Multiparametric analysis of the pathophysiology and etiology of spinal disc degeneration

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Introduction: The majority of chronic back pain is associated with degeneration of the intervertebral disc (IVD). The factors that lead to disc degeneration and its pathophysiology are still not completely understood. Noninvasive imaging techniques provide quantitative biomarkers that could be used to study underlying biophysical and biochemical changes and etiology of the degeneration process. It has long been suspected that poor nutrient delivery to discs is a major factor in the pathogenesis of IVD degeneration [*N Boos, et al. Spine 2002, 27:2631–44*]. This could be caused by disruptions in blood perfusion in the capillary beds of disc endplates (EP). However, this relation has not yet been demonstrated quantitatively in humans. Such an investigation requires an imaging technique to study EP blood perfusion and a quantitative and objective method to assess the degree of disc degeneration. Currently accepted methods classify disc degeneration into a small number of categories based on visual inspection of MR images [*Pfirrmann et al. Spine 2001, 26:1873-8; Thompson et al. Spine 1990, 15: 411-5*]. These are subjective in nature and there is inherent ambiguity because the degenerative process, which is fundamentally a continuum, is represented by a small number of categories. As a result, these grading schemes are prone to yield a large variation and uncertainty in any quantitative measurement of the degenerative process. When correlation between the disc degeneration and biophysical and biochemical changes within disc and EPs are investigated, a quantitative in vivo assessment that is capable of incorporating different aspects of the degenerative process would be needed.

In this study we used a multi-parametric MRI protocol to study the pathophysiology and etiology of IVD degeneration and proposed a new quantitative metric to grade disc degeneration. Using this new metric we studied the associations between disc degeneration, age and EP blood perfusion. We also demonstrated quantitatively for the first time that inferior lumbar discs are more prone to degeneration than superior discs.

Methods: The study was approved by the IRB and written consents were obtained from the subjects. For all scans, 15-sagittal slices (3mm thick) were acquired from nine subjects (age: 27–62y; mean 45y). Dynamic Contrast Enhanced MRI (DCEMRI) was acquired with 3D gradient-echo sequence (TR/TE=3.4ms/1.2ms, flip-angle=30^o, 0.81×0.81mm^2 in-plane res. 22 frames/36.4s frame rate). The contrast (Gd-DTPA-BMA, 0.1 mmol/kg) was administered manually as a bolus via an antecubital vein at the start of the 3rd dynamic frame. We also acquired conventional T2 weighted (T2w) MRI and diffusion weighted MRI (DWI) (TR/TE=4000ms/66ms, NEX=7, 2.4×2.4mm^2 in-plane, b=0 and 600 sec/mm^2). ROIs were drawn manually on pre-contrast images of the DCEMRI set to segment out the 10 subchondral EPs (L1-inferior EP down to S1-superior EP). In each EP, volume-averaged signal enhancement time course was calculated and percent enhancement curve was generated with respect to the pre-injection baseline intensity (Fig.1). To grade the discs, we first used the conventional Pfirmann classification (G1). In Pfirmann classification, T2w signal intensity in the discs is one of the features that is evaluated visually. T2w signal in discs decrease with increased degeneration but the signal in cerebrospinal fluid (CSF) remains unchanged. Therefore, we used IVD/CSF ratio from T2w images as a quantitative biomarker of degeneration, which had strong correlation with G1 (Table 1). Another quantitative imaging marker of degeneration is the apparent diffusion coefficient (ADC) in discs. It has been previously shown that ADC decreases with increasing degeneration [*Kerttula, et al. Acta Radiologica 2001;42:585-591*]. Therefore, we hypothesized that a multi-parametric disc-grading approach should capture the multi-factor etiology and the continuum of disc degeneration better than G1 alone. So, we took the mean of the two quantities from T2w images and DWI and proposed a new quantitative degeneration grade, G2=[mADC+(IVD/CSF)]/2. Here mADC is the mean ADC in disc. Note that G2 decreases with increased degeneration but G1 increases by definition (1: no degeneration, 5: severe degeneration). We first analyzed the correlations between disc grades and MR parameters. In the next step, we investigated the association between EP blood perfusion and disc degeneration using a regression model. We have seen a trend in our data that the perfusion peak decreased with the level of EP. Therefore, *EP level* was used as a covariate in our analysis. *EP level* was defined such that 1 is the most superior (L1-inferior) and 10 is the most inferior (S1-superior) EP. Age was not included as an independent variable since there is significant correlation between age and either grade. DCEMRI$_{peak}$ was used as the dependent variable, which is the value of DCEMRI signal at the 5th time point in the time series (Fig.1). The results of this analysis are shown in Table 2.

Table 1. Pearson's *r* between MR parameters and disc grades

	G1	G2
G2	**-0.87**	
IVD/CSF	**-0.83**	
mADC	**-0.82**	
AGE	**0.34**	**-0.56**
DCEMRI$_{peak}$	-0.16	**0.28**
Disc level	**0.30**	**-0.23**

Results: Fig.1 illustrates average DCEMRI curves for discs within two distinct ranges of G2. Table 1 shows correlations between various MR parameters and degeneration grades. These results reveal several important associations: **1)** increased disc degeneration was significantly associated with age. **2)** DCEMRI$_{peak}$ decreases significantly with increasing disc degeneration measured by G2 (p=0.01). In other words, there is strong association between reduced EP perfusion and reduced T2 signal and ADC in discs. **3)** The proposed quantitative grading method and Pfirmann grades are in close agreement. **4)** Lower lumbar discs (e.g. L4-L5) are more susceptible to degeneration than upper discs (e.g. L1-L2) as evidenced by Disc level – G1 and G2 correlations. The results summarized in Table 2 confirm that DCEMRI enhancement decreases significantly with increasing disc degeneration. It also demonstrates that lower lumbar discs have reduced perfusion than upper ones, confirming our earlier observations.

Table 2. Results for the regression analysis

	t-scores (p-values)	
Indep. var / Dep. Var.	G2	*EP$_{level}$*
DCEMRI$_{peak}$	**2.1** (0.04)	**2.03** (0.05)

Discussion and Conclusion: Here we proposed a new quantitative grading system that could be used as a biomarker of degeneration and complement the existing 5-category grading systems. Using both the conventional and new grading systems, our results demonstrated the quantitative relations between disc degeneration, MR parameters, disc location and age for the first time. The correlation and regression analyses reveal that reduced blood perfusion in IVD EPs is associated with the degree of degeneration of the discs in human volunteers. This is in accord with the literature that suggested that poor nutrient and oxygen delivery could be a major factor in IVD degeneration. However, age is also a significant factor in degeneration and causes changes in MR parameters. Therefore the relationship between perfusion and disc degeneration should be studied within confined age groups so that age factor can be better delineated. These findings could aid us differentiate disc degeneration associated with normal aging versus other pathological conditions that lead to this ailment. If these findings are confirmed in larger patient populations, treatment regimens can be developed to improve EP perfusion and recover degenerating IVDs, as long as there is no major EP damage. Future studies should include protocols to probe EP damage and incorporate that information.

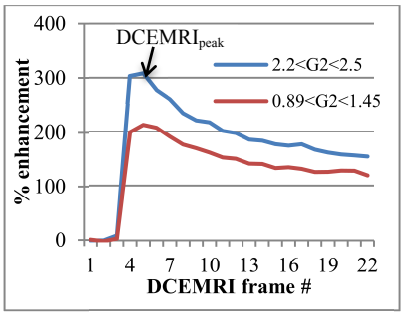

Fig.1. Average DCEMRI curves for two groups of discs, one with high G2 values and the other with low G2 values.