European Spine Journal (2019) 28:2517–2525
https://doi.org/10.1007/s00586-019-06095-x

ORIGINAL ARTICLE

Characterization of the microstructure of the intervertebral disc in patients with chronic low back pain by diffusion kurtosis imaging

Li Li[1,4,5] · Zhiguo Zhou[2] · Wei Xiong[3] · Jicheng Fang[1] · Yang Li[1] · Zhanying Jiao[1] · Alessandro Scotti[4,5] · Feng Li[3] · WenZhen Zhu[1] · Kejia Cai[4,5]

Received: 28 February 2019 / Revised: 19 June 2019 / Accepted: 4 August 2019 / Published online: 13 August 2019

Abstract

Purpose Multivariate analysis of T2-weighted signal, diffusion ADC, and DKI parameters and tractography were used to differentiate chronic non-specific low back pain (CLBP) patients and asymptomatic controls (AC).

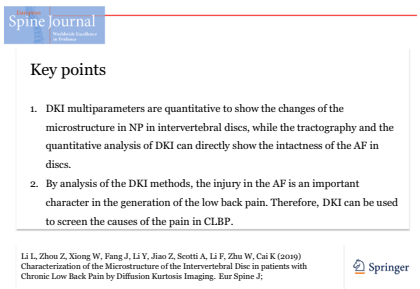
Methods A total of 30 patients with CLBP and 23 AC underwent diffusion kurtosis imaging (DKI) of lumbar spine with a 3T MRI scanner to get the ADC values and seven parameters of DKI in the nucleus pulposus (NP) of the intervertebral disc. The tractography and the tract-related parameters as other parameters were also generated to indicate the intactness of annulus fibrosus (AF). T2-grades of the discs were also quantified based on an eight-grade degeneration grading system. ADC and T2-grades were compared with DKI parameters for the differentiation of CLBP and AC groups.

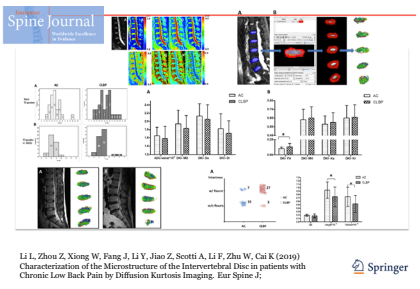
Results There was no difference in the T2 grades, ADC value, and multiple parameters in DKI of NP between CLBP and AC groups ($P > 0.05$). The average FA values in NP in AC group were found significantly higher than in the CLBP group ($P < 0.05$). The scores for the intactness of AF of the intervertebral discs were significantly different in CLBP and AC groups, with 90% of sensitivity and 70% specificity ($P < 0.05$). Additionally, there were significantly differences in the length and volume values of the AF in CLBP and AC groups ($P < 0.05$).

Conclusion DKI is a good noninvasive method, and it might help to differentiate CLBP from AC. Particularly, the continuation of DKI tractography reflects the presence of annulus fibrosus fissures, an important character in the generation of the low back pain.

Graphic abstract

These slides can be retrieved under Electronic Supplementary Material.





Keywords Low back pain · Intervertebral disc degeneration · Microstructure · Diffusion kurtosis imaging · Tractography

Introduction

Low back pain (LBP) is one of the most common causes of disability worldwide [1], and it is frequently associated with intervertebral disc degeneration (IDD) [2]. The

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-019-06095-x) contains supplementary material, which is available to authorized users.

✉ WenZhen Zhu
zhuwenzhen8612@163.com

Extended author information available on the last page of the article

intervertebral discs connect the vertebral bodies, absorbing and distributing applied loads and lending flexibility to the spine [3, 4]. They are composed of the nucleus pulposus (NP), which is a hydrophilic proteoglycan-rich gelatinous core, and the annulus fibrosus (AF), which is a lamellate collagenous ring surrounding the NP [5]. As the degeneration progresses, the composition and organization of the disc matrix in the NP are altered by the loss of water content, the decrease in type II collagen and proteoglycans, and the increase in type I collagen [6]. At the same time, the AF cells undergo some changes in the matrix and the activity, resulting in the loss of organization in the AF matrix [7]. Therefore, the anabolism and catabolism in the NP and AF cause an alteration of the microenvironment and microstructure of the degenerated discs.

MR imaging has been used as a noninvasive method to study IDD [8]. Clinical protocols including T_1- and T_2-weighted sequences are in fact able to show anatomical abnormalities such as disc bulge, protrusion/extrusion, and high-intensity zones [9, 10]. However, the findings associated with LBP are present in the majority of both symptomatic and asymptomatic individuals, and accordingly, the diagnostic value of these findings is limited [9]. Such limitation could find its roots in the failure of conventional imaging protocols to assess the changes in the microstructure and microenvironment of the discs. Diffusion-weighted image (DWI) has been used to show the loss of water content in degenerated discs [11], while diffusion tensor imaging (DTI) can map the principal diffusivity direction of water molecules through the tissue [12]. T_1- and T_2-weighted sequences can in fact only show macroscopic features, and conventional diffusion imaging (DWI & DTI) fails to fully describe the microstructure, e.g. mischaracterizing the orientation of fibres in regions of crossing or fanning [13].

Unlike Gaussian diffusion methods (conventional DWI and DTI), diffusion kurtosis imaging (DKI) is a non-Gaussian diffusion modality which is a clinically feasible extension of DTI by estimating the kurtosis of the displacement distribution [14, 15]. The conventional Gaussian diffusion methods are based on Einstein's original concept that the diffusion of water molecules follows a Gaussian (normal) distribution. This assumption may be true for homogeneous liquids and gels; however, it is overly simplified for complex biological tissues with cell membranes creating compartments and barriers for free diffusion. Hence, DKI is introduced for quantifying the diffusion kurtosis, a dimensionless statistical metric for the non-Gaussianity of an arbitrary probability diffusion distribution [14]. The additional kurtosis information provided by DKI may help to improve upon conventional diffusion MRI, including DTI-based fibre tracking methods [15]. Therefore, DKI has been applied for the successful detection of microstructural changes in tissue [16, 17].

Multiple parameters can be extracted from DKI data, such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (Da), radial diffusivity (Dr), mean kurtosis (MK), axial kurtosis (Ka), and radial kurtosis (Kr), which can be used as biological markers for the diffusion of water molecules and microstructural heterogeneity in the tissue [13, 18]. Additionally, DKI allows for the estimation of the diffusion kurtosis tensor (DKT), which quantifies the non-Gaussian behaviour of water diffusion and provides more accurate tractography than diffusion tensor imaging (DTI) [13].

In the previous study in healthy rat [19] and a rat intervertebral disc degeneration model [20], it was found that DKI can show the differences in the microstructure of nucleus pulposus between sexes and between grade 1 and 2 degeneration in healthy rats, and DKI multi-parameter analysis had been proved to be useful for assessing the microstructural changes consistent with the histopathology results in rat IDD model. Therefore, we hypothesized that DKI can be used to evaluate the microstructural changes in human intervertebral discs and explore their relationship with chronic low back pain. To test our hypothesis, we studied patients with chronic non-specific low back pain and used DKI multi-parameters to assess the microstructural changes in the nucleus pulposus, and DKT to show the integrality of the annulus fibrosus.

Methods

Subjects

With approved IRB protocols and after adequate communication and appropriate explanations of magnetic resonance imaging, all subjects signed informed consent. The study included two groups of subjects: 1). 30 patients with chronic non-specific low back pain (CLBP): 14 males and 16 females, between 18 and 48 (33 ± 8) years old (BMI: 24 ± 3) and 2) 23 asymptomatic controls (AC), 13 males and 10 females, between 18 and 45 (31 ± 6) years old (BMI: 22 ± 2).

The inclusion criteria of CLBP [21, 22] were as follows: 1. low back pain was not attributable to a recognizable, known specific pathology (e.g. infection, tumour, osteoporosis, fracture, structural deformity, inflammatory disorder, radicular syndrome, or caudal equine syndrome) and 2. permanent pain had been suffered in the low back area for at least 1 year (range: 1–8 years).

The exclusion criteria of the two groups were as follows: (1) if subjects have systemic diseases (metabolic disease, cancer, or acute infection) and (2) if subjects have medication history (paregoric drugs, antidepressants, and drug abuse history) and history of surgery and drug allergy.

All subjects were asked to rate the pain intensity during 4 weeks prior to the examination by using the short-form

McGill Pain Questionnaire 2 (SF-MPQ-2) [23], which includes different types of pain, and the pain score ranges from one (corresponding to "no pain") to ten (corresponding to "worst pain imaginable"). Oswestry lumbar and lower limb dysfunction index (Oswestry disability index, ODI) [24] was also used to exclude the patients with dysfunction of lower extremity which suggests the radicular syndrome. In our study, 30 subjects were included in CLBP group after 16 subjects were excluded.

Imaging protocols

Lumbar spine imaging was performed using a 3 Tesla MR scanning system (GE Discovery MR 750; GE Healthcare, Waukesha, WI, USA) with a 32-channel torso coil. All the scans were completed from 1 to 4 pm to minimize the variation in the character of the intervertebral discs [25]. The images of T_2-weighted sagittal images, DWI sagittal section, and DKI sagittal section were collected.

T_2-weighted sagittal images were acquired as follows: fast spin echo sequence with repetition time (TR) of 2500 ms and echo time (TE) of 120 ms; matrix 512*512; field of view (FOV) 32*16 cm^2; NEX = 2.0; slice thickness 4 mm; interslice gap 0.5 mm.

A DWI sagittal section was acquired with a single-shot spin echo EPI sequence (SS-EPI) and the following parameters: *b* values, 0, 600 mm/s^2; TR/ TE = 2000/92 ms; matrix, 256*256; voxel size, 1.25*1.25*4 mm^3; FOV, 32*32 cm; slice thickness = 4 mm; gap = 0.5 mm.

The sagittal diffusion kurtosis images were collected with the parameters: TR/TE = 2500/96 ms; matrix, 256*256; voxel size, 1.25*1.25*4 mm^3; FOV, 32*32 cm; slice thickness = 4 mm; gap = 0.5 mm. The DKI protocol included 2 b0 images and DW images with two different *b* values (1250, 2500 mm/s^2), each applied along 25 directions.

Image processing

An eight-grade modified grading system [26] was adopted to grade the disc degeneration based on the T_2 images. Two radiologists (8 years and 6 years of experience of imaging analysis and radiologic reading in MR imaging of the spine) assessed the MR data. The discs were blindly reviewed by them, and consistent results were reached after further discussion if needed.

The vendor-supplied software (Advantage Workstation; version 4.6, GE Healthcare) was used to calculate the apparent diffusion coefficient (ADC) value from the DWI images. The diffusion parameters derived from DKI included FA, MD, Da, Dr, MK, Ka, and Kr. Mean values were computed averaging the values within elliptic regions of interest (ROI) in the NP. To select the proper anatomical position for the measurement, the ROIs were drawn with uniform size (100–140 mm^2) from the centre of the disc on the T_2-weighted sagittal images and then transposed on DWI and DKI images (Fig. 1).

The tractography by DKT was generated by using MRIcron software (https://www.mricro.com) and DSI Studio (https://dsi-studio.labsolver.org/) (Fig. 2). Discs were drawn manually by a radiologist (5 years of experience of imaging analysis and radiologic reading in MR imaging of the spine), who was blinded to all clinical information, on DKI multiple

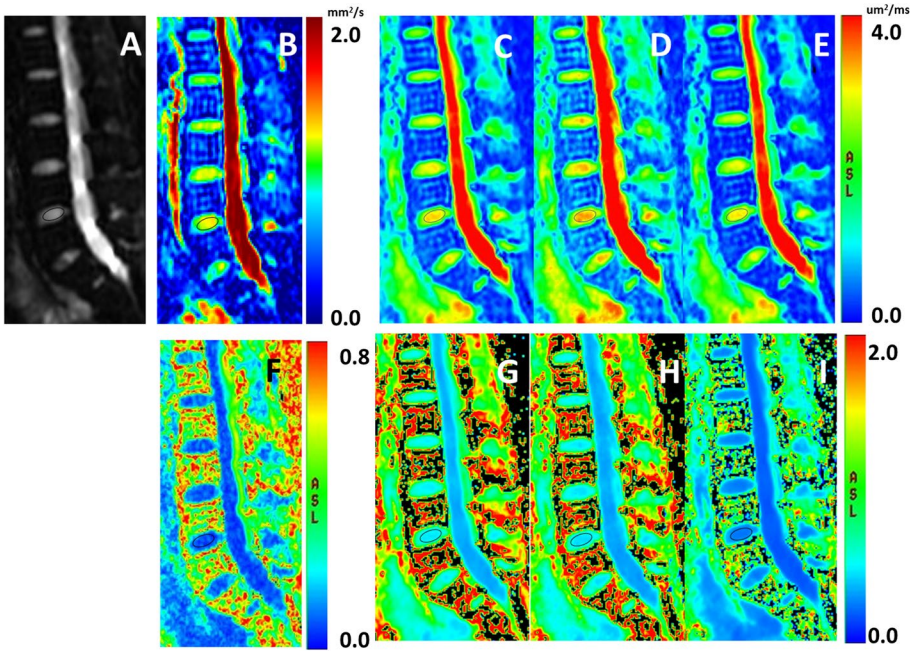


Fig. 1 T_2-weighted and DKI of the lumbar spine. **a** T_2-weighted image, **b** ADC map, **c** MD map, **d** Da map, **e** Dr map, **f** FA map, **g** MK map, **h** Ka map, **i** Kr map. This is a 38-year-old female subject in the asymptomatic controls group. The T_2 grades of L1/2, L2/3, L3/4, L4/5, and L5/S1 were 2, 2, 2, 2, 4

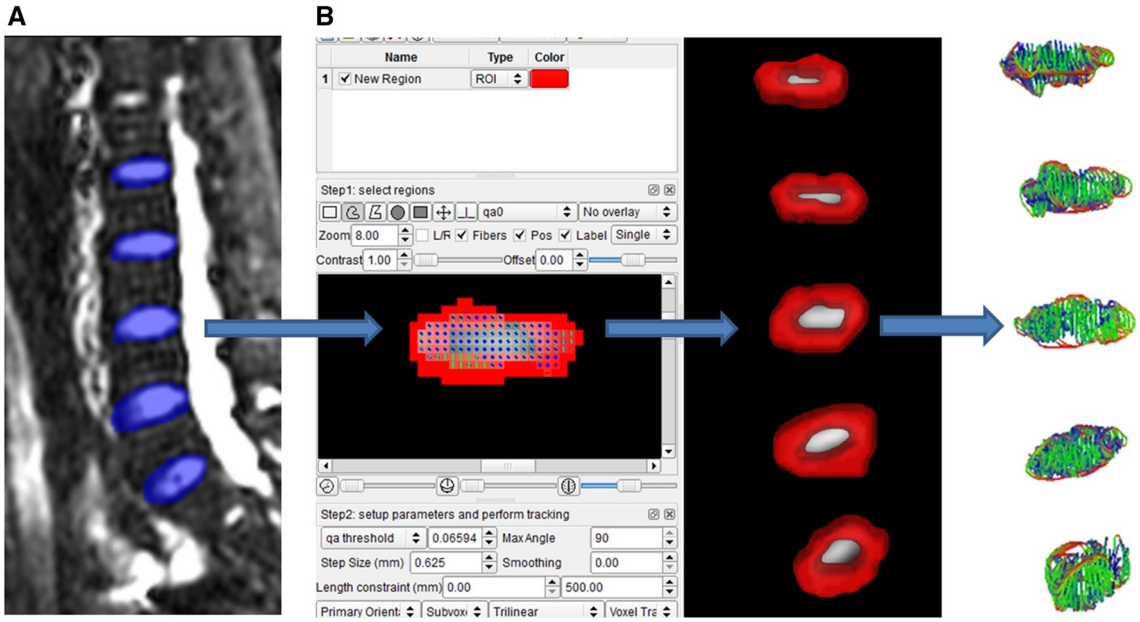


Fig. 2 Generation of DKI tractography. **a** ROI mask by MRIcron software, **b** Delineation of the tractography of the annulus fibrosus by DSI studio. This is a 35-year-old male subject in the CLBP group. The T_2 grades of L1/2, L2/3, L3/4, L4/5, and L5/S1 were 2, 2, 2, 3, and 3. In the tractography of the discs, all discs were intact except L5/S1

images using MRIcron software, and saved as masks of ROIs (Fig. 2a). Then, the masks were imported into the DSI Studio to create the tractography in all the five discs (Fig. 2b). DSI Studio provides a default quantitative anisotropy (QA) threshold (0.06594) to enable tractography. QA overcomes the limitations of FA in assessing the fibre integrity in areas with multiple crossing fibres [25, 26]. Fibre tracking was initiated from manually selected seeds in the area corresponding to the AF using all orientations present within a voxel until 10,000 tracts were detected. To maximize the detection of AF, the following parameters were kept constant across all subjects and longitudinal scans: maximum tract turning angle of 90°, step size of 0.625 mm, and a tract length constraint of 0–500 mm.

The status of each disc in the tractography rendering was scored by the same radiologist. When the annulus fibrosus was intact, the score was 0; otherwise, the score was 1.

From the DSI studio, three parameters were obtained, including mean QA, mean length, and AF volume. QA is related to the tract compactness and less susceptible to partial volume effects [25, 26]. The mean length and volume refer to the average length and the total volume of all tracked fibres in the AF (https://dsi-studio.labsolver.org/).

Statistical analysis

The data were analysed using the SPSS statistics software package (IBM, version 23.0, Chicago, USA).

To compare the grading between the CLBP and AC groups, total T_2 grades and T_2 grades in "most degenerated disc (MDD)" were calculated. For each subject, the total T_2 grades were defined as the sum of all the grades in L1/2, L2/3, L3/4, L4/5, and L5/S1. The "most degenerated disc" was defined as the disc with the highest T_2 grade among the five discs. Because the "most degenerated discs" of the CLBP group were in the L4/5 and L5/S1 level, the AC group discs for comparison were selected from the level which had higher T_2 grade. When the grade in the two levels was the same, the L5/S1 disc was selected. Student's *t* test was used to compare the differences between the CLBP and AC groups.

The Mann–Whitney test was used to compare the differences in ADC, FA, MD, Da, Dr, MK, Ka, and Kr values in the "most degenerated disc" in CLBP and AC groups.

The *t* test was also used to identify differences in the AF integrity scores: mean QA, mean length, and volume in the discs between the groups. The final data were presented as median ± standard error (SE). *P* values smaller than 0.05 were considered statistically significant.

Results

There were no differences in the age, sex, and BMI in the symptomatic and asymptomatic groups. The average pain score in CLBP was 5.45 while the average pain score in AC was 0 ($P < 0.05$).

Comparison of T_2 grades in CLBP and AC groups

The comparison of total T_2 grades and T_2 grades in the "most degenerated disc" is shown in Fig. 3. There were 1 grade 10, 3 grade 11, 5 grade 12, 6 grade 13, 2 grade 14, 4 grade 15, 1 grade 16, and 1 grade 20 in the AC group, while there were 2 grade 10, 2 grade 2, 3 grade 12, 6 grade 13, 2 grade 14, 5 grade 15, 6 grade 16, and 1 each in grade 17, 18, 19, and 20 in the CLBP group. There was no difference in the total T_2 grades in CLBP and AC groups (Fig. 3a, $P > 0.05$). Similarly, there was no difference in the T_2 grades in the "most degenerated disc" in CLBP and AC groups (Fig. 3b, $P > 0.05$). There were 2 grade 2, 12 grade 3, 8 grade 4, and 1 grade 5 in AC group, while there were 2 grade 2, 11 grade 3, 15 grade 4, 1 each in grade 6 and 7 in the CLBP group.

Comparison of ADC values and DKI multi-parameters in NP in CLBP and AC groups.

The comparisons of ADC values and DKI multi-parameters between the two subjects groups are summarized in Fig. 4.

The average FA values in the AC group (0.10 ± 0.03) were found significantly lower than in the CLBP group (0.13 ± 0.06, $P = 0.03 < 0.05$, Fig. 4), while there was no significant difference between the groups in the ADC, MD, Da, Dr, MK, Ka, and Kr values (Fig. 4, Table 1). Compared with the parameters in NP in AC group, the ADC, MD, Das, and Dr values in CLBP group were lower, while the FA, MK, Ka, and Kr values were higher, albeit not significantly ($P > 0.05$, Fig. 4).

Comparison of the microstructure of AF in CLBP and AC groups

The scores for the integrity of AF were significantly different in CLBP and AC groups ($P < 0.05$, Fig. 5a). In the AC group, there were 7 damaged AF which had fissures and 16 intact AF. In contrast, there were 27 damaged AF and 3 intact AF in the discs in the CLBP group (Fig. 5a). Using the criteria of with or without fissure, we can differentiate CLBP from AC with 90% of sensitivity and 70% specificity.

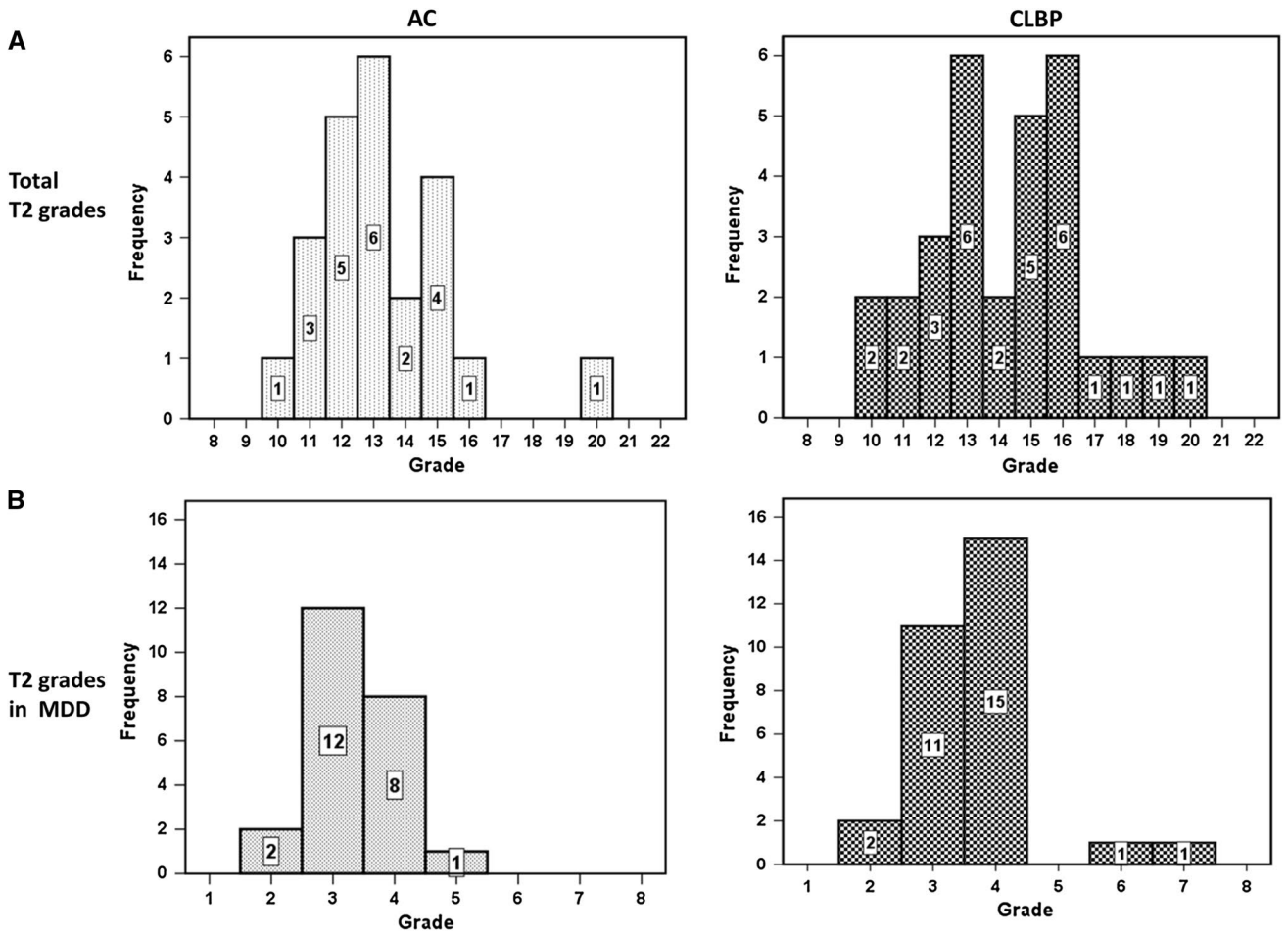


Fig. 3 Total T_2 grades (**a**) and T_2 grades in MDD (most degenerated disc) (**b**) in AC and CLBP groups. AC: asymptomatic controls; CLBP: chronic non-specific low back pain

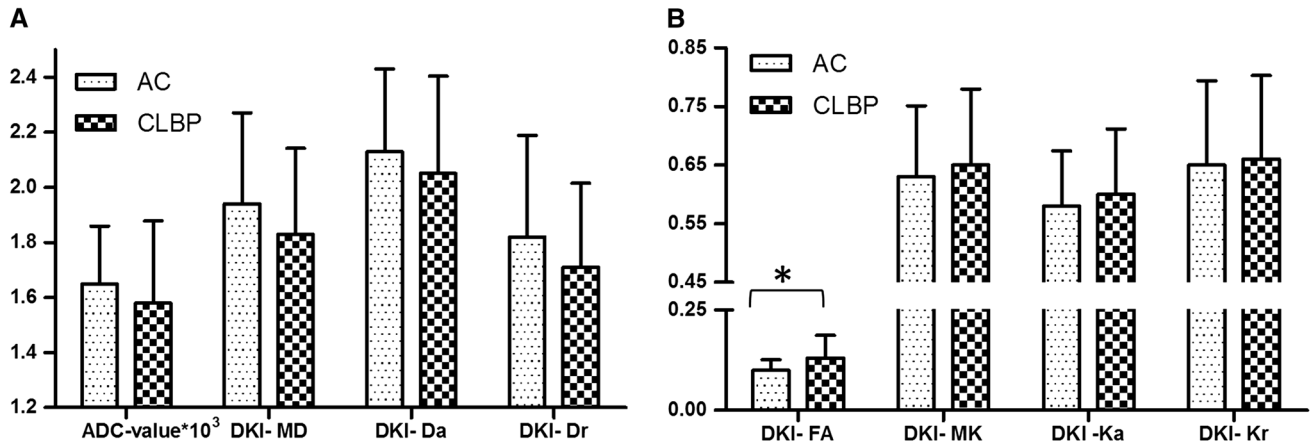


Fig. 4 Comparison of ADC values and DKI parameters between AC and CLBP groups. AC: asymptomatic controls; CLBP: chronic non-specific low back pain (*$P < 0.05$)

Table 1 Mean values of ADC value and DKI parameters in AC group and CLBP group

Parameters	AC	CLBP
ADC value (mm^2/s)	$(1.65 \pm 0.21)*10^{-3}$	$(1.58 \pm 0.30)*10^{-3}$
FA	0.10 ± 0.03	0.13 ± 0.06
MD (um^2/ms)	1.94 ± 0.33	1.83 ± 0.31
Da (um^2/ms)	2.13 ± 0.30	2.05 ± 0.35
Dr (um^2/ms)	1.82 ± 0.37	1.71 ± 0.31
MK	0.63 ± 0.12	0.65 ± 0.13
Ka	0.58 ± 0.09	0.60 ± 0.11
Kr	0.65 ± 0.14	0.66 ± 0.14

The quantitative analysis of the AF integrity is shown in Fig. 5b. The length values ($0.93 \pm 0.24 \times 10^2$) in the AC group were significantly longer than in the CLBP group ($0.74 \pm 0.28 \times 10^2$, $P = 0.014 < 0.05$), the volume in the AC group ($0.74 \pm 0.28 \times 10^2$) was significantly larger than in the CLBP group ($0.52 \pm 0.25 \times 10^2$, $P = 0.008 < 0.05$), while there was no significant difference in mean QA values between AC and CLBP groups. Additionally, the tractography of the discs could directly show the difference of AF in CLBP and AC groups (Fig. 6).

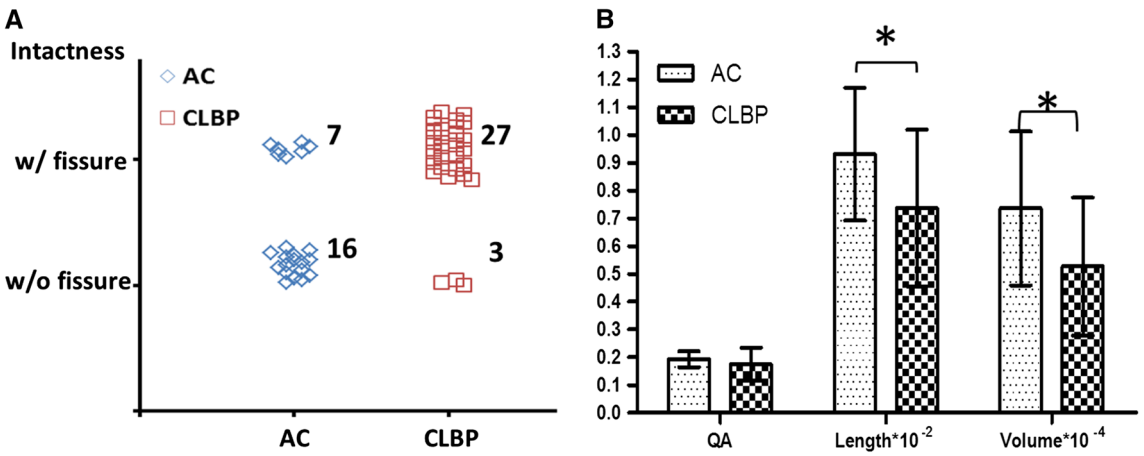


Fig. 5 **a** Scattering plot of the intactness of the AF by DKI tractography in AC and CLBP groups. **b** Comparison of the quantitative parameters of the AF integrity (mean QA, mean tract length, and tract volume) in AC and CLBP groups. **AC:** asymptomatic controls; **CLBP:** chronic non-specific low back pain. **w/fissure:** the AF in the discs with fissure; **w/o fissure:** the AF in the discs without fissure. (*$P < 0.05$)

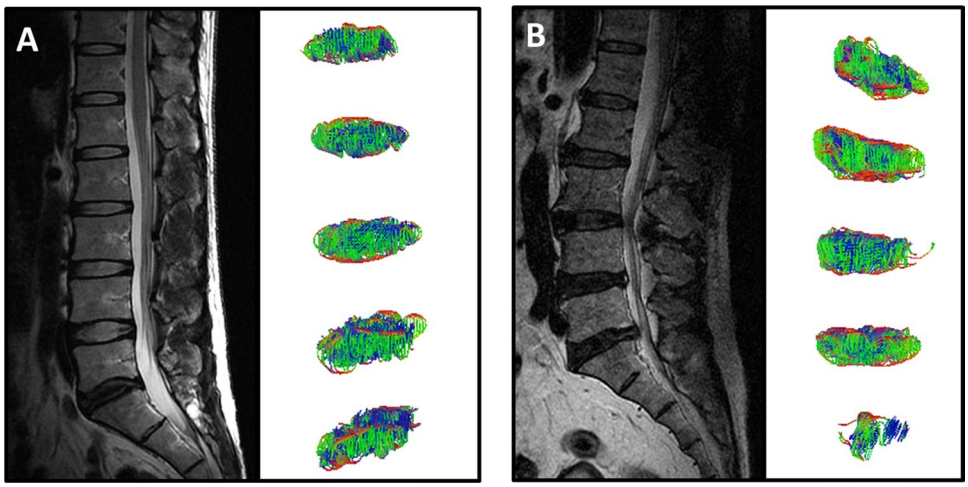


Fig. 6 Tractography of the discs in AC and CLBP groups. **a** This is a 40-year-old male in the AC group. The T_2 grades of L1/2, L2/3, L3/4, L4/5, and L5/S1 were 2, 2, 2, 2, and 4. The tractography shows that all discs were intact. **b** This is a 42-year-old male in the CLBP group. The T_2 grades of L1/2, L2/3, L3/4, L4/5, and L5/S1 were 3, 3, 3, 4, and 4. The tractography shows that the discs in L3/4 and L/S1 were not intact

Discussion

In this study, patients with CLBP but without lumbar nerve compression were investigated to understand the aetiology of disc degeneration. Revealing the microstructural changes in the NP and AF can be an important piece of the puzzle to understanding and diagnosing disc degeneration in CLBP.

Our results showed that tractography and quantitative analysis from DKI were able to indicate significant differences in the AF between CLBP and AC groups, while the T_2 grading system was not able to capture them.

Two main conclusions can be drawn from this study. Firstly, the AF tear [27–29], regardless of the presence of disc herniation [28], is a crucial character in the generation of the low back pain, as was proved by this and other studies. Here we were able to differentiate CLBP and AC patients based on the presence of fissure. Stefanakis [28] found that the fissures in AF are essential for nerve ingrowth into degenerated discs, which was one of the mechanisms leading to discogenic back pain. Additionally, the inflammatory action of the fissures can also result in discogenic back pain as demonstrated in other studies [30, 31]. The DKI tractography can directly show the integrity or injury of the AF, consequently assessing the cause of the back pain in patients and helping to make the decision of treatment.

DKI quantitative analysis on the AF can differentiate CLBP from AC patients. If a fissure is present in the AF of CLBP patients, that is, if the fibres are interrupted, the AF mean length values should be shorter and the mean volume values should be smaller compared to the asymptomatic group. Our results were consistent with this hypothesis. On the contrary, QA values, which reflect the mean tracts' compactness in the whole AF, seemed not to be affected by the fibres' interruption. We conclude that length and volume in DKT are the most informative markers to assess the integrity of the AF, and provide a quantitative measurement alongside the direct injury indication showed by the tractography.

Secondly, slight changes were observed in the microstructure of the NP between the CLBP group and the asymptomatic controls. The average FA values in the CLBP group were higher than in the AC group, indicating a change in the defined structure with proper directional anisotropy. It needs further study to show the relationship between the microstructure in NP and the low back pain. Along the same line, MK, Ka, and Kr values were higher in CLBP group, which reflected the increase in cellular density and consequent narrowing of the extracellular space [18], altering the microstructural environment and favoring an isotropic water restriction. On the other hand, the ADC values, MD, Da, and Dr values decreased in the NP of the patients with CLBP, which suggests that the content of the water reduced [32]. However, the changes were not significant, and even though it has been recently demonstrated that DKI multiple parameters correlate with the grading of disc degeneration [18], the connection to back pain needs further investigation.

The interpretation of diffusion MRI parameters in the development of intervertebral disc degeneration is controversial. Zhang [32] found that the ADC value is inversely proportional to the degeneration stage, but another study [33] showed that ADC in severely degenerated disc can even be normal or slightly increased with respect to the controls. It is possible that the condition of Gaussian diffusion assumed in DWI might heavily underestimate the microstructural complexity in the disc. Free from the constraint of Gaussian diffusion, DKI parameters can show the microstructure of the disc.

There are two main limitations in this study: first, there were not enough subjects in serious degenerated discs (grades 5, 6, 7, and 8). Second, we did not discriminate the types of low back pain in the analysis. We are currently planning on expanding the study, by including more subjects and different types of pain, in order to better guide the management decision.

Conclusion

DKI can noninvasively show the microstructural change of the degenerated intervertebral discs in humans. DKI parameters provide a quantitative measurement of the microstructural modifications in the NP, while the tractography and the tract-related parameters (length and volume) from DKT can directly show the integrity of the AF, which has been confirmed to be an important character in the generation of low back pain. Therefore, we conclude that DKI can be used to assess and monitor the status of intervertebral discs and the causes of pain in CLBP patients.

References

1. Vos T, Flaxman AD, Naghavi M et al (2012) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380(9859):2163–2196
2. Patrick N, Emanski E, Knaub MA (2014) Acute and chronic low back pain. Med Clin North Am 98(4):777–789
3. Risbud MV, Shapiro IM (2014) Role of cytokines in intervertebral disc degeneration: pain and disc content. Nat Rev Rheumatol 10(1):44–56
4. Chan WC, Au TY, Tam V, Cheah KS, Chan D (2014) Coming together is a beginning: the making of an intervertebral disc. Birth Defects Res C Embryo Today 102(1):83–100
5. Pattappa G, Li Z, Peroglio M, Wismer N, Alini M, Grad S (2012) Diversity of intervertebral disc cells: phenotype and function. J Anat 221(6):480–496
6. Fontana G, See E, Pandit A (2015) Current trends in biologics delivery to restore intervertebral disc anabolism. Adv Drug Deliv Rev 84:146–158
7. Guterl CC, See EY, Blanquer SB et al (2013) Challenges and strategies in the repair of ruptured annulus fibrosus. Eur Cell Mater 25:1–21
8. Menezes-Reis R, Salmon CE, Carvalho CS, Bonugli GP, Chung CB, Nogueira-Barbosa MH (2015) T1ρ and T2 mapping of the intervertebral disk: comparison of different methods of segmentation. AJNR Am J Neuroradiol 36(3):606–611
9. Brinjikji W, Diehn FE, Jarvik JG et al (2015) MRI findings of disc degeneration are more prevalent in adults with low back pain than in asymptomatic controls: a systematic review and meta-analysis. AJNR Am J Neuroradiol 36(12):2394–2399
10. Tonosu J, Oka H, Higashikawa A, Okazaki H, Tanaka S, Matsudaira K (2017) The associations between magnetic resonance imaging findings and low back pain: a 10-year longitudinal analysis. PLoS ONE 12(11):e0188057
11. Kealey SM, Aho T, Delong D, Barboriak DP, Provenzale JM, Eastwood JD (2005) Assessment of apparent diffusion coefficient in normal and degenerated intervertebral lumbar disks: initial experience. Radiology 235(2):569–574
12. Tourell MC, Kirkwood M, Pearcy MJ, Momot KI, Little JP (2017) Load-induced changes in the diffusion tensor of ovine anulus fibrosus: a pilot MRI study. J Magn Reson Imaging 45(6):1723–1735
13. Neto HR, Correia MM, Nunes RG, Ferreira HA (2015) Exploring the 3D geometry of the diffusion kurtosis tensor-impact on the development of robust tractography procedures and novel biomarkers. Neuroimage 111:85–99
14. Jensen JH, Helpern JA (2010) MRI quantification of non-Gaussian water diffusion by kurtosis analysis. NMR Biomed 23(7):698–710
15. Tabesh A, Jensen JH, Ardekani BA, Helpern JA (2011) Estimation of tensors and tensor-derived measures in diffusional kurtosis imaging. Magn Reson Med 65(3):823–836
16. Zhu L, Pan Z, Ma Q et al (2017) Diffusion kurtosis imaging study of rectal adenocarcinoma associated with histopathologic prognostic factors: preliminary findings. Radiology 284(1):66–76
17. Grinberg F, Maximov II, Farrher E et al (2017) Diffusion kurtosis metrics as biomarkers of microstructural development: a comparative study of a group of children and a group of adults. Neuroimage 144(Pt A):12–22
18. Zhuo J, Xu S, Proctor JL et al (2012) Diffusion kurtosis as an in vivo imaging marker for reactive astrogliosis in traumatic brain injury. Neuroimage 59(1):467–477
19. Li L, Zhu W, Chen W, Fang J, Li J (2017) The study of the intervertebral disc microstructure in matured rats with diffusion kurtosis imaging. Magn Reson Imaging 42:101–106
20. Li L, Zhou Z, Li J et al (2019) Diffusion kurtosis imaging provides quantitative assessment of the microstructure changes of disc degeneration: an in vivo experimental study. Eur Spine J 28:1005–1013
21. Balagué F, Mannion AF, Pellisé F, Cedraschi C (2012) Non-specific low back pain. Lancet 379(9814):482–491
22. Gussew A, Rzanny R, Güllmar D, Scholle HC, Reichenbach JR (2011) 1H-MR spectroscopic detection of metabolic changes in pain processing brain regions in the presence of non-specific chronic low back pain. Neuroimage 54(2):1315–1323
23. Packham TL, Bean D, Johnson MH et al (2019) Measurement properties of the SF-MPQ-2 Neuropathic Qualities subscale in persons with CRPS: validity, responsiveness, and Rasch analysis. Pain Med 20(4):799–809. https://doi.org/10.1093/pm/pny202
24. Chiarotto A, Boers M, Deyo RA et al (2018) Core outcome measurement instruments for clinical trials in nonspecific low back pain. Pain 159(3):481–495
25. Ludescher B, Effelsberg J, Martirosian P, et al. (2008) T2- and diffusion-maps reveal diurnal changes of intervertebral disc composition: an in vivo MRI study at 1.5 Tesla. J Magn Reson Imaging 28(1): 252–257
26. Griffith JF, Wang YX, Antonio GE, et al. (2007) Modified Pfirrmann grading system for lumbar intervertebral disc degeneration. Spine (Phila Pa 1976) 32(24):E708–E712
27. Shahraki NM, Fatemi A, Agarwal A, Goel VK (2017) Prediction of clinically relevant initiation and progression of tears within annulus fibrosus. J Orthop Res. 35(1):113–122
28. Stefanakis M, Al-Abbasi M, Harding I, et al. (2012) Annulus fissures are mechanically and chemically conducive to the ingrowth of nerves and blood vessels. Spine (Phila Pa 1976) 37(22):1883–1891
29. Osti OL, Vernon-Roberts B, Moore R, Fraser RD (1992) Annular tears and disc degeneration in the lumbar spine. A post-mortem study of 135 discs. J Bone Joint Surg Br 74(5):678–682
30. Ohtori S, Inoue G, Miyagi M, Takahashi K (2015) Pathomechanisms of discogenic low back pain in humans and animal models. Spine J 15(6):1347–1355
31. Peng Y, Lv FJ (2015) Symptomatic versus asymptomatic intervertebral disc degeneration: is inflammation the key. Crit Rev Eukaryot Gene Expr 25(1):13–21
32. Zhang W, Ma X, Wang Y et al (2014) Assessment of apparent diffusion coefficient in lumbar intervertebral disc degeneration. Eur Spine J 23(9):1830–1836

33. Chiu EJ, Newitt DC, Segal MR, Hu SS, Lotz JC, Majumdar S (2001) Magnetic resonance imaging measurement of relaxation and water diffusion in the human lumbar intervertebral disc under compression in vitro. Spine (Phila Pa 1976) 26(19):E437–E444

Affiliations

Li Li[1,4,5] · Zhiguo Zhou[2] · Wei Xiong[3] · Jicheng Fang[1] · Yang Li[1] · Zhanying Jiao[1] · Alessandro Scotti[4,5] · Feng Li[3] · WenZhen Zhu[1] · Kejia Cai[4,5]

1 Radiological Department, Tongji Hospital, Tongji Medical College, HUST, Wuhan 430030, Hubei, People's Republic of China

2 Department of Orthopedics, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, HUST, Wuhan 430030, Hubei, People's Republic of China

3 Department of Orthopedics, Tongji Hospital, Tongji Medical College, HUST, Wuhan 430030, Hubei, People's Republic of China

4 Departments of Radiology, University of Illinois At Chicago, Chicago, IL, USA

5 Department of Bioengineering, and the Center for MR Research, University of Illinois At Chicago, Chicago, IL, USA