Mean ± SD	Limb Symmetry [95% CI]	Z-score [95% CI]	Mean ± SD	Limb Symmetry [95% CI]	Z-score [95% CI]	% Change [95% CI]	Effect Size [95% CI]
Gastrocnemius: MH	1.8 ± 0.4 (I)		-0.9 [-2.1, 0.2] (I)	1.7 ± 0.5 (I)		-1.1 [-2.5, 0.3] (I)	-3.6 [-11.5, 4.3] (I)	-0.1 [-1.5, 1.2] (I)
	1.7 ± 0.2 (U)	7.2 [-2.7, 17.0]	-1.3 [-2.1, -0.6] (U)	1.7 ± 0.3 (U)	1.3 [-8.9, 11.6]	-1.2 [-2.2, -0.2] (U)	1.9 [-3.9, 7.7] (U)	0.1 [-1.3, 1.5] (U)

Abbreviations: I, involved; U, uninvolved; LH, long head; SH, short head; L, longus

Muscle groupings: External Rotators: gemellus superior and inferior; Peroneals: peroneus longus, peroneus brevis; Phalangeal Extensors: extensor digitorum longus, extensor hallucis longus

Limb symmetry indicates the percent difference in muscle volume between limbs, with negative values indicating smaller muscle volumes in the involved limb

% Change indicates the percent difference calculated from muscle volumes pre- to post-surgery, with negative values indicating smaller muscle volumes post-surgery

Cohen’s *d* effect sizes with 95% confidence intervals calculated using the pooled standard deviation; Bolded text indicates the effect size 95% CI does not cross zero

Values = 0.0 < 0.05

[a] 95% CI does not cross zero for percent change on involved limb

[b] 95% CI does not cross zero for percent change on uninvolved limb

[c] 95% CI does not cross zero for percent change on both limbs

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Table 3: Normalized knee extension MVIC torque, superimposed burst torque, and quadriceps activation pre-and post-surgery.

	Mean ± SD[a]		Mean [95% CI][a]	
	Pre	Post	% Change	Effect Size[b]
Knee Extension MVIC torque (Nm/kg)				
Subject 1	2.27 (I)	2.17 (I)	-4.32 (I)	N/A
	3.11 (U)	4.09 (U)	31.33 (U)	N/A
Subject 2	1.61 (I)	1.43 (I)	-11.31 (I)	N/A
	2.38 (U)	2.64 (U)	10.71 (U)	N/A
Subject 3	1.48 (I)	2.27 (I)	52.72 (I)	N/A
	2.03 (U)	2.64 (U)	30.17 (U)	N/A
Subject 4	1.70 (I)	1.93 (I)	13.52 (I)	N/A
	2.39 (U)	2.31 (U)	-3.51 (U)	N/A
Mean	1.77 ± 0.35 (I)	1.95 ± 0.43 (I)	12.65 [-15.45, 40.76] (I)	0.51 [-0.90, 1.92] (I)
	2.48 ± 0.46 (U)	2.92 ± 0.80 (U)	17.18 [0.79, 33.56] (U)	0.68 [-0.75, 2.10] (U)
Limb Symmetry Index (%)	71.4	66.8		
Superimposed Burst Torque (Nm/kg)				
Subject 1	2.30 (I)	-	-	N/A
	3.15 (U)	-	-	N/A
Subject 2	1.75 (I)	1.50 (I)	-14.28 (I)	N/A
	2.61 (U)	3.03 (U)	16.14 (U)	N/A
Subject 3	2.11 (I)	2.36 (I)	11.78 (I)	N/A
	2.53 (U)	3.06 (U)	20.86 (U)	N/A
Subject 4	1.72 (I)	2.00 (I)	16.31 (I)	N/A
	3.05 (U)	3.06 (U)	0.43 (U)	N/A
Mean	1.86 ± 0.22 (I)	1.95 ± 0.43 (I)	4.60 [-11.58, 20.78] (I)	0.27 [-1.33, 1.88] (I)
	2.73 ± 0.28 (U)	3.05 ± 0.02 (U)	12.48 [8.26, 16.66] (U)	1.63 [-0.22, 3.48] (U)
Limb Symmetry Index (%)	68.1	63.9		
Central Activation Ratio (%)				
Subject 1	98.49 (I)	-	-	N/A
	98.80 (U)	-	-	N/A
Subject 2	89.52 (I)	96.40 (I)	7.69 (I)	N/A
	84.02 (U)	84.54 (U)	0.62 (U)	N/A
Subject 3	78.98 (I)	92.10 (I)	15.98 (I)	N/A
	80.02 (U)	84.16 (U)	5.18 (U)	N/A
Subject 4	84.40 (I)	92.67 (I)	13.72 (I)	N/A
	78.59 (U)	75.41 (U)	-4.05 (U)	N/A
Mean	84.30 ± 5.27 (I)	94.66 ± 2.66 (I)	12.46 [8.26, 16.66] (I)	2.48 [0.35, 4.61] (I)

“MRI-Based Assessment of Lower Extremity Muscle Volumes in Patients Before and After ACL Reconstruction”
by Norte GE et al. et al.
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	Mean ± SD[a]		Mean [95% CI][a]	
	Pre	Post	% Change	Effect Size[b]
	80.88 ± 2.81 (U)	81.37 ± 5.16 (U)	0.59 [-3.94, 5.11] (U)	0.12 [-1.48, 1.72] (U)
Limb Symmetry Index (%)	104.2	116.3		

Abbreviations: MVIC, maximal voluntary isometric contraction; I, involved; U, uninvolved; % change, percentage change with 95% confidence intervals

Positive values indicate an increase from pre- to post-surgery

- Indicates missing data point

[a] If applicable (calculated for mean values only)

[b] Cohen’s *d* effect sizes with 95% confidence intervals calculated using the pooled standard deviation

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Table 4: Relationships between quadriceps muscle volumes and knee extension MVIC torque pre- and post-surgery.

	Correlations, *r*	
	Pre-Surgery MVIC Torque	Post-Surgery MVIC Torque
Vastus Medialis Volume (cm^3)	0.833 (I)	0.934 (I)
	0.765 (U)	0.842 (U)
Vastus Lateralis Volume (cm^3)	0.725 (I)	**0.971** (I)
	0.548 (U)	0.613 (U)
Vastus Intermedius Volume (cm^3)	0.791 (I)	**0.987** (I)
	0.658 (U)	0.753 (U)
Rectus Femoris Volume (cm^3)	0.893 (I)	0.895 (I)
	0.824 (U)	0.864 (U)
Total Quadriceps Volume (cm^3)	0.793 (I)	**0.967** (I)
	0.682 (U)	0.756 (U)

Abbreviations: MVIC, maximal voluntary isometric knee extension torque (Nm); I, involved; U, uninvolved

Bolded text indicate correlation is significant at the 0.05 level (2-tailed)