

## RESEARCH ARTICLE

# In vivo fluid transport in human intervertebral discs varies by spinal level and disc region

John T. Martin<sup>1</sup>  | Benjamin Wesorick<sup>1,2</sup> | Alexander B. Oldweiler<sup>1</sup> |  
 Andrzej S. Kosinski<sup>3,4</sup> | Adam P. Goode<sup>1,3,5</sup> | Louis E. DeFrate<sup>1,2,6</sup> 

<sup>1</sup>Department of Orthopaedic Surgery, Duke University School of Medicine, Durham, North Carolina, USA

<sup>2</sup>Department of Biomedical Engineering, Duke University, Durham, North Carolina, USA

<sup>3</sup>Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, USA

<sup>4</sup>Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina, USA

<sup>5</sup>Department of Population Health Sciences, Duke University School of Medicine, Durham, North Carolina, USA

<sup>6</sup>Department of Mechanical Engineering and Materials Science, Duke University, Durham, North Carolina, USA

## Correspondence

Louis E. DeFrate, Duke University Medical Center, Medical Sciences Research Building I, 203 Research Drive, Room 375, DUMC Box 3093, Durham, NC 27710, USA.  
 Email: [lou.defrate@duke.edu](mailto:lou.defrate@duke.edu)

## Funding information

National Institutes of Health, Grant/Award Numbers: F32 AR071223, R01 AR071440, R01 AR075399

## Abstract

**Background:** The lumbar discs are large, dense tissues that are primarily avascular, and cells residing in the central region of the disc are up to 6–8 mm from the nearest blood vessel in adults. To maintain homeostasis, disc cells rely on nutrient transport between the discs and adjacent vertebrae. Thus, diminished transport has been proposed as a factor in age-related disc degeneration.

**Methods:** In this study, we used magnetic resonance imaging (MRI) to quantify diurnal changes in T2 relaxation time, an MRI biomarker related to disc hydration, to generate 3D models of disc fluid distribution and determine how diurnal changes in fluid varied by spinal level. We recruited 10 participants (five males/five females; age: 21–30 years; BMI: 19.1–29.0 kg/m<sup>2</sup>) and evaluated the T2 relaxation time of each disc at 8:00 AM and 7:00 PM, as well as degeneration grade (Pfirschmann). We also measured disc height, volume, and perimeter in a subset of individuals as a preliminary comparison of geometry and transport properties.

**Results:** We found that the baseline (AM) T2 relaxation time and the diurnal change in T2 relaxation time were greatest in the cranial lumbar discs, decreasing along the lumbar spine from cranial to caudal. In cranial discs, T2 relaxation times decreased in each disc region (nucleus pulposus [NP], inner annulus fibrosus [IAF], and outer annulus fibrosus [OAF]), whereas in caudal discs, T2 relaxation times decreased in the NP but increased in the AF.

**Conclusions:** Fluid transport varied by spinal level, where transport was greatest in the most cranial lumbar discs and decreased from cranial to caudal along the lumbar spine. Future work should evaluate what level-dependent factors affect transport.

## KEYWORDS

disc degeneration, magnetic resonance imaging, spine, T2 mapping

## 1 | INTRODUCTION

The lumbar discs are large, dense tissues that are primarily avascular, and cells residing in the central region of the disc are up to 6–8 mm

from the nearest blood vessel in adults.<sup>1</sup> To maintain homeostasis, disc cells rely on nutrient exchange between the discs and adjacent vertebrae.<sup>2–4</sup> In this process, nutrients, such as glucose and oxygen, are transported into the vertebrae from the vascular supply and then

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *JOR Spine* published by Wiley Periodicals LLC on behalf of Orthopaedic Research Society.

into the disc through two mechanisms: the diffusion of nutrients from the vertebral vascular supply that terminates at the vertebral endplate<sup>5-7</sup> and load-induced fluid convection and consequently nutrient influx.<sup>3,8,9</sup> Because of the important role glucose, oxygen, and lactic acid play in disc cell metabolism,<sup>10-12</sup> diminished transport of these nutrients is often proposed as a factor in age-related disc degeneration.<sup>13</sup>

Many age-related spine pathologies develop in consistent patterns that depend on spinal level. For example, disc degeneration, nucleus pulposus (NP) herniations, annulus fibrosus (AF) tears, Modic lesions, disc high-intensity zones, and facet arthritis are all more prevalent in the most caudal lumbar discs.<sup>14-19</sup> Several mechanisms have been proposed to explain differences between upper and lower lumbar pathologies (e.g., spinopelvic alignment,<sup>20</sup> mechanical demands,<sup>21-23</sup> impaired development,<sup>24</sup> sex,<sup>14</sup> and trauma<sup>25</sup>). Level-dependent fluid and nutrient transport into the intervertebral disc may also drive level-dependent patterns in age-related disc disease.

T2 relaxation times measured using magnetic resonance imaging (MRI) are related to the concentration of water in the NP and AF.<sup>26-28</sup> Previous work has demonstrated that the T2 relaxation time of the NP is greatest in the cranial lumbar discs,<sup>29,30</sup> suggesting that these discs are more hydrated and may have different fluid transport properties than the caudal discs. Natural diurnal loading is one way to induce fluid transport; diurnal changes in disc T2 relaxation times may indicate that fluid is transported from the NP from AM to PM.<sup>31,32</sup> The goal of this study was to quantify changes in T2 relaxation time in 3D using volumetric MRI data to determine disc fluid transport patterns in response to diurnal activity.

We quantified diurnal changes in T2 relaxation time in each lumbar disc in young, asymptomatic volunteers. We evaluated total disc fluid transport by calculating AM to PM changes in average disc T2 relaxation time. We inferred the directionality of fluid transport from changes in the T2 relaxation times of the NP, inner AF (IAF), and outer AF (OAF). In a previous cohort of asymptomatic participants between 18 and 30 years of age, approximately 20% of lumbar discs were degenerated (as evaluated by Pfirrmann grade<sup>33</sup>). Therefore, a secondary objective of this study was to quantify the effect of disc degeneration on diurnal fluid transport. Finally, because disc size may be related to fluid transport,<sup>7,34,35</sup> in a subset of individuals, we measured disc height, volume, and perimeter using MRI and 3D modeling<sup>29,36</sup> and performed a preliminary analysis of the relationship between fluid transport and disc geometry. We hypothesized that diurnal changes in disc fluid vary by disc region, spinal level, degeneration grade, and disc geometry.

## 2 | METHODS

### 2.1 | Imaging protocol

With approval from the Duke Health Institutional Review Board, 10 participants (five males/five females; age: mean 25, range 21-30 years; BMI: mean 23.1, range 19.1-29.0 kg/m<sup>2</sup>) with no history of spine disease or low back pain (NIH Research Task Force score<sup>37</sup>:

**TABLE 1** Participant demographics

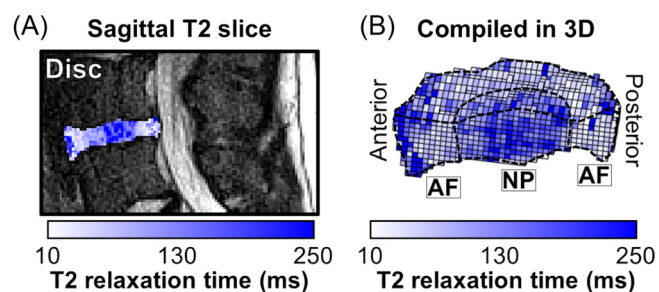
| N                                     | 10               |
|---------------------------------------|------------------|
| Age (years; mean, range)              | 25 (21-30)       |
| BMI (kg/m <sup>2</sup> ; mean, range) | 23.1 (19.1-29.0) |
| NIH RTF score (mean, range)           | 9.2 (9-10)       |
| Gender, female, n (%)                 | 5 (50)           |
| Employment status, n (%)              |                  |
| Student                               | 6 (60)           |
| Working now                           | 4 (40)           |
| Education level, n (%)                |                  |
| Master's degree                       | 1 (10)           |
| Bachelor's degree                     | 8 (80)           |
| High school graduate or GED           | 1 (10)           |
| Race, n (%)                           |                  |
| White                                 | 7 (70)           |
| Black or African American             | 2 (20)           |
| Unknown                               | 1 (10)           |
| Ethnicity, n (%)                      |                  |
| Not Hispanic or Latino                | 8 (80)           |
| Hispanic or Latino                    | 2 (20)           |
| Current smoker, n (%)                 | 0 (0)            |
| Low-back operation, n (%)             | 0 (0)            |

mean 9.2, range 9-10 [minimum score of 9, healthy; maximum score of 50, severely diseased]) were recruited and diurnal changes in the T2 relaxation time of each lumbar disc (T12-L1 through L5-S1) were measured (Table 1). Participants arrived at the MRI facility at 7:15 AM, rested supine for 45 min, and were scanned on a 3T MRI system (Trio Tim; Siemens Medical Systems, Erlangen, Germany). To quantify T2 relaxation time, participants were scanned using a sagittal T2 mapping sequence (repetition time, 3630 ms; echo times, 20, 40, 60, 80, 100, 120, 140, 160 ms; acquisition matrix, 256 × 256; field of view, 260 × 260 mm<sup>2</sup>; slice spacing, 3.0 mm, acquisition time: 5 min, 39 s). Disc health was evaluated using a T2-weighted image from this sequence (TE = 100 ms) and Pfirrmann grades<sup>33</sup> of I (healthy) to V (severely degenerated) were assigned by a postdoctoral fellow with 10 years of spine research experience (JTM). Following these scans, participants went about their normal workday and returned at 7:00 PM for a second T2 mapping scan. In a subset of subjects (n = 7), we performed a preliminary analysis of the relationship between disc geometry and fluid transport, calculating disc height, volume, and perimeter using a 3D T2-weighted sequence (SPACE; repetition time, 1500 ms; echo time, 223 ms; turbo factor, 145; flip angle, 100°; acquisition matrix, 320 × 320; field of view, 280 × 280 mm<sup>2</sup>; slice spacing, 0.90 mm, acquisition time: 5 min, 2 s). Participants were instructed to refrain from strenuous exercise the evening before and the day of their MRI scans.

Image data for this study were acquired during the same imaging session as a concurrent study on the diurnal change in facet joint thickness.<sup>38</sup>

## 2.2 | Image analysis

AM and PM T2 relaxation times were evaluated in 3D for each lumbar disc (Figure 1). Contours were drawn at the boundaries of the T12-L1 through L5-S1 discs on each slice of the sagittal T2 scan using custom software written in MATLAB (Mathworks, Natick, Massachusetts). Contours were drawn on T2-weighted images from the T2 mapping sequence (TE = 80 or 100 ms) and anterior, posterior, and lateral



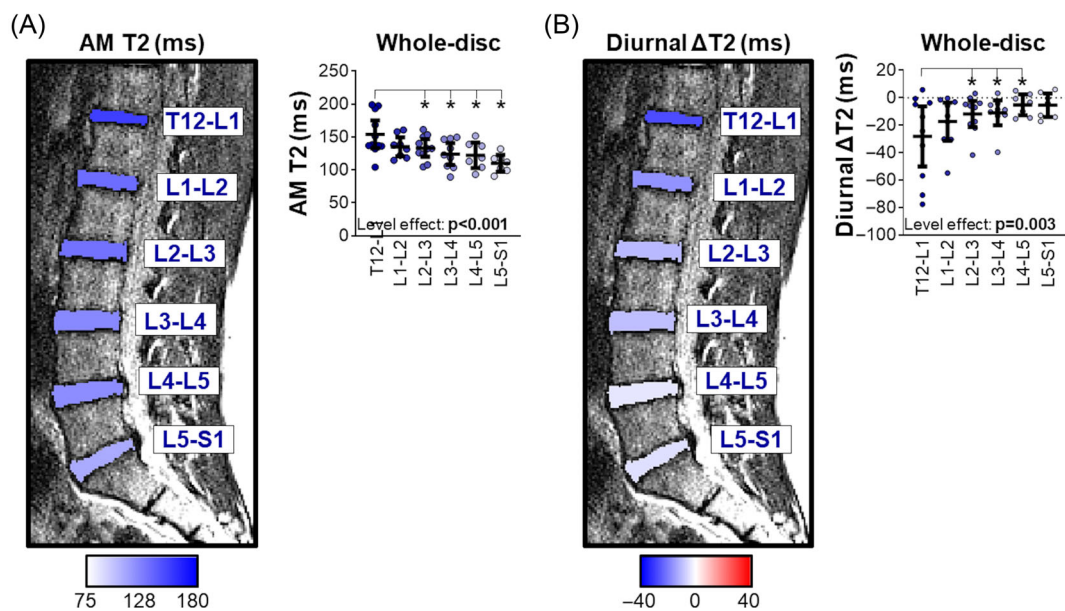
**FIGURE 1** Segmentation procedure. (A) Discs were manually segmented on magnetic resonance imaging (MRI) slices that spanned the lumbar spine. (B) 2D slices were compiled in 3D to calculate the average T2 relaxation time of the discs. The nucleus pulposus (NP), inner annulus fibrosus (IAF), and outer annulus fibrosus (OAF) regions were defined as the regions between 0% and 50%, 50% and 75%, and 75% and 100% of the outer boundary, respectively. Whole-disc averages and averages of the NP, IAF, and OAF regions were calculated. Image: T2-weighted image from T2 mapping sequence (TE = 100 ms)

apices were manually identified to define primary disc axes for rotation and registration to a rectangular coordinate system. T2 relaxation time was calculated at pixels within these contours using a mono-exponential decay.<sup>39</sup> To determine the T2 relaxation time in each disc region, segmented discs were manually rotated, registered to a rectangular coordinate system, and then divided into three regions: NP (0%–50% of outer boundary), IAF (50%–75% of outer boundary), and OAF (75%–100% of outer boundary).

To measure disc height, volume, and perimeter, sagittal slices on T2 SPACE scans were manually segmented across the lumbar discs. Geometry measurements were performed as described previously.<sup>36</sup> Briefly, mean disc height was calculated as the distance between the centroids of the superior and inferior disc boundaries. Disc volume was calculated as the area within each 2D contour spanning the disc space multiplied by the slice thickness, and disc perimeter was defined as the disc axial boundary at the disc mid-height. In a similar analysis of this segmentation method,<sup>36</sup> we determined its intra-rater reliability (mean height: 1.0%, perimeter: 0.6%, volume: 1.9%), inter-rater reliability (mean height: 1.5%, perimeter: 1.1%, volume: 1.0%), and intra-subject variability (mean height: 2.0%, perimeter: 0.4%, volume: 1.1%).

## 2.3 | Statistics

Means with ranges and counts with proportions were used to describe the continuous and categorical variables, respectively. To examine the assumptions of our models, we visually inspected the



**FIGURE 2** Baseline (AM) T2 relaxation time and diurnal change in T2 relaxation time of each disc. (Data displayed are observed values with the mean and 95% confidence interval; difference of least squares means calculated using mixed model: \* $p < 0.05$  vs. T12-L1). (A) Baseline (AM) mean T2 relaxation time of each disc by spinal level (illustrated on a representative spine). T2 was greatest at T12-L1 and decreased caudally. (B) Mean diurnal (AM to PM) change in the T2 relaxation time of each disc by spinal level (illustrated on a representative spine). The T2 of each disc decreased from AM to PM, and the magnitude of this change decreased caudally and was greatest at T12-L1. Image: T2-weighted image from T2 mapping sequence (TE = 100 ms)

residual diagnostics of each model to confirm normality of the residuals. We used linear mixed-effects models with subject as a random effect for all model-based analyses to account for correlations within subjects. Post-hoc analyses were performed by calculating the differences of least squares means (designated as  $\Delta$  in the Results section) and Bonferroni corrections were used to account for multiple comparisons. First, we evaluated the association between spinal level, disc region, and T2 relaxation time. Spinal levels with discs with Pfirrmann grades I and II were considered non-degenerated and included in this analysis ( $n = 52$  discs included,  $n = 8$  excluded). In each model, subject was treated as a random effect while spinal level and disc region were treated as fixed effects. Next, discs from caudal levels (L3-L4, L4-L5, and L5-S1) were separated into Healthy (Pfirrmann grades I and II,  $n = 23$  discs) and Degenerated (Pfirrmann grades III and IV,  $n = 7$  discs from five subjects) groups to evaluate how whole-disc and regional disc measurements were associated with Pfirrmann grade (cranial levels excluded as there was only one degenerated disc). Subject was treated as a random effect while degeneration state (Healthy vs. Degenerated) and disc region were treated as fixed effects. Finally, we performed a preliminary analysis to determine whether geometric measurements (height, perimeter, and volume) influenced the diurnal change in whole-disc T2 relaxation. Here, subject was also treated as a random effect while height, perimeter, and volume were treated as fixed effects. Discs with Pfirrmann grades I and II were included in this analysis ( $n = 7$  subjects;  $n = 35$  discs included, and  $n = 7$  excluded).

Data on figures are displayed as observed values (as opposed to model predicted values) with the mean and 95% confidence interval. All analyses were performed with SAS (SAS 9.4; SAS Institute Inc., Cary, North Carolina). A value of  $p < 0.05$  was used to indicate statistical significance.

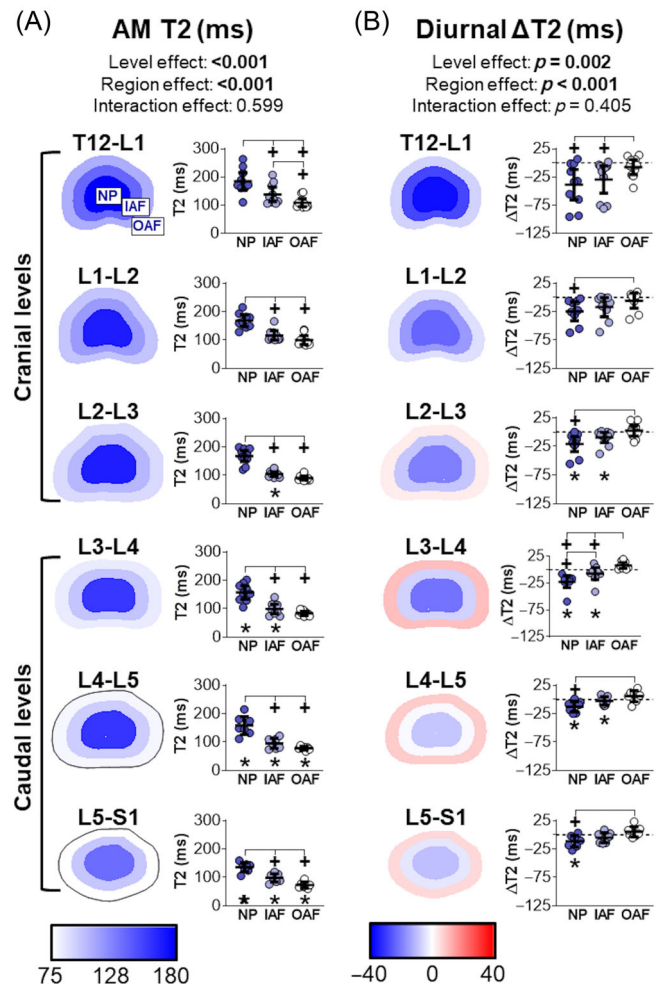
### 3 | RESULTS

#### 3.1 | Baseline (AM) and diurnal change in T2 relaxation time by spinal level and disc region (healthy discs)

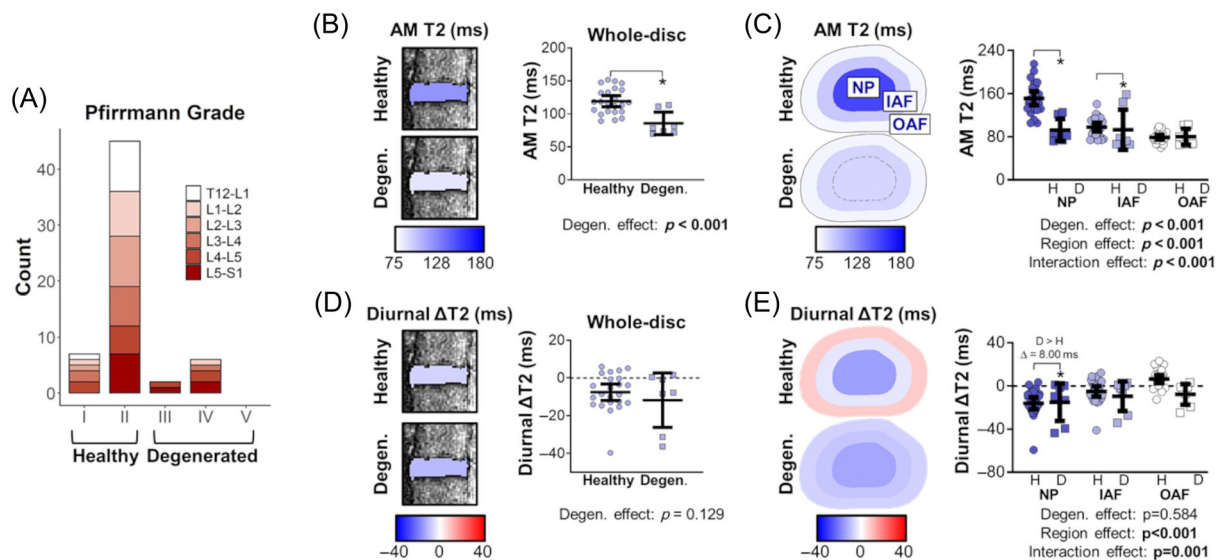
Baseline (AM) T2 relaxation time and the diurnal change in T2 relaxation time were dependent on spinal level, decreasing along the spine from cranial to caudal. Spinal level was significantly associated with baseline T2 ( $p < 0.001$ ), where T2 relaxation times were greatest at T12-L1 and lowest at L5-S1 (T12-L1 vs. L5-S1,  $\Delta = 33.69$  ms [22.21, 45.17]) (Figure 2A). Spinal level was also significantly associated with diurnal change in whole-disc T2 relaxation times ( $p = 0.003$ ), where the greatest change in T2 relaxation times occurred at T12-L1 and the smallest change in T2 relaxation times occurred at L4-L5 (T12-L1 vs. L4-L5,  $\Delta = 21.90$  ms [10.57, 33.24]) (Figure 2B).

Spinal level ( $p < 0.001$ ) and disc region ( $p < 0.001$ ) were both significantly associated with baseline regional T2 relaxation time (Figure 3A). At each level, T2 relaxation times were greatest in the NP and lowest in the OAF (e.g., T12-L1: NP vs. OAF,  $\Delta = 78.20$  ms [31.10, 62.76]). Across spinal levels, the T12-L1 disc had the greatest

NP and IAF T2 relaxation times, whereas the NP and IAF of the caudal levels had the lowest T2 relaxation times (significant differences at L2-L3 through L5-S1) (e.g., T12-L1 NP vs. L5-S1 NP:  $\Delta = 35.12$  ms [17.70, 52.55]; IAF,  $\Delta = 30.88$  ms [14.45, 47.31]; OAF,  $\Delta = 27.12$  ms [10.03, 44.21]). Spinal level ( $p < 0.001$ ) and disc region ( $p < 0.001$ ) were also significantly associated with diurnal change in regional disc T2 relaxation times (Figure 3B). Similar to the diurnal change in



**FIGURE 3** Baseline (AM) T2 relaxation time and diurnal change in T2 relaxation time in each disc region. (Data displayed are observed values with the mean and 95% confidence interval; difference of least squares means calculated using mixed model: \* $p < 0.05$  vs. same region in T12-L1 disc, + $p < 0.05$  vs. region within level). (A) Baseline (AM) mean T2 relaxation time of the NP, IAF, and OAF regions at each spinal level. The NP region had the highest T2 relaxation time at each level, followed by the IAF, and then the OAF. A significant effect was found for spinal level, where the T2 relaxation time of the NP, IAF, and OAF was greatest at T12-L1 and decreased caudally. (B) Mean diurnal (AM to PM) change in T2 relaxation time of the NP, IAF, and OAF regions at each spinal level. In the NP and IAF regions, a loss of T2 relaxation times occurred at each spinal level, the magnitude of which was greatest at T12-L1 and decreased caudally. At the T12-L1 and L1-L2, a modest decrease in T2 relaxation times was observed in the OAF. While from L2-L3 to L5-S1, a modest increase in T2 relaxation times was detected in the OAF



**FIGURE 4** Degeneration-related differences in disc T2 relaxation times at the caudal spinal levels. (Data displayed are observed values with the mean and 95% confidence interval; difference of least squares means calculated using mixed model:  $*p < 0.05$ .) (A) Distribution of discs by Pfirrmann grade. A sufficient number of degenerated caudal discs were obtained; therefore, we performed the subsequent analysis on all healthy (Pfirrmann grades I and II,  $n = 21$ ) and degenerated (Pfirrmann grades III and IV,  $n = 9$ ) discs from the L3-L4, L4-L5, and L5-S1 levels. (B) Baseline (AM) mean T2 relaxation time of healthy and degenerated discs at the caudal spinal levels. Whole-disc T2 relaxation times decreased with degeneration. (C) Baseline (AM) mean T2 relaxation time of the NP, IAF, and OAF regions of healthy and degenerated discs at the caudal spinal levels. Degenerated discs had decreased T2 relaxation times in the NP and IAF regions. (D) Mean diurnal (AM to PM) change in T2 relaxation time of healthy and degenerated discs at the caudal spinal levels. No significant differences were found between groups. (E) Mean diurnal (AM to PM) change in T2 relaxation time of the NP, IAF, and OAF regions of healthy and degenerated discs at the caudal spinal levels. Model effects suggested an interaction between degeneration state and disc region. Image: T2-weighted image from T2 mapping sequence (TE = 100 ms)

whole-disc T2 relaxation times, the greatest magnitude change in T2 occurred at T12-L1, and the smallest change in T2 relaxation times occurred at the caudal levels (significant differences at L2-L3 through L4-L5) (e.g., T12-L1 vs. L4-L5: NP,  $\Delta = 26.81$  ms [12.23, 41.39]; IAF,  $\Delta = 28.44$  ms [13.86, 43.02]). At each level, the greatest change in T2 relaxation times occurred in the NP region, whereas the smallest change in T2 relaxation times occurred in the OAF region (NP vs. AF,  $\Delta = 32.32$  ms [22.62, 42.02]). Interestingly, T2 relaxation times increased in the OAF region of discs L2-L3 through L5-S1 (e.g., L3-L4, change in T2 relaxation times,  $\mu = 7.99$  ms [2.28, 13.70]).

### 3.2 | Degeneration-related differences in disc T2 relaxation time and the diurnal change in T2 relaxation time (healthy vs. degenerated discs)

We compared 23 healthy discs and seven degenerated discs that were distributed across the L3-L4, L4-L5, and L5-S1 caudal levels (Figure 4A). Baseline whole-disc T2 relaxation times decreased with degeneration (Healthy vs. Degenerated,  $\Delta = 48.26$  ms [38.97, 57.54]) (Figure 4B) with diminished T2 relaxation times in the NP and IAF regions (Healthy vs. Degenerated, NP,  $\Delta = 73.31$  ms [59.56, 87.06]) (Figure 4C). No significant differences were detected in the diurnal change in whole-disc T2 relaxation times between healthy and degenerated discs (Figure 4D). Disc region was significantly associated

with diurnal change in regional T2 relaxation times ( $p < 0.001$ ), whereas degeneration state was not. However, a significant interaction was observed between disc region and degeneration state ( $p = 0.001$ ) (Figure 4E). Specifically, the NP of degenerated discs had a smaller change in T2 relaxation times from AM to PM (Healthy vs. Degenerated, NP,  $\Delta = 8.00$  ms [1.78, 14.22]).

### 3.3 | Preliminary associations between disc geometry and the diurnal change in whole-disc T2 relaxation time (healthy discs)

To determine how disc geometry affected fluid transport, we first verified measurable variations in disc size across the lumbar spine. We found that spinal level was significantly associated with disc height ( $p < 0.001$ ), volume ( $p < 0.001$ ), and perimeter ( $p < 0.001$ ), where in each case, the T12-L1 disc was the smallest in size (T12-L1, height,  $\mu = 5.71$  mm [5.02, 6.40]). The size peaked in the mid-lumbar levels (L3-L4, L4-L5) (e.g., L3-L4, height,  $\mu = 7.58$  mm [7.57, 9.43]) and then decreased from L4-L5 to L5-S1 (L5-S1, height,  $\mu = 7.28$  mm [6.99, 7.57]) (Figure S1). Despite the dependence of disc size on spinal level, no associations were found between the diurnal change in whole-disc T2 relaxation time and disc height ( $\beta = 1.36$  [-8.11, 10.82],  $p = 0.770$ ), volume ( $\beta = -0.003$  [-0.012, 0.006],  $p = 0.482$ ), or perimeter ( $\beta = -0.50$  [-0.50, 3.24],  $p = 0.143$ ).

## 4 | DISCUSSION

Age-related spine disease commonly develops in a pattern that is dependent on spinal level, where pathologies, such as disc degeneration and disc herniation, are more prevalent in the caudal lumbar discs. Level-dependent physiological stressors may drive these pathologies. For example, impaired fluid transport may lead to nutrient deficiency that may influence the health of the disc. Here, we found that the magnitude of fluid transport (based on the diurnal change in T2 relaxation time) is greatest in the cranial lumbar discs and decreases along the lumbar spine from cranial to caudal. We did not detect an effect of disc size on transport as previously postulated<sup>7,34,35</sup> but did detect an effect of disc degeneration on transport,<sup>3,4</sup> particularly in the NP region. We hypothesize that level-dependent nutrient transport is a factor in the development of the caudal pattern of degeneration and that degeneration itself further exacerbates these conditions.

The ability to transport more fluid (and, consequently, more nutrients and waste) likely benefits the cranial discs, which are slower to degenerate than the caudal discs.<sup>14,19,40</sup> We aimed to identify which level-dependent factors determined this relationship. We did not detect an effect of disc volume, height, or perimeter on the diurnal change in T2 relaxation times in a preliminary analysis, contrary to convention<sup>7,34,35</sup> and our original hypothesis. Based on these data, focused follow-up studies that are powered to detect the relationship between disc morphology and fluid transport are warranted. However, other level-dependent factors may influence fluid transport. For example, the composition and structure of the cartilage endplate determine solute diffusivity across the disc/vertebra interface<sup>41,42</sup> and consequently impact cell viability.<sup>11</sup> Thus, level-dependent differences in the extracellular matrix of the cartilage endplate may determine transport characteristics. Furthermore, physical loading impacts strain in the cartilage endplate, solute diffusivity,<sup>42</sup> and in vivo fluid transport (measured by changes in T2).<sup>43</sup> Our recent work suggests that regional disc strains vary by spinal level, but we did not detect an effect of average whole-disc strains.<sup>29</sup> Thus, the role that mechanical factors play in level-dependent fluid transport is not clear. Previous work has also identified level-dependent differences in composition of the vertebral bodies as measured by quantitative MRI, suggesting that vertebral fluid content<sup>43,44</sup> and marrow fat<sup>45</sup> vary by spinal level and may be related to disc degeneration. Evaluating other factors that affect disc fluid transport and impact disc health is an area for future work.

We did not detect an effect of disc degeneration on net disc fluid transport, but did find an effect of degeneration on transport in the NP region specifically. This finding is consistent with the changes characteristic of disc degeneration, such as decreased permeability of the NP, AF, and cartilage endplates<sup>46–48</sup> and decreased disc fluid.<sup>26,49,50</sup> Changes in disc fluid may impact cell metabolism as disc cells are sensitive to alterations in osmolarity,<sup>51</sup> oxygen and glucose concentrations,<sup>10</sup> and mechanical loading.<sup>52</sup> Disc cell gene expression follows a circadian rhythm<sup>53</sup> that may be impacted by cyclic fluid transport. Still, in this work we were only able to evaluate a limited

number of degenerated discs from the caudal region of the lumbar spine. Future work should evaluate the full spectrum of degenerated discs across the lumbar spine. In this way, important relationships between transport and degeneration can be further dissected along with the impact of impaired transport on long-term disc health.

In studies using small molecule MRI contrast agents, such as gadodiamide,<sup>4</sup> it is evident that solutes diffuse from the vertebral body, through the vertebral endplate, and into the disc over the course of the day. This process can be influenced by mechanical loading, which affects disc fluid motion and consequently the rate of solute transport into the disc.<sup>3</sup> In this study, we used diurnal loading to induce fluid motion. We determined that, in healthy discs, fluid concentration decreased in the NP and increased in the OAF for discs at the caudal levels. While we can infer that fluid travels from the NP to the AF and then likely exterior to the disc, we are not able to determine this empirically by directly tracking flow (i.e., by tracing labeled particles), only by quantifying the net change in total fluid content. Also, we make this measurement assuming that the diurnal change in T2 relaxation is primarily affected by fluid content and not alterations in fiber alignment. Future work at high MR field strength may elucidate diurnal changes in fiber alignment. Finally, we did not evaluate how specific activities influence fluid transport, as activity levels were not closely controlled in this study. Determining how specific loading protocols affect the magnitude and direction of fluid transport is an area for future work.

## 5 | CONCLUSION

We determined that disc fluid transport (as measured by the diurnal change in T2 relaxation time) varies by spinal level, where transport was greatest in the most cranial lumbar discs and decreased from cranial to caudal along the lumbar spine. Because degeneration was most prevalent in the caudal lumbar discs where fluid transport was relatively lower compared with the cranial lumbar discs, future work should aim to determine what level-dependent factors contribute to fluid transport and disc degeneration. Furthermore, degeneration affected transport in the NP region. Taken together, these data suggest that the diurnal change in T2 relaxation times may be a useful biomarker of disc health.

### ACKNOWLEDGMENTS

The authors would like to thank Jean Shaffer and Raven Boykin from the Duke Center for Advance Magnetic Resonance Development. Funding was received from the National Institutes of Health (F32 AR071223, R01 AR071440, R01 AR075399).

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

### ORCID

John T. Martin  <https://orcid.org/0000-0002-5772-3926>

Louis E. DeFrate  <https://orcid.org/0000-0002-6982-349X>

## REFERENCES

- Fields AJ, Ballatori A, Liebenberg EC, et al. Contribution of the endplates to disc degeneration. *Curr Mol Biol Rep*. 2018;4:151-160.
- Urban JP, Smith S, Fairbank JC. Nutrition of the intervertebral disc. *Spine (Phila Pa 1976)*. 2004;29:2700-2709.
- Gullbrand SE, Peterson J, Ahlborn J, et al. ISSLS prize winner: dynamic loading-induced convective transport enhances intervertebral disc nutrition. *Spine (Phila Pa 1976)*. 2015;40:1158-1164.
- Rajasekaran S, Babu JN, Arun R, et al. ISSLS prize winner: a study of diffusion in human lumbar discs: a serial magnetic resonance imaging study documenting the influence of the endplate on diffusion in normal and degenerate discs. *Spine (Phila Pa 1976)*. 2004;29:2654-2667.
- Urban JP, Holm S, Maroudas A, et al. Nutrition of the intervertebral disk. An in vivo study of solute transport. *Clin Orthop Relat Res*. 1977;129:101-114.
- Ogata K, Whiteside LA. 1980 Volvo award winner in basic science. Nutritional pathways of the intervertebral disc. An experimental study using hydrogen washout technique. *Spine (Phila Pa 1976)*. 1981;6:211-216.
- Huang YC, Urban JP, Luk KD. Intervertebral disc regeneration: do nutrients lead the way? *Nat Rev Rheumatol*. 2014;10:561-566.
- Sampson SL, Sylvia M, Fields AJ. Effects of dynamic loading on solute transport through the human cartilage endplate. *J Biomech*. 2019;83:273-279.
- Gullbrand SE, Peterson J, Mastropolo R, et al. Low rate loading-induced convection enhances net transport into the intervertebral disc in vivo. *Spine J*. 2015;15:1028-1033.
- Bibby SR, Urban JP. Effect of nutrient deprivation on the viability of intervertebral disc cells. *Eur Spine J*. 2004;13:695-701.
- Wong J, Sampson SL, Bell-Briones H, et al. Nutrient supply and nucleus pulposus cell function: effects of the transport properties of the cartilage endplate and potential implications for intradiscal biologic therapy. *Osteoarthr Cartil*. 2019;27:956-964.
- Shirazi-Adl A, Taheri M, Urban JP. Analysis of cell viability in intervertebral disc: effect of endplate permeability on cell population. *J Biomech*. 2010;43:1330-1336.
- Grunhagen T, Wilde G, Soukane DM, et al. Nutrient supply and intervertebral disc metabolism. *J Bone Joint Surg Am*. 2006;88 (Suppl 2):30-35.
- Teraguchi M, Yoshimura N, Hashizume H, et al. Progression, incidence, and risk factors for intervertebral disc degeneration in a longitudinal population-based cohort: the Wakayama Spine Study. *Osteoarthr Cartil*. 2017;25:1122-1131.
- Ebeling U, Reulen HJ. Are there typical localisations of lumbar disc herniations? A prospective study. *Acta Neurochir*. 1992;117:143-148.
- Osti OL, Vernon-Roberts B, Moore R, et al. Annular tears and disc degeneration in the lumbar spine. A post-mortem study of 135 discs. *J Bone Joint Surg Br*. 1992;74:678-682.
- Feng Z, Liu Y, Yang G, et al. Lumbar vertebral endplate defects on magnetic resonance images: classification, distribution patterns, and associations with modic changes and disc degeneration. *Spine (Phila Pa 1976)*. 2018;43:919-927.
- Teraguchi M, Samartzis D, Hashizume H, et al. Classification of high intensity zones of the lumbar spine and their association with other spinal MRI phenotypes: the Wakayama Spine Study. *PLoS One*. 2016;11:e0160111.
- Jarraya M, Guermazi A, Lorgeus AL, et al. A longitudinal study of disc height narrowing and facet joint osteoarthritis at the thoracic and lumbar spine, evaluated by computed tomography: the Framingham Study. *Spine J*. 2018;18:2065-2073.
- Bae J, Lee SH, Shin SH, et al. Radiological analysis of upper lumbar disc herniation and spinopelvic sagittal alignment. *Eur Spine J*. 2016;25:1382-1388.
- Hicks GE, Morone N, Weiner DK. Degenerative lumbar disc and facet disease in older adults: prevalence and clinical correlates. *Spine (Phila Pa 1976)*. 2009;34:1301-1306.
- Dar G, Masharawi Y, Peleg S, et al. Schmorl's nodes distribution in the human spine and its possible etiology. *Eur Spine J*. 2010;19:670-675.
- Samartzis D, Mok FPS, Karppinen J, et al. Classification of Schmorl's nodes of the lumbar spine and association with disc degeneration: a large-scale population-based MRI study. *Osteoarthr Cartil*. 2016;24:1753-1760.
- Li Y, Samartzis D, Campbell DD, et al. Two subtypes of intervertebral disc degeneration distinguished by large-scale population-based study. *Spine J*. 2016;16:1079-1089.
- Pfirmsmann CW, Resnick D. Schmorl nodes of the thoracic and lumbar spine: radiographic-pathologic study of prevalence, characterization, and correlation with degenerative changes of 1,650 spinal levels in 100 cadavers. *Radiology*. 2001;219:368-374.
- Marinelli NL, Houghton VM, Munoz A, et al. T2 relaxation times of intervertebral disc tissue correlated with water content and proteoglycan content. *Spine (Phila Pa 1976)*. 2009;34:520-524.
- Gullbrand SE, Ashinsky BG, Martin JT, et al. Correlations between quantitative T2 and T1rho MRI, mechanical properties and biochemical composition in a rabbit lumbar intervertebral disc degeneration model. *J Orthop Res*. 2016;34:1382-1388.
- Boos N, Wallin A, Gbedegbegnon T, et al. Quantitative MR imaging of lumbar intervertebral disks and vertebral bodies: influence of diurnal water content variations. *Radiology*. 1993;188:351-354.
- Martin JT, Oldweiler AB, Spritzer CE, et al. Lumbar intervertebral disc diurnal deformations and T2 and T1rho relaxation times vary by disc region, spinal level, and degeneration grade. *Eur Spine J*. 2022;31:746-754.
- Blumenkrantz G, Zuo J, Li X, et al. In vivo 3.0-tesla magnetic resonance T1rho and T2 relaxation mapping in subjects with intervertebral disc degeneration and clinical symptoms. *Magn Reson Med*. 2010;63:1193-1200.
- Karakida O, Ueda H, Ueda M, et al. Diurnal T2 value changes in the lumbar intervertebral discs. *Clin Radiol*. 2003;58:389-392.
- Ludescher B, Effelsberg J, Martirosian P, et al. T2- and diffusion-maps reveal diurnal changes of intervertebral disc composition: an in vivo MRI study at 1.5 tesla. *J Magn Reson Imaging*. 2008;28:252-257.
- Pfirmsmann CW, Metzendorf A, Zanetti M, et al. Magnetic resonance classification of lumbar intervertebral disc degeneration. *Spine (Phila Pa 1976)*. 2001;26:1873-1878.
- Horner HA, Urban JP. 2001 Volvo award winner in basic science studies: effect of nutrient supply on the viability of cells from the nucleus pulposus of the intervertebral disc. *Spine (Phila Pa 1976)*. 2001;26:2543-2549.
- Motaghinasab S, Shirazi-Adl A, Urban JP, et al. Computational pharmacokinetics of solute penetration into human intervertebral discs - effects of endplate permeability, solute molecular weight and disc size. *J Biomech*. 2012;45:2195-2202.
- Martin JT, Oldweiler AB, Spritzer CE, et al. A magnetic resonance imaging framework for quantifying intervertebral disc deformation in vivo: reliability and application to diurnal variations in lumbar disc shape. *J Biomech*. 2018;71:291-295.
- Deyo RA, Dworkin SF, Amtmann D, et al. Report of the NIH task force on research standards for chronic low back pain. *Spine J*. 2014;14:1375-1391.
- Oldweiler AB, Martin JT. In vivo relationships between lumbar facet joint and intervertebral disc composition and diurnal deformation. *Clin Biomech (Bristol, Avon)*. 2021;88:105425.
- Smith HE, Mosher TJ, Dardzinski BJ, et al. Spatial variation in cartilage T2 of the knee. *J Magn Reson Imaging*. 2001;14:50-55.
- Miller JA, Schmatz C, Schultz AB. Lumbar disc degeneration: correlation with age, sex, and spine level in 600 autopsy specimens. *Spine (Phila Pa 1976)*. 1988;13:173-178.

41. Dolor A, Sampson SL, Lazar AA, et al. Matrix modification for enhancing the transport properties of the human cartilage endplate to improve disc nutrition. *PLoS One*. 2019;14:e0215218.
42. Wu Y, Cisewski SE, Wegner N, et al. Region and strain-dependent diffusivities of glucose and lactate in healthy human cartilage endplate. *J Biomech*. 2016;49:2756-2762.
43. Hebelka H, Miron A, Kasperska I, et al. Axial loading during MRI induces significant T2 value changes in vertebral endplates—a feasibility study on patients with low back pain. *J Orthopaed Surg Res*. 2018;13:18.
44. Jenkins JP, Stehling M, Sivewright G, et al. Quantitative magnetic resonance imaging of vertebral bodies: a T1 and T2 study. *Magn Reson Imaging*. 1989;7:17-23.
45. Krug R, Joseph GB, Han M, et al. Associations between vertebral body fat fraction and intervertebral disc biochemical composition as assessed by quantitative MRI. *J Magn Reson Imaging*. 2019;50:1219-1226.
46. Johannessen W, Elliott DM. Effects of degeneration on the biphasic material properties of human nucleus pulposus in confined compression. *Spine (Phila Pa 1976)*. 2005;30:E724-E729.
47. Yao H, Justiz MA, Flagler D, et al. Effects of swelling pressure and hydraulic permeability on dynamic compressive behavior of lumbar annulus fibrosus. *Ann Biomed Eng*. 2002;30:1234-1241.
48. DeLucca JF, Cortes DH, Jacobs NT, et al. Human cartilage endplate permeability varies with degeneration and intervertebral disc site. *J Biomech*. 2016;49:550-557.
49. Roberts S, Evans H, Trivedi J, et al. Histology and pathology of the human intervertebral disc. *J Bone Joint Surg Am*. 2006;88 (Suppl 2):10-14.
50. Marinelli NL, Haughton VM, Anderson PA. T2 relaxation times correlated with stage of lumbar intervertebral disk degeneration and patient age. *AJNR Am J Neuroradiol*. 2010;31:1278-1282.
51. Wuertz K, Urban JP, Klasen J, et al. Influence of extracellular osmolarity and mechanical stimulation on gene expression of intervertebral disc cells. *J Orthop Res*. 2007;25:1513-1522.
52. Turner KG, Ahmed N, Santerre JP, et al. Modulation of annulus fibrosus cell alignment and function on oriented nanofibrous polyurethane scaffolds under tension. *Spine J*. 2014;14:424-434.
53. Dudek M, Yang N, Ruckshanthi JP, et al. The intervertebral disc contains intrinsic circadian clocks that are regulated by age and cytokines and linked to degeneration. *Ann Rheum Dis*. 2017;76:576-584.

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Martin, J. T., Wesorick, B., Oldweiler, A. B., Kosinski, A. S., Goode, A. P., & DeFrate, L. E. (2022). In vivo fluid transport in human intervertebral discs varies by spinal level and disc region. *JOR Spine*, 5(2), e1199. <https://doi.org/10.1002/jsp2.1199>