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Original Article

Neural structural alterations correlates of quadriceps muscle strength deficits in patients after anterior cruciate ligament reconstruction

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A R T I C L E I N F O

Keywords:
Anterior cruciate ligament reconstruction
Diffusion tensor imaging
Limb symmetry index
Neuroplasticity
Quadriceps muscle strength

A B S T R A C T

Background: Persistent maladaptive changes of corticospinal tract (CST) and quadriceps strength deficits exist in patients with anterior cruciate ligament reconstruction (ACLR). This study aimed to investigate the relationships between the structural alterations of CST and quadriceps muscle strength deficits in patients with ACLR.
Methods: Twenty-nine participants who had undergone unilateral ACLR (29 males; age = 32.61 ± 6.72 years) were enrolled in a cross-sectional investigation. We chose CST as a region of interest and performed diffusion tensor imaging (DTI) that measured the microstructure of white matter tracts. Maximal voluntary isometric quadriceps muscle strength was assessed using a hand-held dynamometer. Simple and partial correlation analyses were performed between the DTI outcomes and quadriceps muscle strength deficits in patients with ACLR before and after controlling for age, sex, BMI, Tegner activity score, and graft type. Sub-group analyses were also performed to investigate the relationships between the DTI outcomes of CST structure and quadriceps muscle strength deficits according to the graft type before and after controlling for age, sex, BMI, and Tegner activity score.
Results: Lower limb symmetry index (LSI) of quadriceps muscle strength was associated with a higher ratio of radial diffusivity (RD, $r = -0.379$, $p = 0.042$) in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere in ACLR patients after controlling for age, BMI, Tegner activity score and graft type. In subgroup analyses of ACLR patients with hamstring autografts, we found that higher injured quadriceps muscle strength was associated with higher axial diffusivity (AD, $r = 0.616$, $p = 0.033$) of CST structure and lower LSI of quadriceps muscle strength was associated with higher ratio of mean diffusivity (MD, $r = -0.682$, $p = 0.014$) and RD ($r = -0.759$, $p = 0.004$) in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere in ACLR patients after controlling for age, BMI, Tegner activity score.
Conclusion: Decreased integrity (higher ratio of RD) of CST microstructure in ACLR patients was significantly associated with lower quadriceps limb symmetry index, which hinted that quadriceps muscle strength deficits of injured side may be a demyelinating process of CST microstructure in ACLR.

1. Introduction

Anterior cruciate ligament (ACL) tears account for more than 50 % of all of these knee injuries in daily life and sports, and affect more than 120000 people in the United States each year, with annual costs averaging $1 billion.[11] Individuals with ACL tears generally restore the mechanical stability and function of the injured knee joint through anterior cruciate ligament reconstruction (ACLR).[28] However, functional deficits around the knee joint, including injured quadriceps muscle strength and balance deficits, may cause re-rupture during joint movement after surgeries and standardized rehabilitation.[9] Therefore, it

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Abbreviations

ACL	Anterior cruciate ligament
ACLR	Anterior cruciate ligament reconstruction
CNS	Central nervous system
CST	Corticospinal tract
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
FA	Fractional anisotropy
MD	Mean diffusivity
AD	Axial diffusivity
RD	Radial diffusivity
BMI	Body mass index
VAS	Visual analogue scale
LSI	Limb symmetry index.

is essential for clinical workers and rehabilitation therapists to conduct in-depth investigations of the underlying mechanisms of the above functional deficits.

The persistence of quadriceps strength deficits was one of the most common functional deficits to assess the prognostic function in patients with ACLR. Previous studies reported that quadriceps strength deficits were evident even at the end of the initial rehabilitation period, and may persist for more than 20 years in patients with ACLR.[8,30] Quadriceps strength deficits in ACLR patients show small to large deficits in quadriceps cross-sectional area and volume.[5] Meanwhile, Quadriceps strength deficits in patients with ACLR are manifested not only in morphological changes but also in short-term and long-term central nervous system (CNS) alterations with decreased excitability of corticospinal pathways.[29] Therefore, it is beneficial for new ideas and approaches for the future management of patients with ACLR by exploring the associations between quadriceps strength deficits and CNS changes.

The corticospinal tract (CST) is essential for somatosensory and motor function, including quadriceps contractions of lower limbs.[13] Kapreli et al. firstly proposed that ACL rupture would lead to the development of brain functional and structural changes.[12] Then Needle et al. indicated that ACL rupture may induce neuromechanical alterations and considered that the impairment of the corticospinal pathway is involved in the neural origins of muscular deficits following ACL injuries.[21] Based upon the above hypothesis, recent electrophysiological studies have observed that increased corticospinal excitability relates to increased quadriceps strength in patients after ACLR, which indicated that the function of the corticospinal pathway was associated with quadriceps strength.[14,15] Meanwhile, diffusion weighted imaging (DWI) has been applied in ACLR studies to determine white matter fiber tracts via volume and the direction of water diffusion.[21] Lepley et al. initially attempted to study CST by diffusion tensor imaging (DTI) analysis; they reported a significant difference in structural white matter anisotropy and diffusivity outcomes, including fractional anisotropy (FA) and mean diffusivity (MD), between the CST of bilateral hemispheres following ACLR, and found that greater CST excitability was associated with larger CST volume.[16] The FA is the most widely used measure of anisotropy, corresponding to the degree of anisotropic diffusion and ranges from 0 (isotropic diffusion) to 1 (anisotropic diffusion), with higher FA representing the better neural integrity in white matter fiber tracts. The MD is calculated by the mean of the water diffusion in three axes, with higher MD reflecting more increased diffusion of water molecules in white matter fiber tracts. However, the relationships between the CST structural abnormalities and quadriceps strength deficits following ACLR are rarely explored and previous studies did not investigate whether the choice of graft type would influence the relationships between the CST structural abnormalities and quadriceps strength deficits.

Therefore, identifying the associations between the existing abnormalities in the CST microstructure and quadriceps strength deficits in patients with ACLR was imperative. We also utilized advanced neuroimaging, diffusion tensor imaging (DTI), to characterize the structure of CST following ACLR. Specifically, the purpose of this study was to determine the relationships between the structural features of the CST and assessments of quadriceps muscle strength deficits measured by a hand-held dynamometer in patients with ACLR. Based on a previous study, we hypothesized that the DTI outcomes would be correlated with the quadriceps muscle strength deficits (*e.g.*, worse quadriceps muscle strength of ACLR patients, worse CST microstructure).

2. Methods

2.1. Study design

This study utilized a cross-sectional descriptive laboratory design and was performed at ** International Brain Imaging Center of ** University. All methodological protocols were approved by the Institutional Research Ethics Committee of ** Hospital Affiliated to ** University (approval number **). The report of this investigation followed the guidelines of the Strengthened Reporting of Observational Studies in Epidemiology (STROBE) statement.[32]

2.2. Sample size calculation

The r values of relationships between active motor threshold (AMT) of the corticospinal pathway excitability and maximal voluntary isometric contractions (MVIC) of the quadriceps in patients with ACLR were used to calculate the prior sample size (effect size = 0.616).[14] Due to the current study, which was the first article to investigate the relationships between CST microstructure and quadriceps strength in ACLR patients, the same parameters could not be used to calculate the power of this study and we used AMTs to indirectly power this study. A total of 24 participants was required to achieve a power of 0.95 at an alpha level of 0.05 by correlation: point biserial model using G*Power Version 3.1.[6] Therefore, to consider up to a 20 % withdrawal rate, 29 participants were finally enrolled in the local college between March 2023 and November 2023.

2.3. Recruitment of participants

All procedures were conducted following the Declaration of Helsinki, with adequate understanding, and written informed consent from the participants.[1] Twenty-nine participants who had a history of primary unilateral ACLR were recruited from ** hospital, volunteered to participate, and were enrolled in this study between March 2023 and November 2023.

Participants with ACLR were required to be at least six months status post-ACLR and did not meet the following exclusion criteria: a history of knee surgery other than undergoing any type of concurrent meniscal procedures at the time of ACLR surgery, multiple ligament ruptures, or any other lower extremity musculoskeletal injury sustained in the six months prior to the study, any history of a head injury or concussion in the previous six months, stroke, cranial surgery, cancer in the brain, migraines, a diagnosed neurological, or psychiatric disorder, medications that alter neural activity, and/or embedded intracranial metallic clips. Meanwhile, we only included the male patients in the current study.

2.4. Data acquisition

2.4.1. Demographic and clinical features

A single orthopedist conducted the subject interviews and obtained the demographic and clinical data in the same session on the same day, including age, sex, height, weight, body mass index (BMI), injured limb, visual analogue scale (VAS) scores of knee pain including the states of walking and exercising past 24 h, Lysholm knee scoring scale assessment of self-reported knee function, Tegner activity scale score, time from surgery and graft type.

The graft type of patients with ACLR included synthetics and hamstring autografts. All surgeries were performed by a senior sports medicine physician and all surgical procedures of two graft types were reported in the study of Chen T et al.[2]

2.4.2. Assessment of quadriceps muscle strength

Maximal voluntary isometric quadriceps muscle strength was assessed using a hand-held dynamometer (Commander Echo; JTECH Medical, Salt Lake City, Utah, USA), which demonstrated good to excellent intra- and interrater reliability for most measures of isometric lower limb strength be regarded as a reliable and valid instrument for muscle strength assessment in a clinical setting, with the participants sitting on a treatment table with their knee in 90^{o} flexion and their feet were off the ground.[10,19,27] An inelastic strap was secured around the treatment table under the participant, and was used to maintain the position of the hand-held dynamometer and the knee angle during each testing trial, and the hand-held dynamometer was placed on the anterior side of the participants' distal tibia, just superior to the malleoli. The participants were asked to grasp the treatment table with their hands for stabilization and extend their knees with maximal effort. Participants were asked to hold each maximal contraction for 5 s with 15 s of recovery between the contractions, and the maximum force across the trial was recorded. Participants completed the warm-up protocol, including two practice trials on both limbs to become familiarized with the movements before performing official trials. Three official trials were completed, and we normalized the average force of three trials (Newtons [N]) across the three trials to body mass (kg).[17] To randomize and avoid learning effects the right leg was always tested first. Meanwhile, the limb symmetry index (LSI) of quadriceps muscle strength was calculated and expressed as a percentage (LSI = injured/non-injured × 100).

2.4.3. Magnetic resonance imaging data acquisition and analysis

A 3.0 T Prisma scanner (Siemens, Erlangen, Germany) with a 32-channel head coil was used to acquire T1-weighted image and diffusion weighted imaging sequence. Before image processing, all images were manually checked to exclude any potential image abnormalities. The preprocessing of the diffusion data and the Region of Interest analysis followed previously validated protocols using the Functional MRI of the Brain (FMRIB) software library (FSL v5.0.9, University of Oxford, UK).[31] We calculated the individual maps of the DTI outcomes, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) based on the results of the between-limb comparison in the previous study.[16] The mean values of the bilateral/left/right sides of the CSTs were extracted from the voxel within the individual masks registered from Johns Hopkins University International Consortium for Brain Mapping DTI tracts.[33] The values of the ACLR injured limb hemisphere (*i.e.*, the left hemisphere of the right ACLR injured limb) were selected for further analysis. Meanwhile, we also calculated the ratio of diffusion tensor imaging outcomes in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere and expressed as a percentage (injured/non-injured × 100). Detailed image acquisition parameters and image processing steps are provided in Supplementary Appendix A.

2.5. Statistical analysis

All statistical analyses were performed using R, version 4.3.0 (R Foundation). (IBM, Armonk, NY, USA). Descriptive variables were calculated as the mean (standard deviation) or median (interquartile range) according to the normality of the data. The simple Pearson correlation and partial Pearson correlation (with age, BMI, and Tegner activity level scores and graft type as covariates) were performed between DTI outcomes of CST structure and quadriceps muscle strength of injured limb, and between the ratio of DTI outcomes of CST and LSI of quadriceps muscle strength. We also performed sub-group analyses to investigate the relationships between the DTI outcomes of CST structure and quadriceps muscle strength of injured limb and LSI of quadriceps muscle strength according to the graft type. The absolute values of correlation coefficients (r) were classified as weak (0–0.4), moderate (0.4–0.7), or strong (0.7–1.0).[3] All alpha levels were set at $p < 0.05$.

3. Results

3.1. Demographic and clinical features

Based on the inclusion and exclusion criteria, 29 participants with unilateral ACLR (29 males; age, 32.61 ± 6.72 years; height, 177.00 ± 5.35 cm; weight, 77.00 (72.00,81.85) kg; BMI, 24.49 (23.48,25.41) kg/m^2; Tegner activity level scores, 5.00 (4.00,6.00)) were enrolled in this study from the local community and hospitals and included in the further assessment and analyses. The VAS scores for walking and exercising were 0 (0,1.00) and 2.00 (0,3.00), respectively. The Lysholm knee scores were 90.00 (84.00,94.75). The time from surgery of ACLR patients was 21.11 ± 10.79 months in this study. The left and right sides of ACLs were injured in 11 and 18 of the 29 patients with ACLR, respectively. There were 17 patients reconstructed with synthetics and 12 patients using hamstring autografts. Detailed information on the demographic and clinical features of all participants was presented in Table 1.

3.2. The relationships between DTI outcomes and injured quadriceps muscle strength

Among the exploratory correlation analyses, no significant correlations were observed between the DTI outcomes of injured CST and injured quadriceps muscle strength in ACLR patients before controlling the age, BMI, Tegner activity score, and graft type and in subgroup analyses with p-values ranging from 0.154 to 0.887 before controlling

Table 1
The demographic and clinical features of all participants.

	ACLR (Synthetics, n = 17)	ACLR (Hamstring autografts, n = 12)	ACLR (n = 29)
Age (years, mean ± SD)	34.53 ± 6.10	29.5 ± 6.50	32.61 ± 6.72
Sex (female/male)	0/17	0/12	0/29
Height (cm, mean ± SD)	175.88 ± 4.82	178.42 ± 5.73	177.00 ± 5.35
Weight (kg, median [IQR])	77.00 (69.50,80.10)	80.00 (73.00,82.00)	77.00 (72.00,81.85)
BMI (kg/m^2, median [IQR])	24.44 (22.81,25.36)	24.69 (23.99,26.04)	24.49 (23.48,25.41)
Tegner (mean ± SD)	4.35 ± 1.50	5.42 ± 1.73	4.89 ± 1.59
VAS-1 (median [IQR])	0 (0,1.00)	0 (0,0)	0 (0,1.00)
VAS-2 (median [IQR])	2.00 (0,3.50)	2.00 (0,3.00)	2.00 (0,3.00)
Lysholm (median [IQR])	90.00 (73.00,95.00)	90.00 (85.00,91.00)	90.00 (84.00,94.75)
Injured Quadriceps strength (N/kg, mean ± SD)	3.88 ± 0.89	3.82 ± 1.08	3.83 ± 0.96
LSI of quadriceps (%, mean ± SD)	98.48 ± 14.86	98.73 ± 9.46	98.58 ± 12.70
Injured limb (Left/Right)	6/11	5/7	11/18
Time from surgery (month, mean ± SD)	19.41 ± 7.93	22.42 ± 14.27	21.11 ± 10.79

BMI, body mass index; VAS, visual analog scale; VAS-1, VAS-walking; VAS-2, VAS-exercising; LSI, limb symmetry index; SD, standard deviations; IQR, interquartile range.

the age, BMI, Tegner activity score (Fig. 1). Detailed information of r values and p values were presented in Supplementary Appendix B.

There are no significant associations between the DTI outcomes and the injured quadriceps muscle strength in ACLR patients after controlling the age, BMI, Tegner activity score, and graft type and in subgroup analyses of ACLR with synthetics after controlling the age, BMI, and Tegner activity score (Fig. 1).

In subgroup analyses of ACLR with hamstring autografts, lower injured quadriceps muscle strength was associated with lower AD ($r = 0.616$, $p = 0.033$) of CST structure in ACLR patients after controlling for the age, BMI, and Tegner activity score. However, injured quadriceps muscle strength had no significant associations with FA ($r = 0.461$, $p = 0.131$), MD ($r = 0.163$, $p = 0.612$), and RD ($r = -0.237$, $p = 0.459$) of injured CST structure and there are no associations between injured quadriceps muscle strength after controlling for the age, BMI, Tegner activity score. The results were presented in Fig. 1.

3.3. *The relationships between the ratio of DTI outcomes in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere and LSI of quadriceps muscle strength deficits*

Among the exploratory correlation analyses, we only found that lower ratio of RD ($r = -0.596$, $p = 0.041$) in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere was significantly associated with higher LSI of quadriceps muscle strength in subgroup of ACLR with hamstring autografts before controlling the age, BMI and Tegner activity score, but no significant correlations were observed between the ratio of DTI outcomes and LSI of quadriceps muscle strength in ACLR patients before controlling the age, BMI, Tegner activity score and graft type and in subgroup analyses of ACLR with synthetics before controlling the age, BMI and Tegner activity score (Fig. 2). The detailed information were presented in Supplementary Appendix C.

Lower LSI of quadriceps muscle strength was associated with a higher ratio of RD ($r = -0.379$, $p = 0.042$) in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere after controlling for the age, BMI, Tegner activity score and graft type. However, there are no significant associations between the ratio of FA ($r = 0.188$, $p = 0.328$), MD ($r = -0.339$, $p = 0.072$), and AD ($r = -0.161$, $p = 0.404$) in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere and LSI of quadriceps muscle strength deficits after controlling for the age, BMI, Tegner activity score and graft type (Fig. 2).

There are no significant associations between the ratio of DTI outcomes and the LSI of quadriceps muscle strength in subgroup analyses of ACLR with synthetics after controlling the age, BMI, and Tegner activity score. The results were shown in Fig. 2.

In subgroup analyses of ACLR with hamstring autografts, lower LSI of quadriceps muscle strength was associated with the higher ratio of MD ($r = -0.682$, $p = 0.014$) and RD ($r = -0.759$, $p = 0.004$) in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere after controlling for the age, BMI, Tegner activity score. However, injured quadriceps muscle strength had no significant associations with the ratio of FA ($r = 0.479$, $p = 0.115$) and AD ($r = -0.502$, $p = 0.096$) in bilateral CST structure after controlling for the age, BMI, Tegner activity score (Fig. 2).

4. Discussion

To the best of our knowledge, this study was the first attempt to assess the relationships between the CST microstructure in patients with ACLR and the quadriceps muscle strength deficits. We found that the decreased integrity (higher ratio of RD) in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere had a significant correlation with the lower LSI of quadriceps muscle strength (lower LSI of quadriceps, higher ratio of RD).

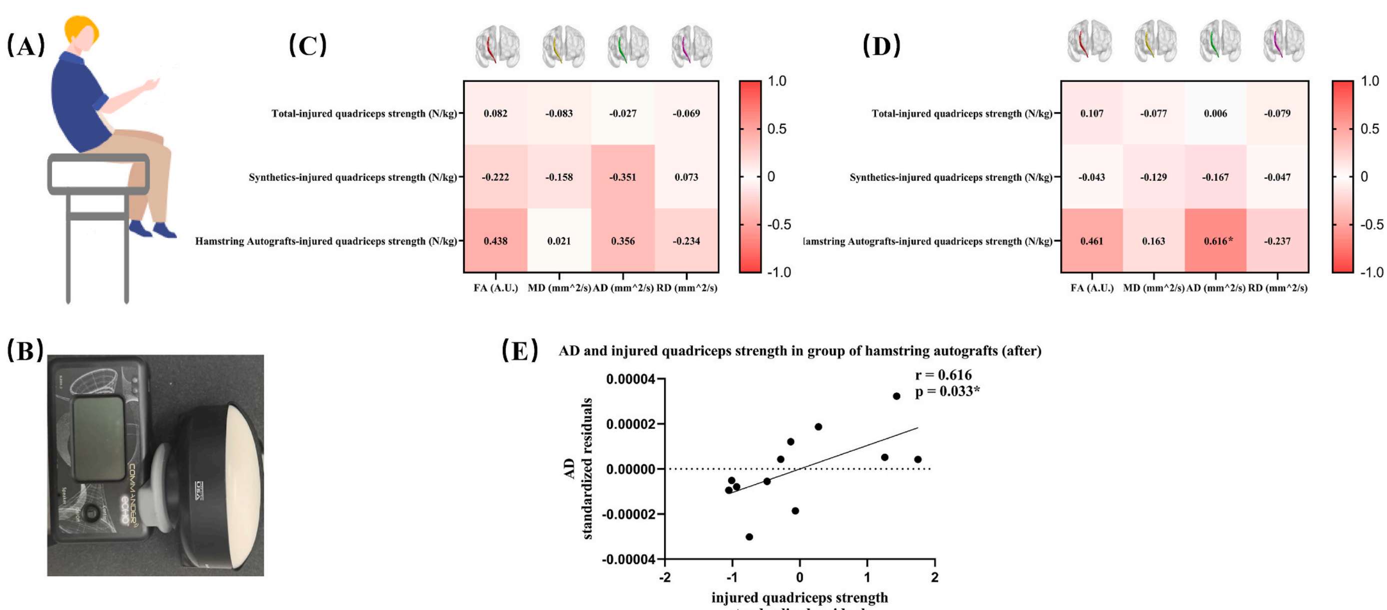

Fig. 1. The associations between CST structure and injured quadriceps strength and masks of corticospinal tracts (in red, yellow, green, and purple) on the images of DTI outcomes. (A) The position of quadriceps strength measurement. (B) The picture of the hand-held dynamometer. (C, D) The hot plots of relationships between DTI outcomes of CST structure and quadriceps strength of injured limb before (C) and after (D) controlling age, BMI, Tegner activity score, and graft type in patients with ACLR and subgroup analyses of synthetics and hamstring autografts before (C) and after (D) controlling age, BMI, Tegner activity score. (E) the scatter plots of significant correlations between the DTI outcomes of CST structure and quadriceps strength of injured limb (E). DTI, diffusion tensor imaging; CST, corticospinal tract; LSI, limb symmetry index; BMI, body mass index. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

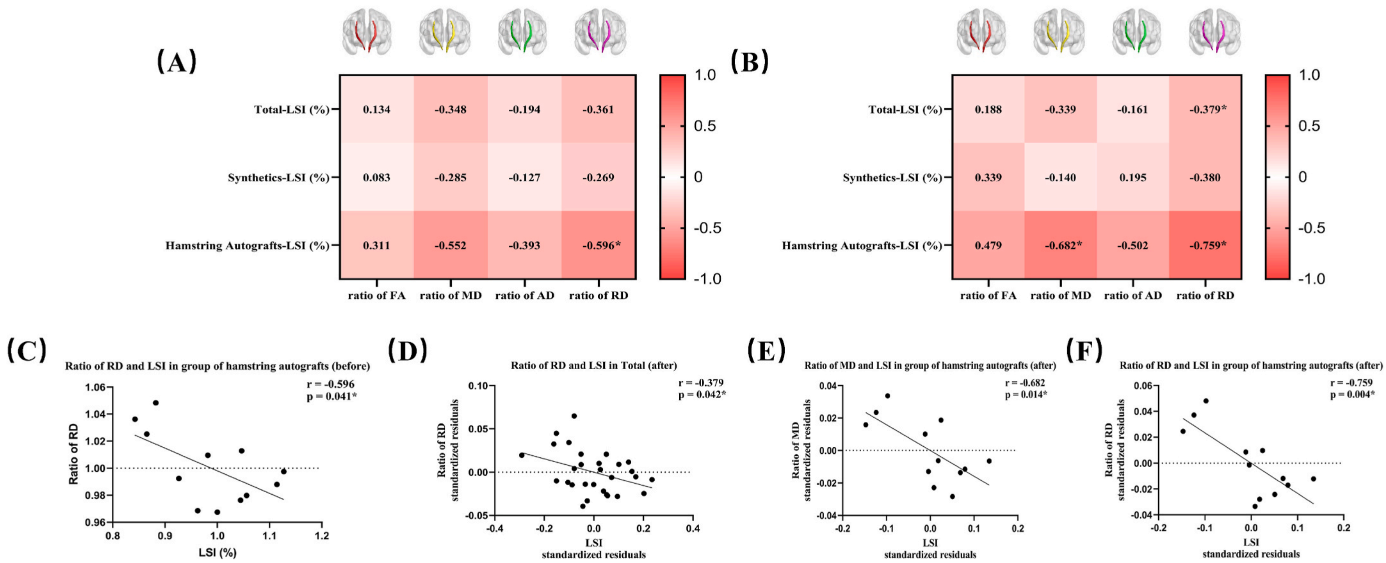

Fig. 2. The associations between the ratio of DTI outcomes in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere and LSI of quadriceps strength, and masks of corticospinal tracts (in red, yellow, green, and purple) on the images of the ratio of DTI outcomes. (A, B) The hot plots of relationships between the ratio of DTI outcomes in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere and LSI of quadriceps strength before (A) and after (B) controlling age, BMI, Tegner activity score, and graft type in patients with ACLR and subgroup analyses of synthetics and hamstring autografts before (A) and after (B) controlling age, BMI, Tegner activity score. (C, D, E, F) the scatter plots of significant correlations between the ratio of DTI outcomes in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere and LSI of quadriceps strength (C, D, E, F). DTI, diffusion tensor imaging; CST, corticospinal tract; LSI, limb symmetry index; BMI, body mass index. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4.1. Neural correlates of quadriceps muscle strength deficits in ACLR patients

It is well known that both peripheral and neural adaptations modify muscle strength in healthy people.[20] Previous studies hypothesized that disruption of sensory input due to the pain, inflammation, and loss of mechanoreceptors following ACL rupture would alter the motor output of the muscles and lead to persistent disuse and atrophy of muscles and maladaptive neuroplasticity of CNS. The CNS controls muscle contractions via spinal reflexes and supraspinal adjustment through the CST, plays multiple roles in sensory and motor performance, and is related to quadriceps strength[7,13,14,21,23] ACLR disrupts sensory input from the quadriceps, which results in reduced sensitivity to electrochemical neuronal signals, an increase in central inhibition of neurons regulating quadriceps control.[22] Previous neurophysiological studies had found that corticospinal pathway excitability was positively correlated with quadriceps strength and CST microstructure.[14,16] In this study, we also observed that maladaptive CST microstructure was associated with quadriceps strength deficits, which complemented existing research gaps.

In the current study, the DTI approach was used to quantify the overall white matter microstructure of the CST. We only observed that lower LSI of quadriceps muscle strength was associated with a higher ratio of RD in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere in patients with ACLR after controlling for the age, BMI, Tegner activity score, and graft type. RD is calculated through the diffusion perpendicular to the longitudinal axis, and increased RD values reflect the occurrence of demyelinating conditions.[25,26] The significant correlation between lower LSI of quadriceps and higher ratio of RD values after controlling covariates suggested that quadriceps weakness after ACLR could lead to deleterious changes in white matter microstructure. Alternatively, the demyelinating condition of the CST microstructure could be one of the sources of ACL rupture, which led to subsequent muscle dysfunction. Therefore, rehabilitation efforts may need to focus on interventions that restore the CST structure, which could improve the chronic quadriceps weakness after ACLR.

However, there were no correlations between the LSI of quadriceps strength and the ratio of other DTI outcomes (FA, MD, and AD) before and after controlling for the age, BMI, Tegner activity score, and graft type. Meanwhile, we did not find that there were significant associations between injured quadriceps strength and DTI outcomes before and after controlling for age, BMI, Tegner activity score, and graft type. Previous studies have found that these DTI outcomes had significant differences between the ACLR patients and healthy controls, which indicated that patients with ACLR had maladaptive changes in the CST microstructure. However, we observed no significant correlations between these DTI outcomes and quadriceps strength deficits. We suggested that the reason for the results may be these parameters of DTI outcomes had no associations with quadriceps strength deficits but had relationships with other sensorimotor deficits such as balance. We still need future research to continue investigating the relationships between the maladaptive neuroplasticity of CNS microstructure and sensorimotor deficits following ACLR.

4.2. Exploratory analyses of relationships between CST microstructure and quadriceps strength deficits in patients with different graft type

Previous studies rarely explore the relationships between the microstructure of CNS and quadriceps in patients with ACLR using different graft types. Due to the two graft types (synthetics and hamstring autografts), we included in the current study, we did the simple and partial correlation analyses between the CST microstructure and quadriceps strength deficits according to the graft type. Previous studies reported that individuals with hamstring autografts were better than BTB hamstring autografts and allograft group on the Y-Balance Test-Posteromedial direction and single-leg hop test.[24]

In subgroup analyses, we found that LSI of quadriceps strength negatively correlated with the ratio of MD and RD values in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere in ACLR patients with hamstring autografts after controlling for the age, BMI, and Tegner activity score, but there were no associations between LSI of quadriceps strength and the ratio of FA and AD values in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere.

However, there were no correlations between injured quadriceps strength and DTI outcomes, and between the LSI of quadriceps strength and the ratio of DTI outcomes in corticospinal tracts of the injured hemisphere to those of the non-injured hemisphere in ACLR patients with synthetics before and after controlling for the age, BMI and Tegner activity score. We suggested that the two reasons may determine no significant correlations between DTI outcomes and quadriceps strength deficits: 1) Hamstring autografts reconstruction took the posterior medial tendon causing muscle imbalance around the knee joint but synthetics reconstruction without taking tendon restored muscle strength faster; 2) Synthetics reconstruction did not have neural fibers and proprioceptors, which might cause that CST microstructure had little control for quadriceps strength.

Unfortunately, due to the cross-sectional nature of this study, we cannot determine causality between quadriceps strength deficits and DTI outcomes of CST microstructure. Therefore, the exact causal relationship between CST and quadriceps deficits needs further investigation through prospective controlled trials with repeated measurements.

4.3. Clinical implication

In clinical practice, previous studies have found that ACLR patients present with persistent quadriceps deficits, but the mechanism was unclear. The peripheral interventions such as Blood Flow Restriction Training Applied with High-Intensity Exercise have ineffectively improved quadriceps strength.[4] In the current study, the results may suggest that the quadriceps deficits are related to the central nervous system. The results of this study, which indicated that decreased integrity of CST was associated with quadriceps strength deficits in patients with ACLR, can help clinicians understand that patients with ACLR have a complex negative influence on both the central nervous system and peripheral musculoskeletal system.

Meanwhile, significant differences in DTI outcomes (FA, AD and RD values) of CST structure were found between ACLR patients and healthy controls in our previous study,[34] In this study, we also found that CST structure was associated with quadriceps strength. These relationships between the maladaptive neuroplasticity of CST and quadriceps strength deficits may be relevant to the clinical management of ACLR patients to develop novel evidence-based therapeutic approaches targeting the corticospinal pathway to improve the functions of muscle function and CST. For example, neuromuscular electrical stimulation might be used to improve both the quadriceps strength and excitability of the corticospinal pathway.[18]

4.4. Research implication

There are several implications for future research to investigate.

First, Quadriceps strength may be one of the results of the maladaptive neuroplasticity of CST microstructure. How the changes in CST structure influence the motor performance and reinjury ratio needs further studies to investigate the relationships between these factors.

Second, the quadriceps strength was associated with dynamic motor performance. Therefore, research in the future needs to explore the relationships between the CNS structure and function and motor performance of quadriceps strength in dynamic tasks following ACLR.

Third, sensorimotor deficits following ACL injury may influence motor performance by changing the Cognition-related senior brain regions.

Finally, the study's results have the potential to advance studies on the central mechanisms of quadriceps strength deficits following ACLR. The results could encourage future longitudinal investigations to identify the causal relationship between the CST microstructure and other sensorimotor deficits (*i.e.,* dynamic balance and voluntary activation).

4.5. Limitation

This study had several limitations to be addressed.

First, Although the results of this study showed a correlation between corticospinal tract structure and lower limb quadriceps muscle strength deficits in patients undergoing anterior cruciate ligament reconstruction, it is difficult to explore a causal relationship between the two as this was a cross-sectional study, and future prospective studies need to be conducted from healthy individuals who exercise regularly.

Second, despite the reliability and sensitivity of hand-held dynamometers for measuring maximal voluntary isometric strength of the quadriceps muscle are good, isokinetic dynamometry is still the gold standard for measuring muscle strength, and future research needs to improve our muscle strength measurements such as isokinetic dynamometers. Due to the time limitation, we only assess the quadriceps strength in this study and further studies need to add the assessment of hamstring strength, which the hamstring autografts reconstruction would influence.

Third, the patients included in this study had a postoperative duration (21.11 ± 10.79 months) of less than 2 years, which was not long. Future studies need to investigate the relationships between the CNS microstructure and quadriceps strength in earlier or longer postoperative duration.

Fourth, confounding factors such as articular cartilage injuries, meniscus injuries, and inconsistencies in postoperative rehabilitation programmes, which patients may not remember, can affect the outcomes of this study. Therefore, further longitudinal studies are needed in the future to explore the effects of these factors.

Fifth, we included only male patients with ACLR due to controlling for gender effects, and future studies need to include equal proportions of men and women.

Sixth, the power for calculating sample sizes for subgroup analyses may be insufficient and we need to be validated by further prospective research.

Seventh, the LSI of quadriceps and asymetry of DTI outcomes may be affected by the particular unilateral sport, leg dominance and injury history to the dominant leg or non-dominant leg. Therefore, future longitudinal studies need to further differentiate in the effects of daily exercise type and dominant side in patients with ACLR.

5. Conclusion

This study revealed that decreased integrity (higher MD and RD) of the CST in patients was significantly associated with lower limb symmetry index of quadriceps muscle strength, which hinted that quadriceps muscle strength deficits of injured side may be a maladaptive process of CST microstructure in ACLR.

Informed consent statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient to publish this paper.

Authors' Contributions

Le Yu, Shanshan Zheng and Yushi Chen carried out the study design, statistical analysis, and manuscript writing; Xiao'ao Xue and Zikun Wang carried out the enrollment of participants and experiments; Jiayan Cheng carried out the data collection; Yang Sun, He Wang, and Yinghui Hua carried out the study design, supervision of the experimental problems, data collection, and manuscript reviewing. Le Yu, Shanshan Zheng, and Yushi Chen contribute equally to this study as co-first authors; and Yinghui Hua, He Wang, and Yang Sun contribute equally to this study as co-senior authors. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Availity of data and materials

The datasets used and/or analyzed during the current study are not public due to patient privacy but are available from the corresponding author on reasonable request.

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Declaration of competing interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asmart.2024.11.001.

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