



Axial loading during MRI reveals deviant characteristics within posterior IVD regions between low back pain patients and controls

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Received: 10 May 2018 / Revised: 27 August 2018 / Accepted: 19 September 2018 / Published online: 9 October 2018
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Abstract

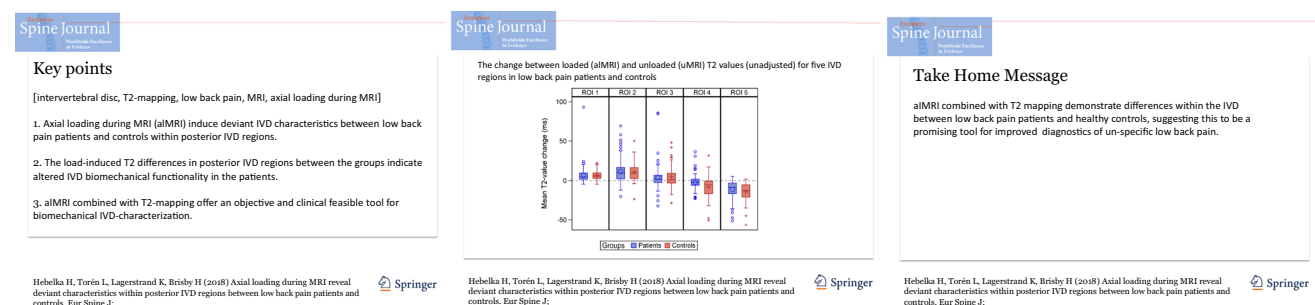
Purpose To investigate differences in functional intervertebral disk (IVD) characteristics between low back pain (LBP) patients and controls using T2-mapping with axial loading during MRI (aMRI).

Methods In total, 120 IVDs in 24 LBP patients (mean age 39 years, range 25–69) were examined with T2-mapping without loading of the spine (uMRI) and with aMRI (DynaWell[®] loading device) and compared with 60 IVDs in 12 controls (mean age 38 years, range 25–63). The IVD T2-value was acquired after 20-min loading in five regions of interests (ROI), ROI1–5 from anterior to posterior. T2-values were compared between loading states and cohorts with adjustment for Pfirrmann grade.

Results In LBP patients, mean T2-value of the entire IVD was 64 ms for uMRI and 66 ms for aMRI ($p = 0.03$) and, in controls, 65 ms and 65 ms ($p = 0.5$). Load-induced T2-differences (aMRI–uMRI) were seen in all ROIs in both patients ($0.001 > p < 0.005$) and controls ($0.0001 > p < 0.03$). In patients, aMRI induced an increase in T2-value for ROI1–3 (23%, 18% and 5%) and a decrease for ROI4 (3%) and ROI5 (24%). More pronounced load-induced decrease was detected in ROI4 in controls (9%/ $p = 0.03$), while a higher absolute T2-value was found for ROI5 during aMRI in patients (38 ms) compared to controls (33 ms) ($p = 0.04$).

Conclusion The aMRI-induced differences in T2-value in ROI4 and ROI5 between patients and controls most probably indicate biomechanical impairment in the posterior IVD regions. Hence, aMRI combined with T2-mapping offers an objective and clinical feasible tool for biomechanical IVD characterization that may deepen the knowledge regarding how LBP is related to altered IVD matrix composition.

Graphical abstract These slides can be retrieved under Electronic Supplementary Material.



Keywords Intervertebral disk · T2-mapping · Low back pain · MRI · Axial loading during MRI

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00586-018-5774-y>) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Introduction

The matrix composition of the intervertebral disk (IVD) plays an essential role for normal spinal function. With degeneration, the disks' functionality is affected with reduced capacity to resist load [1]. IVD degeneration is associated with low back pain (LBP). Yet, despite relentless research, the exact linkage between LBP and degeneration remains unknown. Currently, the knowledge regarding the relation between IVD degeneration and LBP is limited most probably due to insufficient sensitivity and limited specificity within IVD diagnostics [2]. Therefore, improved diagnostic tools with capacity to obtain both detailed IVD matrix composition and biomechanical characteristics are warranted in order to characterize functional IVD impairments, but also to link findings to pain patterns and follow up for regenerative therapies [3–5].

Although not yet used in clinical routine within spine diagnostics, quantitative MRI techniques have emerged during the last decade. For example, T2-mapping enables reliable and objective quantification of the IVD matrix, also in early stages of degeneration [5–7]. Information obtained with these techniques reflects the IVDs biochemical composition and structural integrity, with for example an inverse linear correlation between T2-values and degeneration grade. Further, this technique has demonstrated a linkage between regional T2-values and structural abnormalities like annular fissures and hernias [7–11] and information regarding mechanical IVD properties [7, 8, 10, 12].

Assessment of objective IVD measures during loading conditions can be expected to be of importance within LBP diagnostics, since LBP is usually aggravated in positions with loading of the spine. Several studies have reported load-induced IVD changes, for example volume [13] and height changes [14], altered position of nucleus pulposus [8, 14] and affection on quantitative MRI parameters [6, 14–17]. However, a majority of these *in vivo* studies compare image characteristics before and after various loading maneuvers and not *during* load. Investigation of the spine with upright MRI is possible, and despite lower magnetic field (0.6 T), these scanners provide nowadays image quality comparable to high-field conventional supine MRI scanners [18]. However, the availability of such open MRI systems is limited why portable compression devices, which allow axial loading in conventional supine MRI systems, are an option when to investigate the spine in a loaded position [19, 20]. Recently, T2-mapping combined with axial loading during MRI (aMRI) was reported a promising method to reveal that functional IVD characteristics instantaneously induce regional IVD changes [10]. The aim of the present study was to investigate whether

LBP patients and controls display differences in such load-induced IVD behavior, measured with T2-mapping.

Methods

Participants

Twenty-seven LBP patients, referred from the spine surgery unit at Sahlgrenska University Hospital, Gothenburg, Sweden were examined with T2-mapping without loading of the spine (uMRI) and with aMRI. Three patients were excluded, one due to severe scoliosis that made measurements of reliable T2-values difficult when our methodology with fused T1-weighted and T2 maps was used, and two due to severe motion artifacts in the images.

Totally, 120 IVDs were analyzed in the 24 patients (mean age 39 years, range 25–69 years). The patients were included consecutively among patients referred to the radiology department with non-specific LBP. Inclusion criteria were LBP for more than 6 months, clinically severe enough to be considered for surgery and age between 20 and 70 years. For comparison, 60 control IVDs in 12 age-matched controls (mean age 38 years, range 25–63) were recruited. Inclusion criteria for the controls were age between 20 and 70 years, total absence of any type of LBP during the past 6 months and lack of previous LBP with duration more than 1 week. None of the volunteers suffered from any known medical history of back pain- or spine-related diseases. Exclusion criteria for both patients and controls were previous spine surgery and contraindications for MRI. The study was conducted according to the Declaration of Helsinki. Ethical approval was given by the Regional Ethics Review Board, and oral and written informed consent was obtained from all participants.

Magnetic resonance imaging

All participants were subjected to an MRI examination performed on a 1.5-T scanner (Siemens Magnetom, Aera, Erlangen, Germany), initially with the spine imaged without load (uMRI) for 20 min followed by imaging with aMRI for 20 min. The aMRI was performed with a compression device (DynaWell[®] diagnostics AB, Las Vegas, NV, USA) with applied load corresponding to 50% of the body weight to simulate the loading forces the spine is exposed to in an upright position [19, 20]. This compression device is composed by a footplate attached to a patient harness by side straps, which are tightened by regulators for a controlled axial loading of the lumbar spine. During compression the patient is lying supine with extended hips and knees. To prevent flexion of the spine during compression, a small cushion is placed beneath the lumbar spine.

In Table 1, the imaging protocol is specified. T2-mapping was performed at the end of the protocol. Hence, the T2-mapping with and without axial load was separated in time by 20 min. All MRI examinations were performed between 9 a.m. and 15 p.m. Axial and sagittal T2-weighted images were performed as part of the clinical imaging protocol, to be able to detect any affected nerve roots in case aMRI would induce radiating pain during; however, these images were not further analyzed as part of the study.

Measurements

Sagittal TSE T1-weighted sequences were fused with sagittal SE T2-mapping sequences using the imaging processing software from Syngo.via (Siemens, Erlangen Germany). Fused images were used for the IVD segmentation because the addition of T1 signal improves the resolution of the T2 mapping images. In order to enable volumetric IVD analysis the images were reformatted into 10-mm non-overlapping slices. The three central such slices were used in the analysis, thus covering 30 mm of the IVD width in total (here referred to as “entire IVD”). The IVD segmentation was performed manually, with delineation along the IVD contours (Fig. 1), using a polygonal measuring tool. Each segmented IVD was further divided into five equal regions of interest (ROI) in the sagittal plane, with ROI1 representing anterior parts of the IVD, ROI5 posterior IVD parts and ROI2–4 the parts in between.

Mean T2-values and standard deviations of the means were recorded for each separate ROI. A mean T2-value of all three sagittal slices was calculated separately for the five different ROIs. The analysis was repeated on all aMRI images.

Disk degeneration was graded on uMRI by an experienced radiologist, according to the Pfirrmann classification [21]. Since high-intensity zones (HIZ) potentially could influence regional T2-values, any HIZ, according to April and Bogduks classification [22], was registered.

Reliability measures

A second-year radiologist resident (LT) performed all measurements after an extensive training period, supervised by

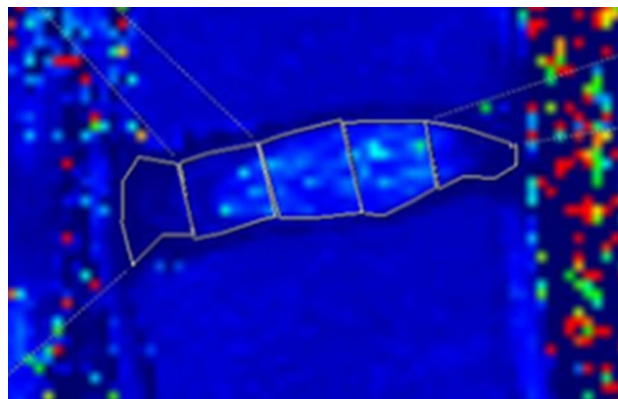


Fig. 1 Illustration of IVD segmentation

an experienced radiologist. The supervised training was performed as part of another study [12], with inter-observer measurements performed approximately 6 months after the supervised training period and the assessment of the IVD segmentation performed independently and blinded to each other. Inter-observer measurements displayed high agreement for all ROIs with an ICC for ROI1–5 ranging between 0.79 and 0.99 [12]. Intraobserver analysis for the method is also known to have high consistency [10].

Statistical analysis

Categorical variables were described by number and percentage. For comparison of T2-values between cohorts and difference aMRI–uMRI within cohorts, a mixed linear model was used that adjusts for multiple observations within subjects and with adjustment for Pfirrmann grade between cohorts. Results from the models are presented as adjusted means (with 95% CI) and *p* value.

Reliability of quantitative measurements for inter-rater agreement was performed using intraclass correlation coefficients (ICC) with 95% confidence intervals. ICC model 2 was used with single measurement to determine consistency in agreement. The coefficients were interpreted according to Landis and Koch [23]. All tests were two-tailed and conducted at

Table 1 Imaging protocol

MRI sequence	Orientation	Flip (<i>a</i>)	TR (ms)	TE (ms)	FOV (mm)	Scan matrix	Slice (mm)	NEX
T1 W	Sagittal	150	630	9	300 × 300	320 × 320	3.5	2
T2 W	Sagittal	150	3500	95	300 × 300	384 × 384	3.5	1
T2 W	Axial	150	5330	97	220 × 220	256 × 256	3.5	
T2 mapping	Sagittal	180	1500	11.1–88.8 (8 echos)	220 × 220	256 × 256	3.5	1

W weighted, *Flip a* flip angle, *TR* repetition time, *TE* echo time, *FOV* field of view, *Slice* slice thickness, *NEX* number of excitations

Table 2 Demographics of HIZ and Pfirrmann grading

	Patients (<i>n</i>)	%	Controls (<i>n</i>)	%
Pfirrmann grade				
1	9	7.5	7	11.7
2	60	50	34	56.7
3	35	29.2	14	23.3
4	16	13.3	4	6.7
5			1	1.7
HIZ	19	15.8	3	5.0

0.05 significance level. All analyses were performed by using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Demographics

The distribution of Pfirrmann grading and the presence of HIZ's in the cohorts are displayed in Table 2.

T2-values of the entire IVD

In the patients, the mean T2-value of the entire IVD differed significantly between uMRI (64 ms) and aMRI (66 ms) ($p=0.04$, adjusted for Pfirrmann grade). Corresponding values in controls were 65 ms and 65 ms ($p=0.98$, adjusted for Pfirrmann grade).

T2-values for sub-regions of the IVD

In all ROIs, aMRI induced significant changes in the T2-value with an increase in ROI1-3 and a decrease in ROI4-5, with similar behavior in both patients and controls, both for unadjusted raw data (Fig. 2) and after adjustment for Pfirrmann grade and intraindividual dependency (Table 3). In the patient cohort, T2-values increased in ROI1-3 with 23%, 18% and 5% with a decrease in ROI4-5 corresponding to 3% and 24%, respectively (Table 3). A significant difference between cohorts regarding load-induced effect (aMRI–uMRI) was detected in ROI4, with a more prominent T2 decrease for the controls (–8 ms/9%) compared with the patients (–3 ms/3%) ($p=0.03$) (Table 3). Additionally, a significant difference between the cohorts was found in ROI5 for aMRI ($p=0.04$, adjusted for Pfirrmann grade).

Discussion

This study, comparing load-induced IVD behavior between LBP patients and controls by combining T2 mapping and aMRI, reveals large T2-value changes within all IVD

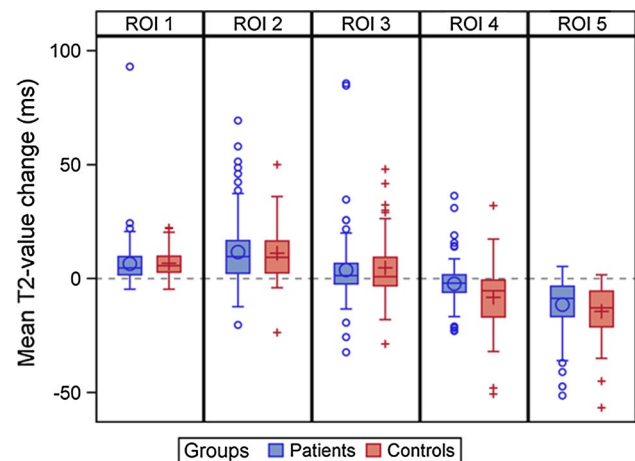


Fig. 2 Boxplot of load-induced T2-value changes (aMRI–uMRI) in the ROIs of the IVD. The boxplot displays the raw data, without adjustment for Pfirrmann grade and not accounting for intraindividual dependency

regions in both groups. Significant differences between patients and controls in loading behavior occurred within the interface NP-posterior AF and posterior AF. Since the T2-value reflects both tissue hydration and content and orientation of collagen fibers [9], the induced changes likely indicate instantaneous IVD matrix reorganization, such as redistribution of water molecules within the collagen network. The differences between the cohorts in load-induced behavior can be assumed to reflect biomechanical impairment within foremost posterior regions.

T2-values of the entire IVD

The slight, but significant load-induced increase in T2-value of the entire IVD, from approximately 64 to 66 ms, in LBP patients is in accordance with the feasibility study published by Nilsson et al. [10]. The change indicates a re-organization of the IVD matrix as a response to the spinal load, rather than ejection of water as previously reported [16, 17]. Spinal compression increases the intradiscal pressure, which in a degenerated IVD is more unevenly distributed [24]. The reason why load induced a change in the entire IVD in patients and not in controls might be a reflection of more anisotropic IVD matrix in the patient cohort, where for example water molecules are forced into annular fissures during load. The increased number of HIZ, representing annular fissures [22], in the LBP cohort strengthens the argument that patients have increased IVD impairment, at least posteriorly where all HIZs were found. Stelzener et al. [15] reported no IVD change comparing T2 mapping directly after load and subsequent unloading in 41 patients. These deviant results likely reflect a higher sensitivity of aMRI to detect tissue-specific differences.

Table 3 Regional T2-values at uMRI, alMRI and alMRI–uMRI

	ROI	Patients			Controls			<i>p</i> value between groups
		Mean T2-value (ms)	95% CI	<i>p</i> value	Mean T2-value (ms)	95% CI	<i>p</i> value	
uMRI	1	31	29–33		33	30–35		0.25
	2	65	61–74		68	61–75		0.88
	3	88	81–95		90	84–96		0.60
	4	86	79–92		88	77–99		0.66
	5	50	46–54		47	41–53		0.40
alMRI	1	37	34–40		39	37–42		0.42
	2	79	72–87		79	72–86		0.90
	3	92	83–101		94	87–102		0.64
	4	83	76–90		80	72–89		0.59
	5	38	35–41		33	30–37		0.038*
alMRI–uMRI	1	7	4–9	< 0.0001*	7	5–9	< 0.0001*	0.98
	2	12	10–14	< 0.0001*	11	7–14	< 0.0001*	0.44
	3	4	1–7	0.015*	4	1–8	0.014*	0.88
	4	–3	–5 to 0	0.03*	–8	–12 to –4	< 0.002*	0.026*
	5	–12	–15 to –9	< 0.0001*	–14	–18 to –10	< 0.0001*	0.39

Mean T2-values (ms) for each region of interest (ROI) at unloaded MRI (uMRI), axial loading during MRI (alMRI) and the difference between the examinations (alMRI–uMRI). The mean values are adjusted for Pfirrmann grade and intraindividual dependence. Significant *p* values are marked with *

T2-values for sub-regions of the IVD

The finding of an induced T2-change in ROI1, ROI2 and ROI5 by alMRI, of approximately 20%, confirms that the IVD instantaneously displays rather large dynamical effects regionally as a response to load [10, 12]. Since alMRI causes extension of the spine, it is expected that the force applied with compression is highest on the posterior elements, thus resulting in re-distribution of water molecules from posterior to anterior parts during load [10, 12] and vice versa during unloading [15]. Our absolute regional T2-values are similar to other studies [25, 26] with minor differences likely due to methodology issues, like IVD segmentation and younger cohorts in previous studies. The results are also in accordance with studies investigating quantitative IVD effects of load indirectly, i.e., MRI after various loading maneuvers [16, 17]. The large load-induced differences (up to 24% within some ROIs) show that it is crucial with regional IVD analysis in order to gain deeper understanding regarding IVD degeneration and functional parameters.

The only significant difference between LBP patients and controls in load-induced behavior (alMRI–uMRI) was detected in ROI4. A difference between the cohorts was however also detected in the loaded state in ROI5 (alMRI). Ogon et al. [27] also found differences in these regions when studying T2-mapping in patients and controls, however at uMRI. Contrary to the current study, they found lower T2-values in posterior AF in patients compared to controls.

The significantly higher T2-values in ROI5 in the patient cohort at alMRI in the current study could be due to the higher frequency of HIZ, supported by previous findings of higher T2-values in ROI5 relative to ROI3 in individuals with annular tears [26]. Several others imply that high T2-values in posterior AF might represent structural weakness, like annular tears or herniation [11, 26, 27]. Messner et al. compared the IVD T2-value in LBP patients with morphological measures like hernias and IVD bulging and concluded that an increase in T2-values in the posterior 10% was associated with herniation, while the posterior 20% (equal to ROI5) displayed significantly lower T2-values in IVDs with hernias compared with IVDs without. The divergent results compared to the current study, with higher T2-values posteriorly in patients, might be caused by the different conditions (patient phenotypes) studied (disk herniation vs. non-specific LBP patients). This implies that T2-mapping with regional analysis might actually differentiate between various structural IVD phenotypes. It seems plausible that the induced differences between the cohorts in ROI4 and ROI5 in the current study might reflect increased anisotropic tissue characteristics in the patient cohort, underlying functional IVD differences. Fluid can be assumed to shift into annular fissures during spinal loading but retain in unloaded position, which would explain significant differences in ROI5 at alMRI but lack of such at uMRI.

Several studies also report that quantitative MRI is sensitive for impaired biomechanical IVD function [5, 7, 14].

T2* has been shown to correlate with decreased range of motion in flexion and increased axial rotation [5], predicting altered IVD functionality better than Pfirrmann grading. *Ex vivo*, Maquer et al. investigated the IVD modulus, calculated from the load–deflection curves, in flexion and extension rotation with axial T2 maps [25] and found high correlation between quantitative T2 parameters within posterior AF and the IVD stiffness. In a previous patient study the T2 weighted center (T2WC; mean position of the points in an ROI, weighted by their T2) was investigated during uMRI and alMRI in 15 LBP patients and 15 controls. In the patient cohort load-induced shift anteriorly of the T2WC was reported, while a discrete posterior shift was found in controls. Seemingly, a relation between altered biomechanics in the posterior IVD regions and LBP seems to exist why this region needs to be focused on regarding the search for biomarker of pain [25, 26].

Limitations

In most published studies, the IVDs are statistically evaluated independently, not accounting for potential inter-individual dependency. In this study, such dependency was accounted for. However, Passias et al. [28] reported hypomobility in a degenerated segment concomitant with hypermobility in the adjacent segment, effects that potentially can counteract each other. This displays the complexity in evaluating individual IVDs, and it cannot be excluded that such factors could have influenced our results. Also, the cohort size did not allow sub-analysis regarding if the T2 depends on IVD level in the lumbar spine, which needs to be investigated in studies with larger cohorts.

No gold standard method for IVD segmentation exists, and the segmentation method may have influenced the results [29]. Moreover, the position of the NP and AP could not be exactly determined. Nevertheless, this study includes the entire IVD craniocaudally as well as including 3 out of 4 cm in mediolateral direction, which likely reflect the behavior in the IVD better as compared with only a small box overlying the central IVD parts where important information in the periphery can be lost. With this methodology it cannot be excluded that signal belonging to the endplate and/or vertebra is included in the segmentation, especially since volumetric images are used for the IVD delineation, which is a limitation. Since compression forces applied to the IVD act circumferential, i.e., not only in anteroposterior direction, any changes within the matrix composition, also in more lateral parts, must be assumed to contribute to altered biomechanics, making the current study superior to similar studies methodologically.

Conclusion

The significant load-induced T2 differences in the posterior borderzone of NP and AF between patients and controls indicate altered IVD functionality that might represent posterior biomechanical impairment within the patients IVDs. Hence, alMRI combined with T2-mapping offers an objective and clinical feasible, diagnostic tool that may deepen the knowledge regarding how LBP is related to altered IVD matrix composition. In extension the ultimate goal with the current work is to obtain compositional or functional IVD measures that can be used as biomarkers of pain.

Acknowledgements The authors acknowledge support from C4I center, Sahlgrenska University Hospital, Konrad Helfrid Johansson's Foundation, Felix Neubergh Foundation, ALF Grant Västra Götaland Region and Grant AFA Insurance Company.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.


Informed consent Oral and written informed consent was obtained from all individual participants included in the study.

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