Marquette University

e-Publications@Marquette

Physical Therapy Faculty Research and Publications

Physical Therapy, Department of

9-2022

Knee Joint Biomechanics During Gait Improve from 3 to 6 Months after Anterior Cruciate Ligament Reconstruction

Kelsey Neal University of Delaware

Jack R. Williams University of Delaware

Abdulmajeed Alfayyadh University of Delaware

Jacob J. Capin Marquette University, jacob.capin@marquette.edu

Ashutosh Khandha University of Delaware

See next page for additional authors

Follow this and additional works at: https://epublications.marquette.edu/phys_therapy_fac

Part of the Physical Therapy Commons

Recommended Citation

Neal, Kelsey; Williams, Jack R.; Alfayyadh, Abdulmajeed; Capin, Jacob J.; Khandha, Ashutosh; Manal, Kurt; Snyder-Mackler, Lynn; and Buchanan, Thomas S., "Knee Joint Biomechanics During Gait Improve from 3 to 6 Months after Anterior Cruciate Ligament Reconstruction" (2022). *Physical Therapy Faculty Research and Publications*. 198.

https://epublications.marquette.edu/phys_therapy_fac/198

Authors

Kelsey Neal, Jack R. Williams, Abdulmajeed Alfayyadh, Jacob J. Capin, Ashutosh Khandha, Kurt Manal, Lynn Snyder-Mackler, and Thomas S. Buchanan

This article is available at e-Publications@Marquette: https://epublications.marquette.edu/phys_therapy_fac/198

Marquette University

e-Publications@Marquette

Physical Therapy Faculty Research and Publications/College of Health Sciences

This paper is NOT THE PUBLISHED VERSION.

Access the published version via the link in the citation below.

Journal of Orthopaedic Research, Vol. 40, No. 9 (September 2022): 2025-2038. <u>DOI</u>. This article is © Wiley and permission has been granted for this version to appear in <u>e-Publications@Marquette</u>. Wiley does not grant permission for this article to be further copied/distributed or hosted elsewhere without the express permission from Wiley.

Knee Joint Biomechanics During Gait Improve from 3 to 6 Months after Anterior Cruciate Ligament Reconstruction

Kelsey Neal Department of Mechanical Engineering, University of Delaware, Newark, Delaware Jack R. Williams Department of Mechanical Engineering, University of Delaware, Newark, Delaware Abdulmajeed Alfayyadh Biomechanics and Movement Science, University of Delaware, Newark, Delaware Jacob J. Capin Biomechanics and Movement Science, University of Delaware, Newark, Delaware Department of Physical Therapy, University of Delaware, Newark, Delaware Department of Physical Therapy, University of Delaware, Newark, Delaware Department of Physical Medicine and Rehabilitation, Physical Therapy Program, University of Colorado, Aurora, Colorado Eastern Colorado VA Geriatric Research Education and Clinical Center (GRECC), Aurora, Colorado Department of Physical Therapy, Marquette University, Milwaukee, Wisconsin

Ashutosh Khandha

Department of Biomedical Engineering, University of Delaware, Newark, Delaware

Kurt Manal

Department of Kinesiology and Applied Physiology, University of Delaware, Newark, Delaware

Lynn Snyder-Mackler

Biomechanics and Movement Science, University of Delaware, Newark, Delaware Department of Physical Therapy, University of Delaware, Newark, Delaware Department of Biomedical Engineering, University of Delaware, Newark, Delaware

Thomas S. Buchanan

Department of Mechanical Engineering, University of Delaware, Newark, Delaware Biomechanics and Movement Science, University of Delaware, Newark, Delaware Department of Biomedical Engineering, University of Delaware, Newark, Delaware

Abstract

Gait alterations after anterior cruciate ligament reconstruction (ACLR) are commonly reported and have been linked to posttraumatic osteoarthritis development. While knee gait alterations have been studied at several time points after ACLR, little is known about how these biomechanical variables change earlier than 6 months after surgery, nor is much known about how they differ over the entire stance phase of gait. The purpose of this study was to examine knee gait biomechanical variables over their entire movement pattern through stance at both 3 and 6 months after ACLR and to study the progression of interlimb asymmetry between the two postoperative time points. Thirty-five individuals underwent motion analysis during overground walking 3 (3.2 ± 0.5) and 6 (6.4 ± 0.7) months after ACLR. Knee biomechanical variables were compared between limbs and across time points through 100% of stance using statistical parametric mapping; this included a 2 × 2 (Limb × Time) repeated measures analysis of variance and two-tailed t-tests. Smaller knee joint angles, moments, extensor forces, and medial compartment forces were present in the involved versus uninvolved limb. Interlimb asymmetries were present at both time points but were less prevalent at 6 months. The uninvolved limb's biomechanical variables stayed relatively consistent over time, while the involved limb's trended toward that of the uninvolved limb. Statement of Clinical Significance: Interventions to correct asymmetrical gait patterns after ACLR may need to occur early after surgery and may need to focus on multiple parts of stance phase.

1 INTRODUCTION

Anterior cruciate ligament (ACL) tears are one of the most common knee injuries among young, active populations.¹ Over the past few decades, the number of individuals who have opted to undergo ACL reconstructive (ACLR) surgery after tearing their ACL has increased.^{2, 3} Many of these individuals undergo this procedure with the hope of restoring stability to their knee and returning to their preinjury level of activity. While this procedure is successful at restoring knee stability, it often fails to resolve alterations in gait mechanics.

Interlimb (involved vs. uninvolved) asymmetries in gait mechanics are commonly reported after surgery and tend to persist even after being cleared to return to sport.^{4, 5} Frequently reported alterations include changes in involved limb peak knee flexion angles (KFAs),⁵⁻¹⁰ peak knee extension angles (KEA),¹¹⁻¹³ peak knee flexion moments (KFMs),¹⁴⁻²⁰ peak knee adduction moments (KAMs),^{15, 16, 18, 21, 22} quadriceps strength,^{17, 23, 24} and peak medial compartment contact forces (MCFs)¹⁵ (vs. uninvolved and healthy controls). The continuation of these

asymmetries are concerning as they leave individuals at risk of reinjury²⁵ and are thought to have long-lasting effects on joint health.^{15, 26-31} While gait abnormalities tend to normalize around 2 years after surgery,^{17, 32} changes in the loading environment that occur during these time periods may contribute to the premature development of posttraumatic knee osteoarthritis (OA).^{15, 28, 30, 31, 33} Understanding how gait aberrations progress during the early months after surgery, when interventions may be most feasible, can help inform new rehabilitative strategies to mitigate asymmetries and preserve long-term joint health.

Three months after ACLR, Lin et al.¹⁰ found an association between reduced involved limb knee flexion range of motion and lower knee extensor moments. Similarly, Sigward et al.⁹ found that asymmetries in knee moments, work, and flexion angles 1 month after surgery that persisted to when individuals were cleared for running (~4 months). Likewise, Di Stasi et al.⁵ found that regardless of return to sport status, at 6 months the involved limb demonstrates smaller knee extensor moments, suggesting that current rehabilitation protocols are not meeting their desired goals. These findings could be associated with quadriceps weakness. Lewek et al.²⁴ found that individuals with quadriceps weakness 4 months after ACLR exhibited reduced knee angles and moments. However, regaining quadriceps strength may not be enough to regain symmetry in gait mechanics. Roewer et al.¹⁷ found that even after quadriceps strength symmetry was regained, asymmetries in KFAs, moments, and power persisted up to 6 months. Similarly, Arhos et al.³⁴ found that restoration of quadriceps strength symmetry was not associated with symmetry in gait mechanics among individuals who were well rehabilitated. While gait mechanics have been assessed before 6 months after surgery, they have relied on surrogate measures for knee loading and have only assessed discrete points in the movement pattern (often peaks).

Many groups rely on surrogate measures for knee loading such as sagittal and frontal plane knee moments, due to the difficulty of obtaining in vivo joint loads.^{9, 35} KFM is used as a surrogate for total joint load and KAM is thought to represent the distribution of load between the medial and lateral compartments of the knee.³⁶⁻³⁸ In older populations, higher knee moments have been correlated to the occurrence and severity of knee OA.³⁸⁻⁴⁰ Early after ACLR, however, peak KFM^{4, 9, 17} is lower and peak KAM is reported to be lower^{15, 16, 18, 21} or no different^{15, 22} in the involved limb compared to the uninvolved limb and healthy controls. While these measures play a role in knee joint loading, neither account for muscle co-contraction, which is heightened in the ACLR population and can also play a major role in joint load.^{41, 42} Thus, an EMG-informed neuromusculoskeletal model, accounting for relative co-contraction of the muscles, may give a more accurate estimate of joint loads.^{43, 44} A study performed by Wellsandt et al.¹⁵ utilized this approach and found that individuals who developed radiographic OA 5 years after ACLR displayed significantly lower peak MCFs in their involved limb 6 months after surgery, compared to those who do not develop OA. These individuals also tended to underload their involved limb (vs. uninvolved).

Many have examined gait mechanics in the months and years following ACLR,^{8, 27} mostly focusing on peak values of knee biomechanical variables during gait. While this approach may be traditional, the reduction of continuous *n*-dimensional (*n*D) data to discrete values (0D) can lead to biasing of statistical results⁴⁵ and does not provide the full picture of how the variable of interest is progressing throughout stance, which may result in missing regions where alterations occur.⁴⁵⁻⁴⁷ Since many biomechanical variables are time-varying (1D) data, employing a continuous analysis technique may give a more accurate and comprehensive view of how these variables are affected after surgery.^{45, 46} Statistical parametric mapping (SPM), the applied form of Random Field Theory,^{48, 49} allows for the statistical analysis of continuous data. SPM was originally developed for neuroimaging,^{50, 51} but recently has been utilized within the biomechanics community.^{13, 52, 53} By utilizing SPM techniques for continuous data analysis, we seek to gain a more accurate and holistic view of how limb asymmetries evolve throughout the stance phase of gait, and over early postsurgery time points when interventions may be most effective.

Therefore, the purpose of this study was to (1) examine knee gait variables (flexion angle, flexion moment, adduction moment, extensor forces, and medial compartment force [MCF]) between limbs at 3 and 6 months after ACLR and (2) assess how these variables change from 3 to 6 months after ACLR. We hypothesized that (1) interlimb asymmetries in knee gait variables would be present at 3 and 6 months after ACLR and (2) these asymmetries would be greater at 3 months than at 6 months, with the involved limb changing over time.

2 METHODS

2.1 Participants

Thirty-five individuals (Table 1) from a cohort study (R01-HD087459) were included in this study. Inclusion criteria were: no previous history of lower leg injury, no concomitant grade III ligament sprains, between the ages of 16 and 45, no meniscus repair, and unilateral primary ACLR. All data were collected at one institution following approval from an Institutional Review Board. All participants provided informed consent before participation in the study. For individuals under the age of 18, both minor assent and parental consent were obtained before enrolment.

Variable	Mean ± standard deviation or number (%)
Age	22 ± 6 years
Sex	18 women (51%), 17 men (49%)
Height	1.7 ± 0.1 m
Weight	72.7 ± 14.0 kg
BMI	24.7 ± 3.7 kg/m ²
Graft type	6 soft-tissue allograft (17%), 11 hamstring autograft (32%), 18 bone-patellar tendon-bone
	autograft (51%)
Meniscal	7 partial lateral meniscectomy (20%), 5 partial medial meniscectomy (14%), 2 partial medial
treatment	and lateral meniscectomy (6%), 21 no meniscectomy (60%)
Walking speed	1.6 ± 0.2 m/s

 Table 1. Participant demographic characteristics (n = 35)

Abbreviation: BMI, body mass index.

2.2 Gait analysis

All participants completed gait analysis during overground walking 3 (3.2 ± 0.5) and 6 (6.4 ± 0.7) months after ACLR using previously described methodologies.^{54, 55}

Retroreflective markers were placed bilaterally on bony landmarks (iliac crests, greater trochanters, femoral epicondyles, malleoli, first and fifth metatarsal heads, and two markers on each calcaneus) and rigid shells containing multi-marker groupings were placed on the shanks, thighs, and pelvis.⁵⁴ Participants were directed to walk down a 6-m walkway at a self-selected speed that was maintained across time points (±5%). Walking speed was monitored using two photoelectric beams (Brower Timing Systems). Once self-selected speed was established through practice trials, eight walking trials were collected for each limb. Kinematic (120 Hz) and kinetic (1080 Hz) data were recorded using an 8-camera Vicon system (Oxford Metrics Limited) and an embedded force platform (Bertec Corporation), respectively. Kinematic data were filtered at 6 Hz using a zero-lag, fourth-order Butterworth filter, while kinetic data were filtered at 25 Hz. Stance phase joint angles and moments were calculated using inverse dynamics in Visual3D using a 6 DOF approach (C-motion) and were normalized to 100% of stance. All joint moments were normalized to body weight (BW) and height (HT) (%BW × HT) and reported as external moments in the tibial coordinate system.

Surface electromyography (EMG) electrodes (MA-300 EMG System, Motion Lab Systems) were placed over seven muscles on each leg (rectus femoris, medial and lateral vasti, semimembranosus, long head of biceps

femoris, medial and lateral gastrocnemii). EMG data were collected at 1080 Hz. Before walking, participants performed maximum voluntary isometric muscle contractions that were used to normalize the EMG signal obtained during overground walking. EMG data were high-passed filtered (30 Hz), rectified, and then low-passed filtered (6 Hz) using a second-order Butterworth filter to create linear envelopes for the seven muscles. Additionally, the semitendinosus was set equal to the linear envelope of the semimembranosus, the short head of the biceps femoris to the long head of the biceps femoris, and the vasus intermedius was calculated by averaging the linear envelopes of the medial and lateral vasti.

The EMG and gait analysis data were used as inputs to a previously validated EMG-informed neuromusculoskeletal model to compute muscle forces and joint contact forces.^{43, 55} Validation was performed using in vivo contact force data recorded from an instrumented knee prosthesis and was found to produce accurate predictions of joint forces.⁵⁵ This model consisted of three components: an anatomical model, an activation dynamics model, and a contractions dynamics model. The anatomical model included a pelvis and femur, tibia, and foot segments that were scaled using subject anthropomorphic measurements and was actuated by 10 muscle-tendon units. The activation dynamics model transformed the EMG data into muscle activations and the contraction dynamics model subsequently transformed muscle activations to muscle forces using a previously described calibration process which varied adjustable muscle activation/contraction parameters so that the sagittal plane moment from the forward and inverse dynamics models matched.⁵⁴ The MCF was then estimated using a frontal plane moment balance between the external and internal frontal plane knee moments.⁴⁴

The variables of interest in this study were chosen based on previous evidence associating them with OA after ACLR.^{15, 26, 27} These variables of interest included: KFA, KFM, KAM, knee extensor forces (KEFs), and knee MCF. Extensor muscle forces were estimated by summing the forces of the rectus femoris, vastus medialis, vastus lateralis, and vastus intermedius.⁵⁶ Both the KEF and the MCF were normalized by BW.

2.3 Statistical methods

Statistical analyses were performed using SPM1D⁵⁷ in MATLAB (MathWorks). For each variable of interest, normality was assessed using D'Agostino–Pearson K^2 tests.⁵⁸ SPM was used to conduct a 2 × 2 (Limb × Time) repeated measures analysis of variance (α = 0.05). Additionally, two-tailed Student's *t*-tests were conducted to assess limb asymmetry at each time point and to assess change in interlimb differences (ILD = involved limb – uninvolved limb) from 3 to 6 months. For both tests, parametric or nonparametric approaches, depending on normality,⁵⁹ were used (SPM1D supports both) to evaluate the data.

3 RESULTS

Significant differences between limbs were observed at both 3 and 6 months for many of the kinematic and kinetic variables of interest. Generally, interlimb differences decreased from 3 to 6 months.

3.1 KFA

A significant limb-by-time interaction for KFA was present during terminal stance (56%–66% of stance, p = 0.038; Figure **1A**) as the knee was extending. During this portion of stance, the ILD significantly decreased from 3 to 6 months (p = 0.010; Figure **1B**). At 3 months, significant differences were present between limbs during weight acceptance through midstance (11%–33% of stance, p = 0.011) and during terminal stance (52%–85% of stance, p = 0.002; Figure **2A**). While the magnitude of interlimb differences decreased at 6 months, the differences were still significant during weight acceptance and part of midstance (8%–30% of stance, p = 0.014) and terminal stance (60%–80% of stance, p = 0.019; Figure **2B**).



Figure 1 (A: top) 3 (blue) and 6 (orange) month knee flexion angle for the involved (dashed line) and uninvolved (solid line) limbs throughout stance. Interlimb differences were present at both time points during weight acceptance and parts of midstance and terminal stance. (A: bottom) Statistical parametric mapping (SPM) Limb × Time repeated measures analysis of variance *F*-statistic over 100% of stance. The red dashed line indicates the critical *F*-value (*F* = 7.99) where results are considered significant ($\alpha \le 0.05$). A significant limb-by-time interaction was seen from 56% to 66% of stance. (B: top) Interlimb differences at 3 and 6 months. ILD significantly decreased over 56%–66% of stance. (B: bottom) Two-tailed paired Student's *t*-test using SPM for ILD at 3 and 6 months. The red dashed line indicates the critical *t*-value ($\alpha = 0.05$)



Figure 2 The top graph of each subfigure shows knee flexion angle (KFA) through 100% of stance \pm 1 standard deviation (shaded regions). The lower graph displays a two-tailed paired Student's *t*-test using statistical parametric mapping (SPM). The red dashed line indicates the critical *t*-value ($\alpha = 0.05$). (A) Involved (dashed line) versus uninvolved (solid line) KFA 3 months after anterior cruciate ligament reconstruction (ACLR); significant differences were present from 11% to 33% and 52% to 85% of stance. (B) Involved (dashed line) versus uninvolved (solid line) KFA 6 months after ACLR; significant differences were seen from 8% to 30% and 60% to 80% of stance. (C) Involved 3 months (blue) versus 6 months (orange); no significant differences were present. (D) Uninvolved 3 months (blue) versus 6 months (orange); significant differences were seen from 0% to 7% of stance

No significant differences were seen when comparing the involved limb across time points (Figure **2C**). The uninvolved limb showed significant differences between time points during heel strike (0%–7%, p = 0.042; Figure **2D**).

3.2 KFM

A significant limb-by-time interaction for KFM was present during the end of weight acceptance and the start of midstance (15%–24% of stance, p = 0.009; Figure **3A**). The ILD significantly decreased from 3 to 6 months during this part of stance (p = 0.007; Figure **3B**). *t*-tests showed significant differences between limbs at 3 months during weight acceptance and part of midstance (5%–36% of stance, p < 0.001), terminal stance (64%–71% of stance, p = 0.014), and preswing (86%–96% of stance, p = 0.005; Figure **4A**). Interlimb differences decreased from 3 to 6 months with significant differences seen only during weight acceptance through midstance at 6 months (5%–31% of stance, p < 0.001; Figure **4B**). During the transition from weight acceptance to midstance, KFM in the involved limb increased from 3 to 6 months (13%–29%, p < 0.001; Figure **4C**). No differences were found for the uninvolved limb between time points (Figure **4D**).



Figure 3 (A: top) 3 (blue) and 6 (orange) month knee flexion moment for the involved (dashed line) and uninvolved (solid line) limbs throughout stance. Interlimb differences were present at both time points during weight acceptance into midstance and terminal stance. These differences decreased from 3 to 6 months during weight acceptance into midstance. (A: bottom) Statistical parametric mapping (SPM) Limb × Time repeated measures analysis of variance *F*-statistic over 100% of stance. The red dashed line indicates the critical *F*-value (*F* = 10.37) where results are considered significant ($\alpha \le 0.05$). A significant limb-by-time interaction was seen from 16% to 23% of stance. (B: top) Interlimb differences at 3 and 6 months. ILD significantly decreased from 3 to 6 months between 15% and 23% of stance. (B: bottom) Two-tailed paired Student's *t*-test using SPM for ILD at 3 and 6 months. The red dashed line indicates the critical *t*-value ($\alpha = 0.05$). BW, body weight; HT, height



Figure 4 The top part of each subfigure shows knee flexion moment (KFM) through 100% of stance \pm 1 standard deviation (shaded regions). The lower portion displays a two-tailed paired Student's *t*-test using statistical parametric mapping (SPM). The red dashed line indicates the critical *t*-value ($\alpha = 0.05$). (A) Involved (dashed line) versus uninvolved (solid line) KFM 3 months after anterior cruciate ligament reconstruction (ACLR); significant differences were present from 5% to 36%, 64% to 71%, and 86% to 96% of stance. (B) Involved (dashed line) versus uninvolved (solid line) KFM 6 months after ACLR; significant differences were seen from 5% to 31% of stance. (C) Involved 3 months (blue) versus 6 months (orange); significant differences were seen from 13% to 29% of stance. (D) Uninvolved 3 months (blue) versus 6 months (orange); no significant differences were present. BW, body weight; HT, height

3.3 KAM

No significant differences were seen between limbs at either time point when assessing KAM (Figures 5 and 6).



Figure 5 (A: top) 3 (blue) and 6 (orange) month knee adduction moment for the involved (dashed line) and uninvolved (solid line) limbs throughout stance. (A: bottom) Statistical parametric mapping (SPM) Limb × Time repeated measures analysis of variance *F*-statistic over 100% of stance. The red dashed line indicates the critical *F*-value (F = 9.94) where results are considered significant. No significant limb-by-time interaction was present. (B: top) Interlimb differences at 3 and 6 months. No significant differences were present. (B: bottom) Two-tailed paired Student's *t*-test using SPM for ILD at 3 and 6 months. The red dashed line indicates the critical *t*-value ($\alpha = 0.05$). BW, body weight; HT, height



Figure 6 The top part of each subfigure shows knee adduction moment (KAM) through 100% of stance \pm 1 standard deviation (shaded regions). The lower portion displays a two-tailed paired Student's *t*-test using statistical parametric mapping (SPM). The red dashed line indicates the critical *t*-value (α = 0.05). (A) Involved (dashed line) versus uninvolved (solid line) KAM 3 months after anterior cruciate ligament reconstruction (ACLR); no significant differences were present. (B) Involved (dashed line) versus uninvolved (solid line) KAM 6 months after ACLR; no significant differences were present. (C) Involved 3 months (blue) versus 6 months (orange); no significant differences were present. (D) Uninvolved 3 months (blue) versus 6 months (orange); no significant differences were present. BW, body weight; HT, height

3.4 KEFs

Interlimb differences were not significantly different between time points and no limb-by-time interaction occurred (Figure 7). Significant differences were present between limbs at 3 months (3%–34%, p < 0.001; 89%– 100%, p = 0.01; Figure 8A), and approached significance at 6 months (Figure 8B). The involved limb's KEFs significantly increased from 3 to 6 months (9%–25%, p = 0.001; 95%–100%, p = 0.038; Figure 8C). There were no statistical differences between the uninvolved limb at 3 and 6 months (Figure 8D).



Figure 7 (A: top) 3 (blue) and 6 (orange) month knee extensor forces for the involved (dashed line) and uninvolved (solid line) limbs throughout stance. (A: bottom) Statistical parametric mapping (SPM) Limb × Time repeated measures analysis of variance *F*-statistic over 100% of stance. The red dashed line indicates the critical *F*-value (F = 9.80). No limb-by-time interaction was seen. (B: top) Interlimb differences at 3 and 6 months. These differences decreased from 3 to 6 months but were not significant. (B: bottom) Two-tailed paired Student's *t*-test using SPM for ILD at 3 and 6 months. The red dashed line indicates the critical *t*-value ($\alpha = 0.05$). BW, body weight



Figure 8 The top part of each subfigure shows the knee extensor forces (KEFs) through 100% of stance \pm 1 standard deviation (shaded regions). The lower portion displays a two-tailed paired Student's *t*-test using statistical parametric mapping (SPM). The red dashed line indicates the critical *t*-value (α = 0.05). (A) Involved (dashed line) versus uninvolved (solid line) KEFs 3 months after anterior cruciate ligament reconstruction (ACLR); significant differences were present from 3% to 34% and 89% to 100% of stance. (B) Involved (dashed line)

versus uninvolved (solid line) KEFs 6 months after ACLR; no significant differences were seen. (C) Involved 3 months (blue) versus 6 months (orange); significant differences were seen from 9% to 25% and 95% to 100% of stance. (D) Uninvolved 3 months (blue) versus 6 months (orange); no significant differences were present. BW, body weight

3.5 MCF

There was no limb-by-time interaction for MCF, nor was there a significant change in ILD over time (Figure 9). The medial compartment of the involved limb was significantly underloaded compared to the uninvolved limb at 3 months (12%-20%, p = 0.019; Figure **10A**). While underloading was still present at 6 months, it was no longer statistically significant (Figure **10B**). The reduction in MCF interlimb difference from 3 to 6 months appears to be driven by changes in the involved limb over time, as the involved limb's MCF increased from 3 to 6 months (Figure **10C**) while the uninvolved limb's MCF stayed relativity consistent (Figure **10D**).



Figure 9 (A) 3 (blue) and 6 (orange) month medial compartment forces for the involved (dashed line) and uninvolved (solid line) limbs throughout stance. Participants underloaded the involved limb at both time points during weight acceptance (vs. uninvolved limb), however, involved limb loading did increase from 3 to 6 months. (A: bottom) Statistical parametric mapping (SPM) Limb × Time repeated measures analysis of variance *F*-statistic over 100% of stance. The red dashed line indicates the critical *F*-value (F = 9.91). No limb-by-time interaction was seen. (B: top) Interlimb differences at 3 and 6 months, no significant differences were present. (B: bottom) Two-tailed paired Student's *t*-test using SPM for ILD at 3 and 6 months. The red dashed line indicates the critical *t*-value ($\alpha = 0.05$). BW, body weight



Figure 10The top part of each subfigure shows the medial compartment force (MCF) through 100% of stance \pm 1 standard deviation (shaded regions). The lower portion displays a two-tailed paired Student's *t*-test using statistical parametric mapping (SPM). The red dashed line indicates the critical *t*-value (α = 0.05). (A) Involved (dashed line) versus uninvolved (solid line) MCFs 3 months after anterior cruciate ligament reconstruction (ACLR); significant differences were present from 12% to 20% of stance. (B) Involved (dashed line) versus uninvolved (solid line) MCFs 6 months after ACLR; no significant differences were seen. (C) Involved 3 months (blue) versus 6 months (orange); no significant differences were present. BW, body weight

4 DISCUSSION

Our first hypothesis was partially supported; asymmetries in KFA and KFM were present at both time points. Asymmetries in KEF and MCF were present only at 3 months, while no asymmetries were found for KAM

regardless of time point. Our second hypothesis, that asymmetries would be greater at 3 months than 6 months, was also partially supported. Descriptively, interlimb asymmetries were greater at 3 months (vs. 6 months) for all our variables of interest except for KAM. However, this was only statistically supported in KFA and KFM, in which interlimb differences improved over time but were still present at the 6-month time point. Gait mechanics in the uninvolved limb stayed relatively consistent between 3 and 6 months, while the involved limb's mechanics trended towards that of the uninvolved limb over time. This pattern indicates that changes in mechanics early after ACLR primarily occur within the involved limb. The data presented here add to the timeline of how gait adapts early after ACLR. Understanding how gait alterations progress in the early months after surgery, when interventions may be most effective, may help inform the design of postoperative treatments aimed at mitigating altered biomechanics that are associated with the early onset of OA.

One of the most unique aspects of this study was the use of SPM to assess biomechanical asymmetries, and their changes, over stance phase. Recent work using SPM has highlighted the importance of considering the entire time-dependent data set rather than using discrete points. A study performed by Pataky et al.⁴⁶ compared SPM to scalar extraction by re-analyzing biomechanical data sets that had been published using traditional OD statistical analyses. These two analysis techniques produced conflicting statistical conclusions. Pataky concluded that discrete analyses may suffer from type I and type II errors as they fail to consider the entire measurement domain and ignore covariance among vector components. The utilization of SPM reduces the chance of these two sources of biases by performing hypothesis tests that consider the whole time series.^{45, 46} Thus, the use of SPM in this study, rather than traditionally used discrete values, reduces the likelihood of producing biased results.

4.1 KFA

Previous studies have reported smaller peak KFAs and peak KEAs in the involved limb (vs. uninvolved and healthy controls) 3 and 6 months after ACLR.^{5-9, 12} Our data align well with these findings showing significant differences between limbs at 3 and 6 months around the peaks of KFA during stance. ILDs were present during weight acceptance into midstance and terminal stance at both time points. While the magnitude of interlimb difference decreased from 3 to 6 months during both these phases of stance, they only significantly decreased during terminal stance. Individuals who demonstrate smaller KFAs typically exhibit quadriceps weakness.²⁴ While quadriceps strength was not collected in this study, we did see an increase in the involved limb's KEFs during weight acceptance into midstance from 3 to 6 months. However, it is unclear if this is driven by changes in neuromuscular activation patterns or increases in strength. Regardless, these increase in KEFs may explain the increases in KFA between these time points.

A reduced KFA after ACLR is of concern as this may result in load being applied to regions of cartilage that are illsuited to the new loading environment.²⁹ From 0° to 30° of flexion, the point of contact within the medial compartment shifts posteriorly as KFA increases.⁶⁰⁻⁶² This means that individuals who exhibit a reduction in KFA may load more anterior regions of cartilage, which are normally thinner and less capable of load bearing.⁶²⁻ ⁶⁴ Stress alterations in these newly loaded areas could be initiating irreversible cartilage damage.⁶⁴ The involved limb's peak KFA tends to increase up to 1 year following ACLR, after which no differences between limbs have been reported.^{8, 26} A new concern arises when the point of contact within the joint now moves posteriorly as these flexion angles increase, as this region of cartilage may have experienced lower loads and stresses since ACLR.^{29, 62, 65} During this period of relative unloading, the cartilage is at risk of being altered to resemble nonweight bearing cartilage, potentially leaving the tissue unable to withstand the return to preinjury loads.^{64, 65} Therefore, it may not only be the reduction of KFA after ACLR that leads to irreversible cartilage damage but also the recovery of range of motion over this 1-year timeline. Further studies are warranted to explore this hypothesis and to identify what is considered a clinically meaningful change in KFA over the entire stance phase.

4.2 KFM

KFM showed ILDs at both 3 and 6 months however these ILDs significantly decreased by the 6-month time point. The decrease in interlimb difference from 3 to 6 months is driven by a significant increase in the involved limb's KFM. Asymmetries have been reported to persist in peak KFM up to 2 years after surgery^{14, 17, 20} and are partly attributed to insufficient quadriceps strength.^{6, 24, 66} Experiencing lower KFM after ACLR may also be attributed to lack of confidence, as assessed by patient-reported outcomes, in the individual's knee.⁶⁷ Future work looking at patient-reported outcomes could help clarify if kinesiophobia is playing a role in these changes.

While decreases in interlimb difference are seen in these data, the involved limb is still experiencing significantly lower KFMs during weight acceptance into midstance at 6 months. A recently published study by our group using the same cohort found an association between lower involved limb (vs. uninvolved) KFMs and quantitative magnetic resonance imaging (MRI) values indicative of cartilage degradation 3 months after ACLR.⁶⁸ This agrees with reports that healthy individuals who walked with higher peak KFM had thicker (and thus healthier) cartilage.⁶⁹ However, conflicting evidence does exist as Teng et al.⁷⁰ found that higher KFMs 6 months after ACLR were associated with worsening of joint cartilage (as assessed via quantitative MRI measures).⁷⁰ It remains unclear if regaining symmetry in KFM from 3 to 6 months after ACLR will help preserve healthy knee cartilage, or if these adaptations may actually spur changes in the cartilage's biochemical health.

4.3 KAM

KAM did not show any significant differences between limbs at either time point. These data align well with previous studies that have found no difference in peak KAM between limbs at 6 months²² and 1 year¹⁵ after ACLR. However conflicting evidence suggesting lower peak KAM during this time also exists.^{15, 20, 71} In individuals with medial compartment knee OA, increases in peak KAM have been associated with increases in OA severity.^{26, 72} This association, in conjunction with the results seen here, may suggest that altered KAM is a result of OA rather than an initiating factor; however, future work is needed to explore this idea.

4.4 KEFs

There were significant differences between limbs in KEFs during weight acceptance into midstance at 3 months. These differences decreased from 3 to 6 months as the involved limb's KEFs significantly increased. While there were no statistical differences between limbs at 6 months, it should be noted that no significant changes in interlimb differences occurred from 3 to 6 months. This is not necessarily surprising as there is a high degree of variability in KEFs at 6 months; likely reflective of the large variability in ability to regain quadriceps strength early after surgery.⁷³ A previous study from our lab assessing a different cohort reported KEF between 2 and 3 BW at peak MCF which align well with the results of the current study.⁵⁶

Quadriceps weakness after ACLR is common in the involved limb and has been linked to alterations in gait.^{74, 75} Individuals who were classified as having weak quadriceps were shown to have similar gait patterns to individuals who were ACL deficient, while those classified as having strong quadriceps were similar to healthy controls.²⁴ While it cannot be determined if differences in extensor forces reported here are due to muscle strength or how the muscle is being activated, these data suggest that regaining symmetric quadriceps forces could be essential to return to preinjury gait patterns. However, recent evidence from a separate cohort indicates that improving quadriceps strength alone is not sufficient to restore symmetrical gait mechanics.³⁴

4.5 MCF

The magnitude, peak values (~2–3 BW), and shape of MCF curves in this study align well with previous studies utilizing the same model^{15, 44, 76} and a study that reported values from instrumented knee implants.⁷⁷ We found significant asymmetries in MCFs at 3 months, but not 6 months. These results contradict previous findings from our lab that reported lesser loading in the involved limb at 6 months after ACLR.¹⁵ These findings highlight the

importance of using EMG-driven models to assess joint loading as we saw different "loading" patterns when assessing KAM (no differences between limbs) and KFM (differences at 3 and 6 months) when compared to the MCF.

It is still unclear how changes in loading magnitude and distribution affect the health of the cartilage over time. Since cartilage is conditioned for specific loading environments,²⁹ the combination of changes in load and altered gait patterns may cause excessive loading in regions of cartilage that were once considered nonloadbearing.⁶² A study by Kaiser et al.⁷⁸ provided evidence of this by using a combination of dynamic and quantitative MRI to assess joint contact and cartilage biochemical health. They found that reconstructed knees exhibited increased contact areas along the medial spine of the medial tibial plateau and exhibited quantitative MRI values that are indicative of early cartilage degeneration in this area when compared to the contralateral limb and healthy controls.

4.6 Limitations and future work

There are several limitations that should be considered when interpreting the results of this study. First, no strength measurements were performed. While we can estimate the muscle forces exerted throughout gait, no conclusions can be drawn about how muscular strength deficits progressed in the early months after surgery and how they relate to changes in knee mechanics. Another limitation is that we were not able to control for participants' postoperative rehabilitation and graft types used during surgery. Participants were recruited from multiple clinics from the surrounding area and therefore may have undergone different rehabilitation protocols. Similarly, participants underwent their ACL reconstructive surgery from a variety of surgeons who used different graft types and surgical techniques. While controlling these measures would be ideal, this would limit the generalizability of this study to the broader ACLR population. This study excluded individuals who required a meniscal repair due to the extended nonweight-bearing period that is required after this procedure; however, individuals who received a meniscectomy are not required to remain nonweight bearing for an extended time due to the procedure and therefore were eligible for this study. It is unlikely that all the participants included in this study will develop OA. Future work will examine the effect early changes in gait mechanics have on long-term cartilage health.

While SPM has been shown to be a useful tool for analyzing biomechanical data it is not without limitations as a statistical analysis technique. Biomechanical curves may require registration due to data misalignment. For this study, we normalized our curves to 100% of stance, which helped with data alignment. However, applying nonlinear registration may also be a helpful approach to mitigating misalignment of data and should be investigated. Another limitation is that significance does not necessarily indicate meaningful differences. Previous studies have reported clinically meaningful differences at discrete points during gait,^{26, 79} but none currently exist for continuous data analysis. Future work should establish these thresholds for SPM. Finally, no power analysis was performed for the current study. Since the data for this study is a subset of data from a larger cohort, if a power analysis were performed it would be classified as a postexperimental power analysis, which has been shown to be an inappropriate test for power.^{80, 81}

5 CONCLUSION

In this study, we utilized SPM to assess how gait adapts from 3 to 6 months after ACLR. We found significant asymmetries between limbs in KFA, KFM, KEF, and MCF 3 months after ACLR but by 6 months KEF and MCF were no longer significantly different. While differences between limbs were still present for KFA and KFM, these asymmetries had significantly decreased by 6 months. These early time points after surgery may be the ideal period for interventions to develop a healthy gait pattern, since abnormal gait biomechanics as early as 6 months after ACLR is linked to the development of posttraumatic OA.^{15, 31, 35, 82}

The use of discrete values to analyze gait after ACLR underutilizes the wealth of data that is collected during gait analyses. Through the use of SPM to assess the entire gait cycle we can paint a more holistic picture of alterations in gait after ACLR. This study expands upon the existing literature which has focused on discrete values to understand aberrations in gait mechanics. Altogether, this study adds to our understanding of how biomechanical alterations are changing over stance phase during the early months after surgery. These results may be used to help inform the design of future studies investigating the pathogenesis of OA and may ultimately be useful in the design of early gait interventions aimed at mitigating the development of the disease.

ACKNOWLEDGMENTS

Funding was provided by the National Institutes of Health (NIH) including Eunice Kennedy Shriver National Institute of Child Health and Human Development: R01-HD087459, F30 HD096830, and F32 AG066274. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Thank you to Martha Callahan, Jennifer Marmon, and the Delaware Rehabilitation Institute Clinical Research Core for assistance with subject recruitment and retention, and Bryn Bonner for her assistance with data processing.

AUTHOR CONTRIBUTIONS

Kelsey Neal contributed to research design, data acquisition, data analysis, data interpretation, and manuscript drafting. Jack R. Williams, Abdulmajeed Alfayyadh, Jacob J. Capin, and Ashutosh Khandha contributed to data acquisition, data analysis, data interpretation, and critical review of the manuscript. Kurt Manal contributed to data interpretation and critical review of the manuscript. Lynn Snyder-Mackler and Thomas S. Buchanan contributed to research design, funding acquisition, data interpretation, and critical review. All authors have read and approved the manuscript before submission.

References

- 1 Kiapour A, Kiapour AM, Kaul V, et al. Finite element model of the knee for investigation of injury mechanisms: development and validation. *J Biomech Eng*. 2014; **136**(1):011002.
- 2 Mall NA, Chalmers PN, Moric M, et al. Incidence and trends of anterior cruciate ligament reconstruction in the United States. *Am J Sports Med.* 2014; **42**(10): 2363-2370.
- 3 Herzog MM, Marshall SW, Lund JL, Pate V, Mack CD, Spang JT. Trends in incidence of ACL reconstruction and concomitant procedures among commercially insured individuals in the United States, 2002–2014. *Sports Health*. 2018; **10**(6): 523-531.
- 4 White K, Logerstedt D, Snyder-Mackler L. Gait asymmetries persist 1 year after anterior cruciate ligament reconstruction. *Orthop J Sport Med*. 2013; **1**(2).
- 5 Di Stasi SL, Logerstedt D, Gardinier ES, Snyder-Mackler L. Gait patterns differ between ACL-reconstructed athletes who pass return-to-sport criteria and those who fail. *Am J Sports Med.* 2013; **41**(6): 1310- 1318.
- 6 Capin JJ, Zarzycki R, Ito N, et al. Gait mechanics in women of the ACL-SPORTS randomized control trial: interlimb symmetry improves over time regardless of treatment group. J Orthop Res. 2019; 37(8): 1743- 1753.
- 7 Capin JJ, Khandha A, Zarzycki R, et al. Gait mechanics and tibiofemoral loading in men of the ACL-SPORTS randomized control trial. *J Orthop Res.* 2018; **36**(9): 2364- 2372.
- 8 Hart HF, Culvenor AG, Collins NJ, et al. Knee kinematics and joint moments during gait following anterior cruciate ligament reconstruction: a systematic review and meta-analysis. *Br J Sports Med*. 2016; **50**(10): 597-612.
- 9 Sigward SM, Lin P, Pratt K. Knee loading asymmetries during gait and running in early rehabilitation following anterior cruciate ligament reconstruction: a longitudinal study. *Clin Biomech*. 2016; **32**: 249- 254.
- 10 Lin PE, Sigward SM. Contributors to knee loading deficits during gait in individuals following anterior cruciate ligament reconstruction. *Gait Posture*. 2018; **66**: 83- 87.

- 11 Ektas N, Scholes C, Kulaga S, Kirwan G, Lee B, Bell C. Recovery of knee extension and incidence of extension deficits following anterior cruciate ligament injury and treatment: a systematic review protocol. *J Orthop Surg Res.* 2019; **14**(1): 1-7.
- 12 Shabani B, Bytyqi D, Lustig S, et al. Gait knee kinematics after ACL reconstruction: 3D assessment. *Int Orthop.* **39**(6), 2015: 1187- 1193.
- 13 Hughes-Oliver CN, Harrison KA, Williams DSSBB, Queen RM. Statistical parametric mapping as a measure of differences between limbs: applications to clinical populations. *J Appl Biomech*. 2019; **35**(6): 377-387.
- 14 Hooper DM, Morrissey MC, Drechsler WI, Clark NC, Coutts FJ, McAuliffe TB. Gait analysis 6 and 12 months after anterior cruciate ligament reconstruction surgery. *Clin Orthop Relat Res.* 2002; (403): 168- 178.
- 15 Wellsandt E, Gardinier ES, Manal K, Axe MJ, Buchanan TS, Snyder-Mackler L. Decreased knee joint loading associated with early knee osteoarthritis after anterior cruciate ligament injury. *Am J Sport Med*. 2016; **44**(1): 143- 151.
- 16 Zabala ME, Favre J, Scanlan SF, Donahue J, Andriacchi TP. Three-dimensional knee moments of ACL reconstructed and control subjects during gait, stair ascent, and stair descent. *J Biomech*. 2013; **46**(3): 515- 520.
- 17 Roewer BD, Di Stasi SL, Snyder-Mackler L. Quadriceps strength and weight acceptance strategies continue to improve two years after anterior cruciate ligament reconstruction. *J Biomech*. 2011; **44**(10): 1948- 1953.
- 18 Webster KE, Feller JA. The knee adduction moment in hamstring and patellar tendon anterior cruciate ligament reconstructed knees. *Knee Surg Sports Traumatol Arthrosc*. 2012; **20**(11): 2214- 2219.
- 19 Webster KE, Wittwer JE, O'Brien J, Feller JA. Gait patterns after anterior cruciate ligament reconstruction are related to graft type. *Am J Sports Med.* 2005; **33**(2): 247-254.
- 20 Davis-Wilson HC, Pfeiffer SJ, Johnston CD. Bilateral gait 6 and 12 months post-anterior cruciate ligament reconstruction compared with controls. *Med Sci Sports Exerc*. 2020; **52**(4): 785-794.
- 21 Patterson MR, Delahunt E, Caulfield B. Peak knee adduction moment during gait in anterior cruciate ligament reconstructed females. *Clin Biomech*. 2014; **29**(2): 138- 142.
- 22 Varma RK, Duffell LD, Nathwani D, McGregor AH. Knee moments of anterior cruciate ligament reconstructed and control participants during normal and inclined walking. *BMJ Open*. 2014; **4**(6):e004753.
- 23 Shi H, Huang H, Ren S, et al. The relationship between quadriceps strength asymmetry and knee biomechanics asymmetry during walking in individuals with anterior cruciate ligament reconstruction. *Gait Posture*. 2019; **73**: 74-79.
- 24 Lewek M, Rudolph K, Axe M, Snyder-Mackler L. The effect of insufficient quadriceps strength on gait after anterior cruciate ligament reconstruction. *Clin Biomech*. 2002; **17**(1): 56-63.
- 25 Paterno MV, Schmitt LC, Ford KR, et al. Biomechanical measures during landing and postural stability predict second anterior cruciate ligament injury after anterior cruciate ligament reconstruction and return to sport. *Am J Sports Med*. 2010; **38**(10): 1968- 1978.
- 26 Khandha A, Manal K, Wellsandt E, Capin J, Snyder-Mackler L, Buchanan TS. Gait mechanics in those with/without medial compartment knee osteoarthritis 5 years after anterior cruciate ligament reconstruction. *J Orthop Res.* 2017; **35**(3): 625- 633.
- 27 Slater LV, Hart JM, Kelly AR, Kuenze CM. Progressive changes in walking kinematics and kinetics after anterior cruciate ligament injury and reconstruction: a review and meta-Analysis. *J Athl Train*. 2017; **52**(9): 847-860.
- 28 Andriacchi TP, Mundermann A, Smith RL, et al. A framework for the in vivo pathomechanics of osteoarthritis at the knee: 2nd special edition on musculoskeletal bioengineering. *Ann Biomed Eng.* 2004; **51**(1): 31- 39.
- 29 Andriacchi TP, Koo S, Scanlan SF. Gait mechanics influence healthy cartilage morphology and osteoarthritis of the knee. J Bone Joint Surg Am. 2009; **91**(suppl 1): 95-101.
- 30 Butler RJ, Minick KI, Ferber R, Underwood F. Gait mechanics after ACL reconstruction: implications for the early onset of knee osteoarthritis. *Br J Sports Med.* 2009; **43**(5): 366- 370.
- 31 Shimizu T, Samaan MA, Tanaka MS, et al. Abnormal biomechanics at 6 months are associated with cartilage degeneration at 3 years after anterior cruciate ligament reconstruction. *Arthrosc.* 2019; **35**(2): 511- 520.

- 32 Paterno MV, Ford KR, Myer GD, Heyl R, Hewett TE. Limb asymmetries in landing and jumping 2 years following anterior cruciate ligament reconstruction. *Clin J Sport Med*. 2007; **17**(4): 258- 262.
- 33 Chandra A, Kar O, Wu K-C, et al. Prognosis of anterior cruciate ligament reconstruction: a data-driven approach. *Proc Math Phys Eng Sci.* 2015; **471**(2176):20140526.
- 34 Arhos EK, Capin JJ, Buchanan TS, Snyder-Mackler L. Quadriceps strength symmetry does not modify gait mechanics after anterior cruciate ligament reconstruction, rehabilitation, and return-to-sport training. *Am J Sports Med*. 2021; **49**(2): 417- 425.
- 35 Pietrosimone B, Blackburn JT, Harkey MS, et al. Greater mechanical loading during walking is associated with less collagen turnover in individuals with anterior cruciate ligament reconstruction. *Am J Sports Med*. 2016; **44**(2): 425- 432.
- 36 Zhao D, Banks SA, Mitchell KH, D'Lima DD, Colwell CW, Fregly BJ. Correlation between the knee adduction torque and medical contact force for a variety of gait patterns. *J Orthop Res.* 2007; **25**(6): 789-797.
- 37 Duffell LD, Southgate DFL, Gulati V, McGregor AH. Balance and gait adaptations in patients with early knee osteoarthritis. *Gait Posture*. 2014; **39**(4): 1057-1061.
- 38 Lewek MD, Rudolph KS, Snyder-Mackler L. Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. *Osteoarthr Cartil*. 2004; **12**(9): 745-751.
- 39 Mündermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. *Arthritis Rheum*. 2005; **52**(9): 2835- 2844.
- 40 Foroughi N, Smith R, Vanwanseele B. The association of external knee adduction moment with biomechanical variables in osteoarthritis: a systematic review. *Knee*. 2009; **16**(5): 303- 309.
- 41 Khandha A, Manal K, Capin J, et al. High muscle co-contraction does not result in high joint forces during gait in anterior cruciate ligament deficient knees. *J Orthop Res.* 2019; **37**(1): 104- 112.
- 42 Blackburn T, Pietrosimone B, Goodwin JS, Johnston C, Spang JT. Co-activation during gait following anterior cruciate ligament reconstruction. *Clin Biomech*. 2019; **67**: 153-159.
- 43 Buchanan TS, Lloyd DG, Manal K, Besier TF. Neuromusculoskeletal modeling: estimation of forces and joint moments and movements from measurements of neural command. *J Appl Biomech*. 2006; **20**(4): 367-395.
- 44 Winby CR, Lloyd DG, Besier TF, Kirk TB. Muscle and external load contribution to knee joint contact loads during normal gait. *J Biomech*. 2009; **42**(14): 2294- 2300.
- 45 Pataky TC, Vanrenterghem J, Robinson MA. The probability of false positives in zero-dimensional analyses of one-dimensional kinematic, force and EMG trajectories. *J Biomech*. 2016; **49**(9): 1468- 1476.
- 46 Pataky TC, Robinson MA, Vanrenterghem J. Vector field statistical analysis of kinematic and force trajectories. *J Biomech*. 2013; **46**(14): 2394- 2401.
- 47 Pataky TC. Generalized *n*-dimensional biomechanical field analysis using statistical parametric mapping. *J Biomech*. 2010; **43**(10): 1976- 1982.
- 48 Hasofer AM. Upcrossings of random fields. *Adv Appl Probab*. 1978; **10**: 14.
- 49 Adler RJ, Hasofer AM. Level crossings for random fields. *Ann Probab.* 1976; **4**(1): 1- 12. <u>doi:10.1214/aop/1176996176</u>
- 50 Friston KJ, Holmes AP, Poline JB, et al. Analysis of fMRI time-series revisited. *Neuroimage*. 1995; **2**(1): 45-53.
- 51 Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RSJ. Spatial registration and normalization of images. *Hum Brain*

Mapp. 1995; 3(3): 165–189. https://doi.org/10.1002/hbm.460030303

- 52 Li W, Kornak J, Harris T, et al. Identify fracture-critical regions inside the proximal femur using statistical parametric mapping. *Bone*. 2009; **44**(4): 596-602.
- 53 Pataky TC, Goulermas JY. Pedobarographic statistical parametric mapping (pSPM): a pixel-level approach to foot pressure image analysis. *J Biomech*. 2008; **41**(10): 2136- 2143.
- 54 Gardinier ES, Manal K, Buchanan TS, Snyder-Mackler L. Gait and neuromuscular asymmetries after acute anterior cruciate ligament rupture. *Med Sci Sport Exerc*. 2012; **44**(8): 1490- 1496.

- 55 Manal K, Buchanan TS. An electromyogram-driven musculoskeletal model of the knee to predict in vivo joint contact forces during normal and novel gait patterns. *J Biomech Eng*. 2013; **135**(2):021014.
- 56 Wellsandt E, Khandha A, Capin J, et al. Operative and nonoperative management of anterior cruciate ligament injury: differences in gait biomechanics at 5 years. *J Orthop Res.* **38**(12), 2020: 2675- 2684.
- 57 Pataky TC. One-dimensional statistical parametric mapping in Python. *Comput Methods Biomech Biomed Engin.* 2012; **15**(3): 295- 301.
- 58 D'agostino RB, Belanger A. A suggestion for using powerful and informative tests of normality. *Amer Statist*. 1990; **44**(4): 316- 321.
- 59 Pataky TC, Vanrenterghem J, Robinson MA. Zero- vs. one-dimensional, parametric vs. non-parametric, and confidence interval vs. hypothesis testing procedures in one-dimensional biomechanical trajectory analysis. *J Biomech*. 2015; **48**(7): 1277- 1285.
- 60 Wretenberg P, Ramsey DK, Németh G. Tibiofemoral contact points relative to flexion angle measured with MRI. *Clin Biomech*. 2002; **17**(6): 477- 485.
- 61 Masouros SD, Bull AMJ, Amis AA. (i) Biomechanics of the knee joint. *Orthop Trauma*. 2010; **24**(2): 84–91. <u>https://doi.org/10.1016/j.mporth.2010.03.005</u>
- 62 Scanlan SF, Favre J, Andriacchi TP. The relationship between peak knee extension at heel-strike of walking and the location of thickest femoral cartilage in ACL reconstructed and healthy contralateral knees. J Biomech. 2013; **46**(5): 849- 854.
- 63 Koo S, Gold GE, Andriacchi TP. Considerations in measuring cartilage thickness using MRI: factors influencing reproducibility and accuracy. *Osteoarthr Cartil*. 2005; **13**(9): 782-789.
- 64 Andriacchi TP, Mündermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. *Ann Biomed Eng*. 2004; **32**(3): 447- 457.
- 65 Chu CR, Andriacchi TP. Dance between biology, mechanics, and structure: a systems-based approach to developing osteoarthritis prevention strategies. *J Orthop Res.* **33**(7), 2015: 939- 947.
- 66 Capin JJ, Zarzycki R, Arundale A, Cummer K, Snyder-Mackler L. Report of the primary outcomes for gait mechanics in men of the ACL-SPORTS trial: secondary prevention with and without perturbation training does not restore gait symmetry in men 1 or 2 years after ACL reconstruction. *Clin Orthop Relat Res.* 2017; **475**(10): 2513- 2522.
- 67 Perraton LG, Hall M, Clark RA, et al. Poor knee function after ACL reconstruction is associated with attenuated landing force and knee flexion moment during running. *Knee Surg Sports Traumatol Arthrosc.* 2018; **26**(2): 391- 398.
- 68 Williams JR, Neal K, Alfayyadh A, et al. Knee cartilage T2 relaxation times 3 months after ACL reconstruction are associated with knee gait variables linked to knee osteoarthritis. *J Orthop Res.* 2021: 1-8.
- 69 Schmitz RJ, Harrison D, Wang HM, Shultz SJ. Sagittal-plane knee moment during gait and knee cartilage thickness. *J Athl Train*. 2017; **52**(6): 560- 566.
- 70 Teng HL, Wu D, Su F, et al. Gait characteristics associated with a greater increase in medial knee cartilage T1p and T2 relaxation times in patients undergoing anterior cruciate ligament reconstruction. *Am J Sports Med*. 2017; **45**(14): 3262- 3271.
- 71 Webster KE, Feller JA, Wittwer JE. Longitudinal changes in knee joint biomechanics during level walking following anterior cruciate ligament reconstruction surgery. *Gait Posture*. 2012; **36**(2): 167-171.
- 72 Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5year cartilage changes in patients with medial knee osteoarthritis. *Osteoarthr Cartil.* 2014; **22**(11): 1833- 1839. <u>doi:10.1016/j.joca.2014.08.009</u>
- 73 Buckthorpe M, La Rosa G, Villa F Della. restoring knee extensor strength after anterior cruciate ligament reconstruction: a clinical commenTARY. *Int J Sports Phys Ther*. 2019; **14**(1): 159-172.
- 74 Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. *Rheum Dis Clin North Am*. 1999; **25**(2): 283-298.
- 75 Hart JM, Turman KA, Diduch DR, Hart JA, Miller MD. Quadriceps muscle activation and radiographic osteoarthritis following ACL revision. *Knee Surg Sports Traumatol Arthrosc*. 2011; **19**(4): 634- 640.

- 76 Gardinier ES, Di Stasi S, Manal K, Buchanan TS, Snyder-Mackler L. Knee contact force asymmetries in patients who failed return-to-sport readiness criteria 6 months after anterior cruciate ligament reconstruction. *Am J Sports Med*. 2014; **42**(12): 2917- 2925.
- 77 D'lima DD, Patil S, Steklov N, Slamin JE, Colwell CW Jr. Tibial forces measured in vivo after total knee arthroplasty. *J Arthroplasty*. 2006; **21**(2): 255-262.
- 78 Kaiser J, Vignos MF, Liu F, Kijowski R, Thelen DG. American Society of Biomechanics Clinical Biomechanics Award 2015: MRI assessments of cartilage mechanics, morphology and composition following reconstruction of the anterior cruciate ligament. *Clin Biomech*. 2016; **34**: 38- 44.
- 79 Di Stasi SL, Snyder-Mackler L. The effects of neuromuscular training on the gait patterns of ACL-deficient men and women. *Clin Biomech*. 2012; **27**(4): 360.
- 80 Zumbo BD, Hubley AM. A note on misconceptions concerning prospective and retrospective power. J R Stat Soc Ser D Stat. 1998; **47**(2): 385- 388.
- 81 Hoenig JM, Heisey DM. The abuse of power: the pervasive fallacy of power calculations for data analysis. *Am Stat.* 2001; **55**(1): 19- 24.
- 82 Saxby DJ, Bryant AL, Van Ginckel A, et al. Greater magnitude tibiofemoral contact forces are associated with reduced prevalence of osteochondral pathologies 2–3 years following anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc.* 2019; **27**(3): 707-715.