Longitudinal changes in vertebral bone marrow fat and disc proteoglycans in patients with chronic low back pain

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INTRODUCTION: Disc degeneration causes chronic low back pain in a subset of people [1]. The positive associations between disc degeneration and age reported in cross-sectional studies suggest that disc degeneration increases progressively over time. However, longitudinal changes in disc health occurring in individual human discs have not been robustly measured, and thus the time course of disc degeneration remains unknown. For example, it is unclear whether degenerating discs undergo gradual deterioration over long periods of time, or periods of rapid deterioration interspersed with periods of stability. Likewise, the extent of simultaneous changes in the adjacent vertebral bone marrow are also unknown. Declines in marrow vascularity could negatively affect vertebral perfusion and thus nutrient transport to the cells in the disc. Although increased disc degeneration and decreased vascular/hematopoietic bone marrow independently associate with age, temporal links to changes in adjacent bone marrow vascularity. This knowledge gap obscures the etiology and natural history of disc degeneration, and thus hinders the development of strategies for clinically managing chronic low back pain. The objective of this study was to discover the time course and etiology of disc degeneration by quantifying longitudinal changes in disc and vertebral bone marrow composition in patients with chronic low back pain using imaging biomarkers derived from quantitative MRI.

METHODS: Following informed consent, 48 patients with chronic low back pain (>3 mo. duration) undergoing conservative (non-prescribed and non-surgical) care were prospectively recruited for this longitudinal IRB-approved study. To measure compositional changes in the vertebral bone marrow and intervertebral discs, participants were imaged with 3T MRI at baseline and 12-months follow-up using two quantitative MRI sequences: a six-echo chemical shift encoding-based water-fat MRI sequence—previously validated to accurately measure bone marrow fat fraction (BMFF) within trabecular bone [2]—was used to assess the vertebral bone marrow, and a T1ρ mapping sequence with four spin-lock times—which estimates T1ρ relaxation times which are highly correlated with intradiscal GAG and water contents [3]—was used to measure T1ρ values in the nucleus pulposus (NP). All imaging was performed prior to 11 am to mitigate diurnal effects. After imaging, lumbo-sacral vertebrae and discs were segmented using previously developed neural networks [4,5]. Disc and vertebral segmentations were then bisected into inferior and superior halves (MATLAB), thus enabling sublevel analysis of the inferior/superior bone marrow and adjacent disc regions. The mean BMFF in the multi-vertebral region adjacent to each disc was used as a biomarker of bone marrow composition, and the mean T1ρ relaxation time in the NP (defined as the central A/P 40% region) was used as a biomarker of disc composition. Mixed effects linear regression accounting for multiple measurements per patient (from multiple spinal levels) was used to assess associations between longitudinal changes in NP T1ρ (ΔNP T1ρ; follow-up – baseline; outcome) and changes in BMFF (ΔBMFF), adjusted for age, sex, and spinal level.

RESULTS: To-date, 14 of 48 patients had completed their baseline and follow-up scans (7 female, 7 male; age = 53.2 ± 13.7 years; Oswestry Disability Index = 27 ± 13). Thus, this interim analysis included 130 sublevels (i.e., inferior/superior regions of each disc and adjacent vertebrae). Across all sublevels, the mean longitudinal changes in NP T1ρ and vertebral BMFF were small (pair-wise ΔNP T1ρ = -0.2 ± 9.2 ms, ΔBMFF = 0.3 ± 4.9%); however, there was substantial inter- and intra-patient heterogeneity: individual ΔNP T1ρ values ranged from -37.4 to 35.6 ms and ΔBMFF values ranged from -12.8 to 16.2% (Fig 1). Results from mixed effects regression showed that variations in ΔNP T1ρ were significantly and negatively associated with ΔBMFF, both in terms of the absolute longitudinal changes in the biomarker values (p = 0.04) and the relative changes (i.e., percent change relative to baseline, p = 0.01). Thus, decreases in NP T1ρ (indicating more severe biochemical disc degeneration) were associated with increases in BMFF (indicating fattier and less vascularized marrow), whereas increases in NP T1ρ (indicated a healthier disc at follow-up) were associated with decreases in BMFF (this latter behavior occurred for 25/130 [19%] of sublevels; Fig 2).

DISCUSSION: Both large positive and large negative changes in NP T1ρ were measured during the 12-month study period, which suggests that the natural history of disc degeneration does not exclusively involve monotonic decline. Instead, there may be appreciable improvements in disc health during a 12-month period. We found that longitudinal changes in disc composition were negatively associated with contemporaneous increases in vertebral BMFF. Since greater BMFF reflects lower layers of perfusion [2], and since the vertebral vascular structures provide a critical nutrient source to the disc cells, it follows that fluctuations in nutrient supply from alterations in vertebral vascularity may be one physiologic mechanism explaining our findings. The reasons for an improvement in disc/marrow health are unknown but could relate to systemic improvements in body composition (e.g., a decrease in BMI) following physical therapy or exercise as part of a patient’s conservative care—this will be investigated in as more patients complete their follow-up scans.

SIGNIFICANCE: Biochemical disc degeneration was highly heterogeneous over time and associated with the conversion of hematopoietic/vectorial elements to fat in the vertebral bone marrow. These novel results challenge the notion that disc degeneration is inherently characterized by monotonic declines in GAG and water contents; rather, temporal periods of recovery/anabolism may occur in some discs, and such variations may relate to changes in hematopoietic/vectorial elements in the vertebral bone marrow.