Observational Study

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Correlation between T2* (T2 star) relaxation time and cervical intervertebral disc degeneration

An observational study

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Abstract

Purpose: To demonstrate the potential benefits of T2* relaxation time of intervertebral discs (IVDs) regarding the detection and grading of degenerative disc disease using 3.0-T magnetic resonance imaging (MRI) in a clinical setting.

Materials and Methods: Cervical sagittal T2-weighted, T2* relaxation MRI was performed at 3.0-T in 61 subjects, covering discs C2–3 to C6–7. All discs were morphologically assessed based on the Pfirrmann grade, and regions of interests (ROIs) were drawn over the T2* mapping. Receiver operating characteristic (ROC) analysis was performed among grades to determine the cut-off values.

Results: Cervical intervertebral discs (IVDs) of patients were commonly determined to be at Pfirrmann grades III to V. The nucleus pulposus (NP) values did not differ significantly between sexes at the same anatomic level ($P > 0.05$). In the NP, the T2* values tended to decrease with increasing grade ($P < 0.000$), and a significant difference was found in the T2 values between grades I to V ($P < 0.05$). T2* values based on disc degeneration level classification were as follows: grade I (>30 milliseconds), grade II (24.55–29.99 milliseconds), grade III (21.65–24.54 milliseconds), grade IV (18.35–21.64 milliseconds), and grade V (<18.34 milliseconds).

Conclusion: Our standardized method of region-specific quantitative T2* relaxation time evaluation seems capable of characterizing different degrees of disc degeneration quantitatively. The T2* values obtained in these cervical IVDs may serve as baseline values for future T2* measurements in both healthy and degenerated cervical discs.

Abbreviations: AF = annulus fibrosus, AUC = area under the curve, C = cervical, FSE = fast spin echo, GAG = glycosaminoglycan, IVDs = intervertebral discs, IVDD = intervertebral disc degeneration, MRI = magnetic resonance imaging, NP = nucleus pulposus, ROC = receiver operating characteristic, ROIs = regions of interests, T2WIs = T2-weighted images, TE = echo time, TR = repetition time.

Keywords: intervertebral disc degeneration, magnetic resonance imaging, T2 star relaxation time

1. Introduction

Neck and back pain are two of the most common musculoskeletal symptoms, their prevalence is remarkable, and 1 of the main causes of these symptoms is cervical intervertebral disc (IVD) degeneration.[1–3] Early signs of disc degeneration are manifested by biochemical changes, including proteoglycan loss and decreased osmotic pressure and hydration.[4,5] In the later stages of disc degeneration, morphological changes occur, including a loss of disc height, disc herniation, annular tears, and radial bulging.[6]

Imaging has an important role in the diagnosis of cervical degenerative disease, and magnetic resonance imaging (MRI) is the most useful modality for characterizing IVD lesions. Signal variations of the discs on T2-weighted images (T2WIs) determinate the degrees of disc degeneration.[7,8] Among the MRI technologies, T2* mapping provides information on spatial macromolecule architecture and its interaction with water molecule mobility, can be used to detect early abnormalities in the lumbar IVD and endplate, and track response to therapy.[9–12]

T2* values has been proposed as a robust biomarker of human articular cartilage degeneration in several joints.[13,14] Previous studies have demonstrated the feasibility of IVD assessment with T2* values,[10] histological correlation of the T2* values and degree of degeneration,[11] and biochemical correlation of the T2* values and low glycosaminoglycan (GAG) content with decreased lumbar mechanical function.[12] Detiger et al[11] validated T2* mapping for disc degeneration by correlating this technique with accepted parameters of IVD degeneration with biochemical assays and macroscopic and histological scoring by using 48 goat IVDs. The results confirmed that a linear positive correlation was observed between T2* relaxation time and GAG content ($r = 0.64$), Pfirrmann grades ($r = -0.67$), macroscopic ($r = -0.33$) and histological ($r = -0.45$) findings. The researchers

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concluded that this MRI technique allows measurements on a continuous scale, minimizing observer bias compared to grading systems. Ellingson et al[12] determined the relationship between $T2^*$ relaxation time and proteoglycan and collagen contents throughout the degenerative spectrum by using 18 human cadaveric lumbar discs. They found that the $T2^*$ relaxation time was correlated with sulfated GAG and hydroxyproline contents. They confirmed that $T2^*$ MRI assessment of disc health is a clinically promising feasible tool as a biomarker for distinguishing degenerative changes. However, research in the cervical spine is rare even it is nevertheless relevant to the causes of spinal pain. Furthermore, a disc degeneration classification that is quantifiable may be of value for research purposes related to disc abnormalities.

Thus, the aim of this study was to use $T2^*$ mapping to quantify intervertebral degeneration based on the Pfirrmann classification and to propose an objective borderline value for the classification based on $T2^*$ relaxation time.

2. Materials and methods

2.1. Ethics statement and study sample

This study recruited 61 volunteers (31 male; 30 female; mean age, 44.02 ± 15.07 years; range, 22–76 years) who underwent MRI of the cervical spine (a total of 305 cervical discs) because of neck pain and upper numbness, including paresthesia. All subjects were confirmed to have no other spine diseases except disc degeneration. The study was approved by the institutional review board of the First Affiliated Hospital, Wenzhou Medical University, and all participants provided written informed consent before enrollment.

2.2. Magnetic resonance imaging

MRI was performed by a 3.0-T MR scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany) with a maximum gradient strength of 45 mT/m and slew rate of 200 mT/m/ms, and equipped with spine matrix coils (Siemens Healthcare). All MR images in this study were obtained in the afternoon to minimize the diurnal variation of $T2^*$ values in the IVDs. Pulse sequences included axial, coronal, and sagittal T2-weighted turbo spin echo imaging (repetition time [TR]/echo time[TE], 3000/96 milliseconds; section thickness, 4 mm for sagittal and coronal and 3 mm for axial; intersection gap, 0.4 mm; field of view, 260 mm × 260 mm for sagittal and coronal and 160 mm × 160 mm for axial; matrix, 320 × 240; parallel imaging factor of 2; 2 signals acquired), sagittal T1-weighted turbo spin echo imaging (TR/TE, 550/9 milliseconds; section thickness, 4 mm; intersection gap, 0.4 mm; field of view, 260 mm × 260 mm; matrix, 320 × 240; parallel imaging factor of 2; 2 signals acquired), and sagittal $T2^*$ maps (TR/TE, 419/4.36 milliseconds, 11.90, 19.44, 26.98, 34.52, 40.73, 46.50; section thickness, 4 mm; intersection gap, 0.4 mm; field of view, 220 mm × 220 mm; matrix, 288 × 288) were calculated (MapIt, Siemens Healthcare), and mean $T2^*$ values were recorded using MMWP workstation (Syngo Multimodality Workplace, Erlangen, Germany).

2.3. Image analysis

Morphological evaluation of images was carried out by 2 radiologists in consensus (MH, 10 years of experience with a special interest in musculoskeletal radiology, and LC, more than 20 years of experience in orthopedic radiology). Five IVDs (C2–C7) of the cervical spine were assessed on the sagittal T2-weighted fast spin echo (FSE) images. We decided to adopt the method reported by previous studies.[15–17] To minimize the error in identifying nucleus pulposus (NP) anatomic structure, free hand regions of interests (ROIs) for Pfirrmann grades I to V manually drawn on the inner portion of each cervical disc were carefully matched to the NP shape on the T2WI images and copied to the corresponding $T2^*$ maps (Fig. 1). $T2^*$ values were reported as mean ± SD.

2.4. Inter- and intraobserver analysis

An interobserver evaluation of $T2^*$ maps was performed in 305 discs by 2 independent observers with different skill levels (a musculoskeletal radiologist with 10 years of experience [observer A] and an orthopedic surgeon with 20 years of experience [observer B]). All observers are experienced in musculoskeletal MRI ROI selection (at least 1 year experience). Moreover, observers A and B repeated the same analysis to evaluate intraobserver agreement 1 month apart independently.

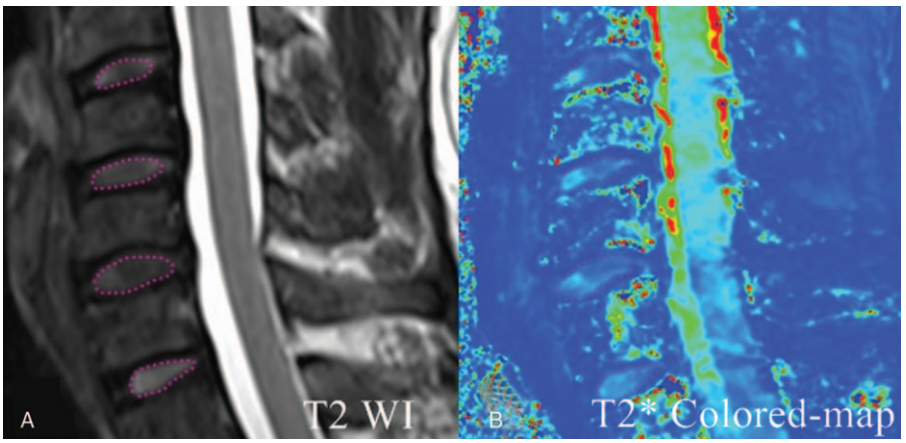

Figure 1. For the representative intervertebral disc, regions of interests (ROIs) evaluation on the sagittal T2WI (A), an ellipse ROI was selected for the nucleus pulposus (NP). Then these ROIs inT2WI were copied to the $T2^*$ colored map (B). $T2^*$ values were measured.

Table 1

Degeneration grade according to Pfirrmann scale, sex, and disc level of the cervical intervertebral discs analyzed in study.

Degeneration grade	Sex		Disc levels					Total
	Male	Female	C2–3	C3–4	C4–5	C5–6	C6–7	
I	14	19	11	7	7	1	7	33
II	39	20	18	11	11	8	11	59
III	64	83	19	25	23	20	15	102
IV	27	42	12	10	9	19	19	69
V	11	32	1	8	11	13	9	43
Total	155	150	61	61	61	61	61	305

C = cervical.

2.5. Statistical analysis

Statistical analysis and all graphs were performed in SPSS 19.0 (SPSS, Inc., Chicago, IL). The $T2^*$ values of genders of both NP according to the anatomic level of each disc were compared by using 1-way analysis of variance (ANOVA). Intraobserver and interobserver agreements were tested by using *k* statistics for evaluating the reliability of Pfirrmann grading. Univariate ANOVA and post hoc tests were performed for Pfirrmann group comparisons. Welch correction was used in cases of heteroscedasticity. In addition, a Spearman rank correlation was performed to assess the correlation of NP $T2^*$ values and Pfirrmann grading. In addition, boxplot and receiver operating characteristic (ROC) curves were generated. All above-mentioned tests were considered significant with $P < 0.05$.

3. Results

A typical set of discs containing the Pfirrmann grades are shown in Fig. 1, with their $T2^*$ maps. T2WI-based Pfirrmann grade classification consisted of the following: grade I, 33 discs; grade II, 59 discs; grade III, 102 discs; grade IV, 69 discs; and grade V, 43 discs. The intraobserver test yielded *k* values ranging from 0.785 ($P = 0.000$) to 0.805 ($P = 0.000$), whereas the interobserver test produced *k* values of 0.793 ($P = 0.000$) (Table 1). A tendency toward an increase in NP from C2–3 to C4–5 was observed, which was a reversal of the increase from C4–5 to C6–7. Moreover, evaluation of the sex difference in $T2^*$ values at different levels showed no significance (Tables 1–3).

In the NP, $T2^*$ values tended to decrease with increasing grades, and $T2^*$ values were significantly different when comparing grades I to V, with highly significant differences between each grade ($P < 0.000$; Table 4). Spearman correlation analysis demonstrated that Pfirrmann grades were inversely significantly correlated with $T2^*$ values in the NP ($r = -0.673$, $P < 0.000$). The $T2^*$ cut-off value between grades I and II was 30.00 milliseconds, which corresponded to the sensitivity, specificity, and area under the ROC curve of 81.70%, 71.80%, and 0.767, respectively; 24.55 milliseconds, 72.5%, 84.92%, and 0.814 between grades II and III, respectively; 21.65 milliseconds, 72%, 75.92%, and 0.725 between grades III and IV, respectively; and 18.35 milliseconds, 63.6%, 66.72%, and 0.716 between grades IV and V, respectively (Table 5).

Table 2

Intraobserver and interobserver reliability of the Pfirrmann grade.

Observer	*k*	*P*
Intraobserver		
A1–A2	0.805	0.000
B1–B2	0.785	0.000
Interobserver		
A1–B1	0.793	0.000

4. Discussion

In this prospective study, we developed and investigated an MRI method, applicable to conventional 3.0-T units, for sagittal $T2^*$ mapping of cervical IVDs in symptomatic patients, and then compared against the Pfirrmann grades, which can be used in a clinical setup. The present study was composed of both symptomatic volunteers and patients with neck and upper limb pain. We evaluated 22- to 76-year-old subjects, an age range where in a broad spectrum of disc degeneration, including early degeneration, is expected. The results suggest negative correlations with disc degeneration grades. More importantly, the results indicated that the $T2^*$ values differ even among grades IV to V. This study suggests that $T2^*$ relaxation time may be sensitive to early degenerative changes and clinical symptoms in intervertebral disc degeneration (IVDD).

Zobel et al[18] found that the T1ρ values of NP at L3–4 and L4–5 discs were significantly lower in women. They speculated that proteoglycan loss in NP may begin earlier in women than in men; however, a new finding was observed with no difference between sexes in their report.[18] The reasons may be attributed to the different volunteers and different anatomical structures compared to our study. These results suggest that water loss from the NP or annulus fibrosus (AF) in cervical IVDs may begin at the same time for both sexes, which is consistent with a previous study.[19] Moreover, IVD changes (grades III–V) and non-degenerated discs (grades I–II) assessed by T2WI MRI Pfirrmann grading were observed in 70.16% and 29.84% of the subjects, respectively.

Our previous researches also confirmed the sensitivity and reliability of T2 relaxation time correlation with biochemical and

Table 3

T2 values of male and female on NP according to the anatomic level of each disc expressed as median and interquartile range.

Disc levels	T2 values (ms) of the NP		
	Male	Female	*P*
C2–3	22.91 ± 6.62	23.45 ± 6.11	0.74
C3–4	24.62 ± 6.96	26.12 ± 7.35	0.41
C4–5	24.85 ± 7.18	26.75 ± 7.67	0.32
C5–6	21.09 ± 5.54	22.21 ± 6.63	0.47
C6–7	22.65 ± 4.99	21.38 ± 7.09	0.07

NP = nucleus pulposus.

Table 4

T2* values for discs at different Pfirrmann grades.

	T2* values (mean ± SD, ms)	
Grade	**N**	**NP**
I	33	33.17 ± 7.60
II	59	27.17 ± 5.76*
III	102	22.90 ± 5.47*,†
IV	69	19.87 ± 4.37*,†,‡
V	43	16.90 ± 4.31*,†,‡,§
P-value	—	0.000
Total	305	23.45 ± 7.11

SD = standard deviation.

* Compared with T2* values of nucleus pulposus (NP) of grade I, $P < 0.05$.

† Compared with T2* values of NP of grade II.

‡ Compared with T2* values of NP of grade III.

§ Compared with T2* values of NP of grade IV. *P*-value: compared with NP among grades I, II, III, IV, and V.

histological analyses of large animals for IVDs, even for cartilage endplate.[19] The results confirmed that T2 values decreased significantly in the NP, AF, and cartilage endplate separately at preoperation, 4, 8, and 12 weeks when compared each time, and biochemical and histological analysis showed changes consistent with T2 signal intensities for early-stage degeneration.[19] A previous report on T2* values in histologically evaluated healthy ovine IVDs of the cervical spine in 5 regions described zonal T2* distribution with high values in the central NP and low values in the anterior and posterior AF; the authors of this report speculated that these T2* values could provide baseline measures.[20] However, the authors also mentioned that the current literature undoubtedly still lacks human baseline T2* values and their clinical correlation in various age groups.[20] Therefore, to the best of our knowledge, the present study is the first to use symptomatic population to examine the T2* and Pfirrmann changes in the inner portion of IVDs.

A research studying the correlation between T2 values and Pfirrmann grades of cervical IVD reported a decrease of NP T2 values in asymptomatic healthy young adults.[16] Compared with healthy young adults, the different grades of T2 values were much smaller (grade I: 33.17 vs 72.25 milliseconds; grade II: 27.17 vs 59.36 milliseconds; grade III: 22.90 vs 51.73 milliseconds). Moreover, we studied the NP T2 values in patients experiencing neck or upper lamb pain in our unpublished results. The same results were also confirmed between T2* values and T2 values (grade I: 33.17 vs 62.99 milliseconds; grade II: 27.17 vs 59.36 milliseconds; grade III: 22.90 vs 51.73 milliseconds; grade IV: 19.27 vs 40.20 milliseconds; and grade V: 16.90 vs 34.93 milliseconds). This observation might support that T2* relaxation is determined by the intrinsic "true" T2 relaxation and additional relaxation due to magnetic in homogeneities and is also susceptible to the spatial macromolecule architecture and its influence on water molecule mobility.[9,21] Moreover, T2* is influenced by the variations in tissue composition at microscopic level, such as the change from cartilage to bone, annulus to NP, or susceptibility-induced changes related to para- or diamagnetic depositions within the disc.[22] However, the T2* values of human patients of cervical IVDD was similar with the lumbar spine IVDs of sheep in previous studies.[20] Third, the T2 value in the IVD is known to be sensitive to water content and the composition of the collagen network structure. It is influenced by both rotational and translational motions by dipole–dipole interaction of water molecules in the collagen matrix.[23,24]

Some previous studies did not discern a significant difference in the T2* values between grades IV and V[20,21] of the lumbar disc, which was unlike our present study. A difference was still found between Pfirrmann grades IV and V in our study. Therefore, T2* relaxation time is more promising than T2 mapping in diagnosing IVDD in routine clinical practice. Consistent with our present study, the T2* values of the lumbar discs were lower than previously reported.[9,15,20] This difference may arise from the different biochemical properties between cervical and lumbar IVDs and different measurement methods due to different chemical changes from cervical, thoracic, and lumbar discs.[25]

It is important to note that the correlation coefficients of NP T2 values obtained in the present study are moderate because of the relatively large sample size. Recent studies have demonstrated the low-to-moderate correlation between T2* value and Pfirrmann grade, as well as T2* value and GAG content in IVDD.[10,11] Previous study groups also reported a significant negative correlation of degeneration signs and T2* values.[10,20,21] In the present study, T2* values were negatively correlated with Pfirrmann grades ($r = -0.673$, $P < 0.000$). Zhang et al[21] investigated that Pfirrmann grades were inversely significantly correlated with T2* values in the NP in patients experiencing low back pain, which was comparable with our results.

The principal finding in the present study is that ROC curves differ substantially the cut-off values of the NP in the ability to distinguish Pfirrmann grades, as verified by the T2* values. The cut-off points for ROC curve can be determined with approximate reliability from the area under the curve (AUC) values (0.9–1.0, high, 0.9–0.7, moderate, and 0.5–0.7, low accuracy). In this study, the AUC values were all within the range of the moderate accuracy. The results proposed that this T2* value-based grade scale is useful, with a moderate degree of objectivity.

There are some limitations in this study. The present results were not verified by histological and biochemical findings, partly because of the inability in obtaining specimens from human subjects. In contrast, partial volume effects still exist because of subjectivity and bias in selecting ROIs. Third, although results of some advanced imaging techniques such as T1ρ, chemical exchange saturation transfer, ultra-short TE, or apparent diffusion coefficient, were not compared with those of T2* relaxation time, several studies verified the usefulness of this technique alone to diagnose IVDD.[18,26–28] Fourth, the sample size in the present study, especially after further grade or age classification, was not adequate. Multicenter studies with larger sample sizes, more rigorous designs, and evidence-based reviews should be conducted.

Table 5

Correlation with T2* relaxation time with intervertebral disc degeneration.

	Grade I	Grade II	Grade III	Grade IV	Grade V
Nucleus pulposus, ms	>30	24.55–29.99	21.65–24.54	18.35–21.64	<18.34

5. Conclusions

These morphologic changes might reflect the alterations in biochemical content during degeneration. Further investigation is compulsory to establish the relationship between $T2^*$ relaxation times and precise biochemical content, such as water, proteoglycans, and collagen content. Nonetheless, our work highlights the quantitative correlation between Pfirrmann grades and $T2^*$ values derived from clinically available MRI sequence ($T2^*$). This functional methodology and analysis technique may advance quantitative data on the degenerative cascade and improve the decision for therapeutic strategies with the currently available technology.

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