Diffusion tensor imaging of the anterior cruciate ligament graft following reconstruction : a longitudinal study

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Abstract

Objective To longitudinally monitor remodelling of human autograft following anterior cruciate ligament (ACL) reconstruction with DTI.

Methods Twenty-eight patients underwent DTI follow up at 3, 8 and 14 months after clinically successful ACL reconstruction with tendon autograft. Among these, 18 patients had a concomitant lateral extra-articular procedure (LET). DTI data from 7 healthy volunteers was also obtained. Diffusion parameters (fractional anisotropy, FA; mean diffusivity, MD; axial diffusivity, AD; and radial diffusivity, RD) were evaluated within the fiber tractography volumes of the ACL graft and posterior cruciate ligament (PCL) in all patients. Data were analysed using a linear mixed effects model with post-hoc testing using Bonferroni-Holm correction for multiple testing. The effect of additional LET was studied.

Results ACL graft showed a significant decrease of FA over time (F=4.00, p=0.025), while the diffusivities did not significantly change over time. For PCL there were no significant DTI changes over time. A different evolution over time between patients with and without LET was noted for all diffusivity values of ACL graft with reduced AD values in patients with LET at 8 months postoperatively (p=0.048; adjusted p=0.387). DTI metrics of ACL graft differed largely from both native ACL and tendon at 14 months postoperatively.

Conclusion Our study has shown the potential of DTI to longitudinally monitor the remodelling process in human ACL reconstruction. DTI analysis indicates that graft remodelling is incomplete at 14 months postoperatively.

Keywords: Humans . Diffusion Tensor Imaging . Follow-Up Studies . Tendons . Autografts . Anterior Cruciate Ligament Reconstruction

Key points:

- *DTI can be used to longitudinally monitor the remodelling process in human ACL reconstruction.*
- *DTI analysis indicates that autograft remodelling is incomplete at 14 months postoperatively.*
- *DTI may be helpful for evaluating new ACL treatments.*

Abbreviations and acronyms:

ACL Anterior cruciate ligament

AD Axial diffusivity

FA Fractional anisotropy

LET Lateral extra-articular tenodesis

MD Mean diffusivity

PCL Posterior cruciate ligament

PT Patellar tendon

RD Radial diffusivity

ST Semitendinosus tendon

Introduction

Anterior cruciate ligament (ACL) reconstruction (ACL-R) using tendon autograft is one of the most common procedures performed worldwide [1,2]. Despite advances in surgical techniques, there is limited knowledge on the biology of ACL graft [3]. Although most authors agree that tendon graft remodels into a ligamentous *ACL-like* structure, there is considerable disagreement about the precise outcome of the graft [3-5]. Furthermore, the time required to complete the remodelling process varies across studies, ranging from 12 to 36 months [3]. This is clinically important as it determines the graft's mechanical strength, and thus, is related to the safe return to sports [6].

Human biopsy studies have shown different results of the appearance of the transplanted tendon. Classically, 3 remodelling stages are described: 1) an early stage with limited graft necrosis, 2) a proliferation stage characterized by graft revascularization and cellular repopulation and 3), a maturation stage in which restructuring towards the native ACL occurs [3-5,7]. However, others reported that ACL graft maintains microscopic characteristics of the original tendon and that remodelling only occurs in perigraft tissue [8]. These variable results are likely related to inaccurate (superficial) biopsy sites and small biopsy volumes, which are not representative for the entire graft [3,8].

Diffusion tensor imaging (DTI) is a potential candidate to assess ACL graft remodelling. It allows for noninvasive quantification of water diffusion in tissue and assessment of its anisotropy, thereby providing a proxy measure of tissue organization [9]. Despite technical challenges, previous research established DTI with fiber tractography (FT) as a reproducible and reliable technique to evaluate ACL graft [10,11]. However, to our knowledge, DTI has not yet been reported for monitoring graft remodelling following ACL-R. The goal of this study was therefore to longitudinally monitor remodelling of autograft following ACL-R with DTI. Building on previous DTI studies in brain [12,13] and muscle [14,15], we hypothesized that, as the graft remodels, fractional anisotropy (FA) values would increase (due to an increase of water diffusion directionality) along with a decrease of mean diffusivity (MD) (due to decrease of overall water diffusion).

Materials and Methods

Participants

This prospective study was approved by our institutional review board . Written informed consent was obtained from all subjects. Inclusion criteria were (1) ACL-R at our institution between December 2015 and February 2017, (2) no signs of clinical laxity during follow-up and (3) consent to undergo DTI. Patients who had concomitant lateral extra-articular tenodesis (LET) to the ACL-R were also included. Exclusion criteria were (1) concomitant injuries beyond medial collateral ligament or meniscal tear, (2) previous knee surgery, and (3) the general contraindications for MRI. Twenty-eight patients (21 men, 7 women; mean age (±SD), 33 (±10) years; age range, 17-53 years; right knee, n=16) were included. The mean time from injury to surgery was 49 days (range, 19-75 days). Seven healthy subjects were also recruited (5 men, 2 women; mean age (±SD), 32 (±5) years; age range, 26-39 years; right knee, n=4). The controls were also included in a previous study [~~blinded~~16].

Surgical technique and Rehabilitation

All patients underwent single-bundle ACL-R using semitendinosus (ST) autograft with or without additional LET [17]. If an unstable meniscal tear was diagnosed at arthroscopy, surgery was performed. All patients followed a standardized rehabilitation program designed to get them back to full activity within 9 months after surgery.

MRI Acquisition

All scans were acquired on a 3T system (Magnetom PrismaFit, Siemens Healthcare) with a maximum gradient amplitude of 80 mT/m and maximum slew rate of 200 T/m/s. A 15-channel knee-coil (Quality Electrodynamics) was used. Diffusion-weighted (DWI) volumes were acquired using a multislice single-shot spin-echo echo planar imaging (SE-EPI) sequence. Each DWI series consisted of two b-values (400s/mm^2 and 800s/mm^2) using 10 gradient directions, and one b=0 image. Automatic B_0 shimming was applied to reduce field inhomogeneities. High receiver bandwidth (1860 Hz/px) was choosen to decrease echo spacing (0.65ms). Spectral adiabatic inversion recovery (SPAIR) was used for fat suppression (FS). To boost signal-to-noise ratio (SNR), the sequence was repeated 16 times (336 DWI volumes). Parallel imaging (acceleration factor 3) and Partial Fourier (6/8 in phase encoding) techniques were applied resulting in a scan time of 7 minutes 25 seconds. The following scan parameters were used: TR/TE=1300/45ms, voxel size 1.5 x 1.5 x 6 mm^3, and FOV 192 x 192 x 60 mm. SNR was calculated in ACL graft using random matrix theory [18]. Data were analyzed visually to check the presence of distortions. Scans with severe geometric distortions or signal dropouts were excluded [19]. For reference, conventional MRI was performed, including sagittal proton-density (PD), coronal T1 and axial and sagittal FS intermediate-weighted images. These were used to assess ACL graft healing [20].

Data Preprocessing

First, the DWI series were corrected for noise and subject motion [21]. They were affinely registered to the first b=0 image, taking into account reorientation of the B-matrix and intensity modulation [22]. The b=0 image and co-registered series were aligned to the sagittal PD image without resampling. The diffusion tensor was computed using an iteratively reweighted least-squares routine with outlier rejection [23,24]. Finally, DTI maps were derived from the diffusion tensor images.

Fiber Tractography and Parameter Estimation

To obtain the ACL segmentation, a probabilistic tensor-based FT algorithm [25] was used, as implemented in MRtrix [26]. Spherical regions of interest (ROI) with 15mm diameter were manually drawn by one radiologist (~~blinded~~PVD) on anatomical images at the femoral and tibial bone tunnel apertures or near ACL insertions using 3D Slicer (version 4.4.0). FT was performed twice, using one ROI as seed region and the other as end region, and vice versa. The tract initiation and cut-off threshold were set to an FA of 0.1, with step size 0.2 and angle 20° [10]. In addition to the cut-off for low FA values, an additional mask was defined to avoid tracts leading to surrounding areas of bone and tissue, based on the PD image intensity. The threshold for masking was defined by the 75th percentile intensity, and averaged across subjects. Furthermore, streamline length was limited to 100mm. If no tracts were found, FA-threshold was reduced and/or allowed angle increased. The voxels traversed by both tractograms were used as the ACL segmentation. If the intersection of both tractograms was empty, the best tractogram was selected. Median DTI values were obtained within the segmentation. To account for longitudinal drift and normal anatomical changes over time, PCL was selected and FT was performed using the same approach as for ACL [27]. If delineation failed using either seed region, ACL and PCL were manually delineated on multiple slices. Finally, DTI parameters were evaluated in spherical ROIs placed on the ST and patellar tendon (PT) in controls.

Clinical Follow-up

All patients had routine clinical assessment at 3 and 6 months postoperatively, including anterior drawer, Lachman and pivot-shift test. The laxity tests were subjectively interpreted and considered as being positive or negative.

Statistical analysis

A linear mixed model was fitted for each DTI parameter evaluated in ACL with time (as a categorical variable) as fixed effect and a random intercept per patient. In case of significant time-effect, post-hoc testing was done comparing time points (3, 8 and 14 months) two-by-two. P-values are reported unadjusted and adjusted for multiple testing using a Bonferroni-Holm correction [28]. The same analysis was performed for DTI parameters in PCL. Assumptions of normality and homoscedasticity were checked graphically using the scaled marginal residuals and no violations were found. For DTI parameters of ACL graft, the effect of additional LET, meniscal status and patient age was examined by including these variables in an interaction term with time. In case of no significant interaction, main effects of the variables were studied. A Fisher's exact test was used to compare categorical variables and a Mann-Whitney test was used to compare continuous variables between patients and controls. Statistical significance was set at $p< 0.05$. Analyses were conducted using R 3.6.2 programming environment and SAS 9.4 Software.

Results

Participants and Clinical Follow-up

There were no differences in age, gender, and laterality between patients and controls ($p\geq0.80$). Twenty-three of 28 patients had concomitant surgeries (LET, n=9; LET and meniscal surgery, n=9; and meniscal surgery, n=5). All patients had a stable knee at follow-up without instability complaints.

Image Acquisition and Fiber Tracking

Time points of MRI follow-up ranged from 3 to 15 months post-intervention. All patients had MRI at 3 months and between 6-9 months (mean, 8 months) postoperatively. Of these, 16 patients had a third scan between 12-15 months (mean, 14 months) postoperatively. Conventional MRI showed normal ACL graft in all patients with increase in graft signal during the first postoperative year, and slight decrease thereafter **(Fig. 1)**.

All DWI scans were included in the analysis **(Fig. 2)**. For unprocessed data, mean SNR (±SD) of ACL graft was 12.32 (±2.48, range 6.19-19.45), 6.80 (±1.20, range 4.00-10.07) and 4.40 (±0.54, range 3.52-5.77) for the b0, b400, and b800 images, respectively. In 80%of cases, there was a valid intersection of ACL tracts seeded from the femur and the tibia. For PCL, in 40% of cases both tractographies overlapped. Two 3 month DTI scans did not yield a realistic FT result for PCL and were discarded. A patient example is illustrated in **Fig. 3**. In volunteers, PCL delineation failed in all subjects using either seed region. Therefore, for consistency, both ACL and PCL were manually delineated in controls **(Fig. 4)**.

Mean DTI parameters in patients and controls are summarized in **Table 1** and **Table 2**, respectively. A detailed list of DTI parameters for all subjects is provided as a supplement. A significant time effect was detected in the ACL graft only for FA (FA: F=4.00, p=0.025; MD: F=0.68, p=0.511; RD: F=0.57, p=0.570; AD: F=0.89, p=0.419). DTI parameters in PCL did not significantly change over time (FA: F=0.11, p=0.899; MD: F=1.20, p=0.312; RD: F=1.27, p=0.292; AD: F=1.26, p=0.294). The longitudinal DTI analysis is illustrated in **Fig. 5**. Post-hoc tests with estimates of the pairwise differences between time points are given in **Table 3**.

FA

FA values in ACL graft decreased between 3 and 14 months postoperatively (raw p=0.007, adjusted p=0.022), with the largest decrease between 8 and 14 months (raw p=0.040, adjusted p=0.081). At 14 months postoperatively, FA values of ACL graft were lower compared to healthy tendon (0.17 vs 0.25-0.30, p<0.001) and they were higher compared to healthy ACL (0.17 vs 0.14, p=0.033).

MD, RD and AD

Albeit not significant, diffusivities of ACL graft increased between 3 and 8 months postoperatively, followed by a decrease between 8 and 14 months postoperatively, whereas continuing decreasing values were seen for PCL. Diffusivity values of ACL graft remained higher compared with healthy tendon at 14 months postoperatively (1.0-1.3 x 10^{-3} mm^2/s vs 0.31-0.73 10^{-3} mm^2/s, p<0.001).

Effect of LET, Meniscus and Patient Age

There was a significant interaction effect between LET status and time for MD, RD (borderline), and AD of ACL graft (p=0.037, 0.059 and 0.029, respectively), but not for FA (p=0.571). Post-hoc tests with estimates of the pairwise differences between time points within each LET group are given in **Table 4**. In patients without LET, diffusivities of ACL graft increased between 3 and 8 months postoperatively (p≤ 0.024; adjusted p≤0.144). In contrast, a trend of continuing decreasing diffusivities was observed in patients with LET (p>0.05) (**Fig. 6**). Patients with LET showed reduced graft diffusivity values at 8 months postoperatively as compared with patients without LET (MD: p=0.075; adjusted p=0.603; RD: p=0.108; adjusted p=0.866; AD: p=0.048; adjusted p=0.387). There were no significant differences in DTI parameters in either patients with or without meniscus surgery, nor did we find a significant effect of patient age (for both variables no significant interaction and no significant main effect).

Discussion

Our study performed DTI-based FT of ACL graft following reconstruction. Longitudinal measurements in 28 patients showed a significant decrease of FA over time, while the diffusivities did not significantly change over time. The diffusion properties of tendon graft differed largely from healthy tendon and native ACL. The DTI findings indicate that graft remodelling is incomplete at 14 months postoperatively.

Building on previous studies [3-5], we hypothesized that, as ACL graft reaches maturity, the fibers regain their organization, resulting in an increase of FA over time. However, ACL graft showed a significant decrease of FA over time, suggesting a rather low degree of organization when compared with healthy controls. Also, we observed lower FA values for native ACL (0.14) than for tendon (graft). This confirms the known microstructural organization of the fibrous matrix of the respective tissues, with tendons appearing more mature histologically than ligaments [29,30].

Although ACL graft diffusivities did not significantly change over time, possibly related to the small sample size of our study, a trend was observed. After an increase between 3 and 8 months postoperatively, we found diffusivities of ACL graft to decrease over time. Based on previous studies using conventional MRI, and confirmed by ours, this could be expected as, in the first months postoperatively, there is fluid accumulation in ACL graft due to active remodeling [4,5,20]. Thereafter, when patients regain mobility, the amount of water in the graft decreases and diffusion becomes more hindered. Although the trend of decreasing diffusivities can be a sign that the graft reaches an equilibrium state, all diffusivities remained at higher values compared with controls, indicating active graft remodeling even at 14 months postoperatively. Of note, diffusivities of normal ACL were approximately twice the values of PCL (p=0.016), reflecting the normal biological difference between them (with collagen density in ACL being significantly lower than that in PCL) [31].

Poor rotational control following ACL-R may predispose to graft failure, which leads to believe there may be a role for augmenting the ACL-R with a LET [32,33]. Our study found lower diffusivity values of ACL graft at 8 months postoperatively in patients with LET as compared with patients without LET, suggesting a protective effect of LET on graft remodelling. These results show that DTI is sensitive to measure subtle changes in tendon status, which go undetected in clinical examination.

DTI of ligament and tendon is technically challenging because of the small size and short T_2 values of these tissues [34]. We took advantage of studying remodeling ACL grafts, as they have larger volume and higher MRI signal compared to native ACL [35]. We also avoided gross magnetic field inhomogeneity at the apertures of bone tunnels. To reduce susceptibility artifacts, we used high-performance gradients, allowing DWIs to be acquired at short TE (45ms), as well as parallel imaging [12]. In our study, raw DWI data had a mean SNR of 12.3, 6.8 and 4.4 for the b0, b400, and b800 images, respectively. With 16 averages, this resulted in an effective SNR of 49.2, 27.2 and 17.6 for the b0, b400, and b800 images, respectively. In this SNR regime, our tensor fitting routine is nearly unbiased [36]. SNR greatly affects DTI parameter estimation, which hinders comparison of multi-site diffusion studies [37]. In a previous simulation study [38], it was shown that FA is overestimated and MD is underestimated at low SNR.

There is clinical need for improved noninvasive quantitative MRI measures of ACL graft properties to inform decisions concerning return to sports for individual patients [39,40]. T2* mapping seems a potential candidate biomarker to monitor ACL graft maturation [41,42]. To our knowledge, our study is the first to longitudinally investigate the remodelling process of ACL grafts using DTI. Our results show that this process extends beyond 12 months postoperatively, which is of clinical relevance given that most evaluation of return to sports is performed before 9 months postoperatively, and that an accelerated rehabilitation protocol is recommended in certain cases [40].

This study has limitations. First, DTI was performed with thick slices for SNR purpose. Although high in-plane resolution was used, partial volume effects (PVE) may have occurred and higher spatial resolution would be beneficial. However, besides reduced FA values, any significant PVE would also yield erroneously elevated diffusivity values [37]. As we only found a significant decrease of FA over time, while the diffusivities did not significantly change, we believe PVE is not the sole driving force of the observed changes. Super-resolution reconstruction (SRR) of 2D MRI can improve the trade-off between SNR, spatial resolution and scan time [43]. Recently, a SRR method that reconstructs high resolution diffusion parameters from a set of low resolution DWI images was proposed [44]. We plan future research to increase the spatial resolution of our DTI protocol with SRR in a clinically feasible scan time. Second, we did not obtain histological specimen to confirm graft healing since this was a preliminary study in patients who successfully recovered after ACL-R. However, all patients had normal postoperative stability and intact ACL graft confirmed by conventional MRI. Third, we found no significant effect of meniscal status and patient age on graft DTI measures. Further studies in a larger patient group including later time points of DTI follow-up are needed. Fourth, ROIs were manually placed by one radiologist, which may affect our tractography results. To ensure reproducible tracking, ROIs were drawn as large as possible (15mm) and their positions were verified on conventional MRI. The interobserver reliability of this method was already described in detail [10]. Fifth, we used conventional

DTI with relatively long TE (=45ms). Therefore, DTI parameters may relate more to vascularity of ACL graft than to collagen structure. Further optimization of the DTI protocol is mandatory, including higher spatial resolution and ultra-short echo times (<10ms), to increase the robustness of the proposed method [34]. Sixth, we used a small control group, that was not age- and gender matched to the patient group. Moreover, DTI results in patients were obtained using FT, whereas manual segmentation was performed in controls. Finally, we did not look at the association between clinical and patient-reported outcomes and DTI measures. Future studies should seek to assess whether these measures can predict traditional subjective outcomes after ACL-R.

In conclusion, the present study has shown the potential of DTI to longitudinally quantify diffusion changes of the ACL graft following reconstruction. DTI analysis indicates that graft remodeling is incomplete at 14 months postoperatively.

References

1. Harris JD, Abrams GD, Bach BR, et al (2014) Return to sport after ACL reconstruction. Orthopedics 37:e103–108

2. Hofbauer M, Muller B, Murawski CD, van Eck CF, Fu FH (2014) The concept of individualized anatomic anterior cruciate ligament (ACL) reconstruction. Knee Surg Sports Traumatol Arthrosc 22:979-986

3. Claes S, Verdonk P, Forsyth R, Bellemans J (2011) The "ligamentization" process in anterior cruciate ligament reconstruction: what happens to the human graft? A systematic review of the literature. Am J Sports Med 39:2476-2483

4. Janssen RP, Scheffler SU (2014) Intra-articular remodelling of hamstring tendon grafts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 22:2102-2108

5. Janssen RP, van der Wijk J, Fiedler A, Schmidt T, Sala HA, Scheffler SU (2011) Remodelling of human hamstring autografts after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 19:1299-1306

6. Kaplan Y, Witvrouw E (2019) When is it safe to return to sport after ACL reconstruction? Reviewing the Criteria. Sports Health 11:301-305

7. Falconiero RP, DiStefano VJ, Cook TM (1998) Revascularization and ligamentization of autogenous anterior cruciate ligament grafts in humans. Arthroscopy 14:197-205

8. Johnson LL (1993) The outcome of a free autogenous semitendinosus tendon graft in human anterior cruciate reconstructive surgery: a histological study. Arthroscopy 9:131-142

9. Budzik JF, Balbi V, Verclytte S, Pansini V, Le Thuc V, Cotten A (2014) Diffusion tensor imaging in musculoskeletal disorders. Radiographics 34:E56-72

10. Van Dyck P, Froeling M, De Smet E, et al (2017) Diffusion tensor imaging of the anterior cruciate ligament graft. J Magn Reson Imaging 46:1423-1432

11. Yang X, Chen D, Li M, Shi D, Zhu B, Jiang Q (2015) Diffusion tensor imaging of the anterior cruciate ligament graft after reconstruction: repeatability and diffusion tensor imaging metrics. J Comput Assist Tomogr 39:244-249

12. Mukherjee P, Chung SW, Berman JI, et al (2008) Diffusion tensor MR imaging and fiber tractography: technical considerations. AJNR Am J Neuroradiol 29:843–852

13. Bao Y, Yang L, Chen Y, et al (2018) Radial diffusivity as an imaging biomarker for early diagnosis of non-demented amyotrophic lateral sclerosis. Eur Radiol 28:4940-4948

14. Froeling M, Oudeman J, Strijkers GJ, et al (2015) Muscle changes detected with diffusion-tensor imaging after long-distance running. Radiology 274:548–562

15. Rehmann R, Schlaffke L, Froeling M, et al (2019) Muscle diffusion tensor imaging in glycogen storage disease V (McArdle disease). Eur Radiol 29:3224-3232

16. Van Dyck P, Froeling M, Heusdens CHW, Sijbers J, Ribbens A, Billiet T (2020) Diffusion tensor imaging of the anterior cruciate ligament following primary repair with internal bracing: a longitudinal study. J Orthop Res doi: 10.1002/jor.24684~~Blinded~~

17. Moran CJ, Verdonk PC, Lagae K, DeClercq G (2014) Extra-articular augmentation of anterior cruciate ligament reconstruction: the monoloop procedure. In: Siebold R, Dejour D, Zaffagnini (eds) Anterior cruciate ligament reconstruction, 1st ed. Springer Heidelberg New-York Dordrecht London, pp 317-326

18. Veraart J, Fieremans E, Novikov DS (2016) Diffusion MRI noise mapping using random matrix theory. Magn Reson Med 76:1582-1593

19. Tournier JD, Mori S, Leemans A (2011) Diffusion tensor imaging and beyond. Magn Reson Med 65:1532–1556

20. Howell SM, Clark JA, Blasier RD (1991) Serial magnetic resonance imaging of hamstring anterior cruciate ligament autografts during the first year of implantation. A preliminary study. Am J Sports Med 19:42-47

21. Andersson JL, Sotiropoulos SN (2016) An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. NeuroImage 125:1063–1078

22. Leemans A, Jones DK (2009) The B-matrix must be rotated when correcting for subject motion in DTI data. Magn Reson Med 61:1336–1349

23. Chang LC, Jones DK, Pierpaoli C (2005) RESTORE: robust estimation of tensors by outlier rejection. Magn Reson Med 53: 1088-1095

24. Collier Q, Veraart J, Jeurissen B, et al (2015) Iterative reweighted linear least squares for accurate, fast, and robust estimation of diffusion magnetic resonance parameters. Magn Reson Med 73:2174-2184

25. Basser PJ, Pajevic S, Pierpaoli C, et al (2000) In vivo fiber tractography using DT-MRI data. Magn Reson Med 44:625-632

26. Tournier JD, Calamante F, Connelly A (2012) MRtrix: Diffusion tractography in crossing fiber regions. Int J Imaging Syst Technol 22:53–66

27. Vos SB, Tax CM, Luijten PR, et al (2017) The importance of correcting for signal drift in diffusion MRI. Magn Reson Med 77:285-299

28. Holm S (1979) A simple sequentially rejective multiple test procedure. Scand J Stat 6:65–70

29. Amiel D, Frank C, Harwood F, Fronek J, Akeson W (1984) Tendons and ligaments: a morphological and biochemical comparison. J Orthop Res 1:257-265

30. Hadjicostas PT, Soucacos PN, Paessler HH, et al (2007) Morphologic and histologic comparison between the patella and hamstring tendons grafts: a descriptive and anatomic study. Arthroscopy 23:751-756

31. Mommersteeg TJ, Blankevoort L, Kooloos JG, et al (1994) Nonuniform distribution of collagen density in human knee ligaments. J Orthop Res 12:238-245

32. Getgood A, Brown C, Lording T, Amis A, Claes S, Geeslin A, Musahl V; ALC Consensus Group (2019) The anterolateral complex of the knee: results from the International ALC Consensus Group Meeting. Knee Surg Sports Traumatol Arthrosc 27:166-176

33. Williams A, Ball S, Stephen J, White N, Jones M, Amis A (2017) The scientific rationale for lateral tenodesis augmentation of intra-articular ACL reconstruction using a modified Lemaire procedure. Knee Surg Sports Traumatol Arthrosc 25:1339-1344

34. Robson MD, Gatehouse PD, So PW, et al (2004) Contrast enhancement of short T2 tissues using ultrashort TE (UTE) pulse sequences. Clin Radiol 59:720-726

35. Thein R, Spitzer E, Doyle J, et al 2016 The ACL graft has different cross-sectional dimensions compared with the native ACL: implications for graft impingement. Am J Sports Med 44:2097-2105

36. Veraart J, Sijbers J, Sunaert S, Leemans A, Jeurissen B (2013) Weighted linear least squares estimation of diffusion MRI parameters: strengths, limitations, and pitfalls. Neuroimage 81:335-346

37. Soares JM, Marques P, Alves V, Sousa N (2013) A hitchhiker's guide to diffusion tensor imaging. Front Neurosci 7:31

38. Froeling M, Nederveen AJ, Nicolay K, Strijkers GJ (2013) DTI of human skeletal muscle: the effects of diffusion encoding parameters, signal-to-noise ratio and T2 on tensor indices and fiber tracts. NMR Biomed 26:1339-1352

39. Kaplan Y, Witvrouw E (2019) When is it safe to return to sport after ACL reconstruction? Reviewing the Criteria. Sports Health 11:301-305

40. Sousa PL, Krych AJ, Cates RA, Levy BA, Stuart MJ, Dahm DL (2017) Return to sport: Does excellent 6-month strength and function following ACL reconstruction predict midterm outcomes? Knee Surg Sports Traumatol Arthrosc 25:1356-1363

41. Fleming BC, Vajapeyam S, Connolly SA, Magarian EM, Murray MM (2011) The use of magnetic resonance imaging to predict ACL graft structural properties. J Biomech 44:2843-2846

42. Chu CR, Williams AA (2019) Quantitative MRI UTE-T2* and T2* show progressive and continued graft maturation over 2 years in human patients after anterior cruciate ligament reconstruction. Orthop J Sports Med 7(8):2325967119863056

43. Plenge E, Poot DH, Bernsen M, et al (2012) Super-resolution methods in MRI: can they improve the trade-off between resolution, signal-to-noise ratio, and acquisition time? Magn Reson Med 68:1983-1993

44. Van Steenkiste G, Jeurissen B, Veraart J, et al (2016) Super-resolution reconstruction of diffusion parameters from diffusion-weighted images with different slice orientations. Magn Reson Med 75:181-195

Figure legend

Fig. 1 Sagittal fat-saturated intermediate-weighted images at 3 (left), 8 (middle) and 14 (right) months following ACL reconstruction using tendon autograft (arrow). Increased graft signal is seen during the first year of implantation, with slight signal decrease thereafter.

Fig. 2 DTI scan of the left knee showing ACL graft at the intercondylar notch. Diffusion-weightings are b=0 (a), b=400 s/mm^2 (b), and b=800 s/mm^2 (c). (d) overlay with anatomical image. ACL tendon graft, large arrow; PCL, small arrow.

Fig. 3 Conventional MR images with overlay of 3D fiber tractography of the ACL graft and PCL at 3 (upper row), 8 (middle row), and 14 (lower row) months following ACL reconstruction. The patient had a clinically stable knee at all time points.

Fig. 4 Conventional MR images with overlay of manually delineated ACL (row 2) and PCL (rows 2 and 3) in a healthy subject. Additionally, spherical regions-of-interest were placed in the patellar tendon (row 1) and semitendinosus tendon (row 4).

Fig. 5 Longitudinal DTI analysis of the ACL graft and PCL at 3 months, between 6 and 9 (mean 8) months, and between 12 and 15 (mean 14) months following ACL reconstruction. Data represent mean values with 95% CI for the 28 patients. DTI values of healthy ACL/PCL and ST are also indicated. ACL, anterior cruciate ligament; PCL, posterior cruciate ligament; ST, semitendinosus tendon; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity.

Fig. 6 Longitudinal DTI analysis of the ACL graft at 3 months, between 6 and 9 (mean 8) months, and between 12 and 15 (mean 14) months following ACL reconstruction according to LET status. Data represent mean values with 95% CI for the 28 patients. FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; LET, lateral extra-articular tenodesis (0=absent, 1=present).

Table 1 DTI parameters in patients.

Table 2 DTI parameters in healthy subjects.

Table 3 Results from posthoc tests of the linear mixed model on longitudinal DTI measurements of ACL graft .

Table 4 Results from posthoc tests of the linear mixed model on longitudinal DTI measurements of ACL graft according to LET status.