



Published in final edited form as:

Spine (Phila Pa 1976). 2012 June 15; 37(14): 1224–1230. doi:10.1097/BRS.0b013e31824b2450.

T_{1ρ} Magnetic Resonance Imaging Quantification of Early Lumbar Intervertebral Disc Degeneration in Healthy Young Adults

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Abstract

Study Design—Cross-sectional study using T_{1ρ} magnetic resonance imaging (MRI) of lumbar spine in healthy young adults.

Objective—To evaluate early intervertebral disc degeneration (IDD) quantified by T_{1ρ} - and T₂-weighted MRI in asymptomatic young adults and to correlate T_{1ρ} value with Pfirrmann degenerative grade, sex, and body mass index (BMI).

Summary of Background Data—Intervertebral disc starts early to degenerate losing proteoglycan content in the nucleus pulposus (NP). A potential tool for the study of early stage of IDD is T_{1ρ} MRI. T_{1ρ} relaxation time of human discs has been correlated to proteoglycan content in previous studies.

Methods—T_{1ρ} - and T₂-weighted images of the lumbar spine were obtained for 63 asymptomatic young subjects (34 men and 29 women; mean age, 22.95 ± 1.8 yr), with a 1.5-T MRI scanner. T_{1ρ} mapping and values in the NP and anulus fibrosus (n = 315) were obtained. Degenerative grade was assessed using T₂-weighted images, according to the Pfirrmann scale. Differences in T_{1ρ} value between sexes, BMI, and linear regression analyses with degenerative grade were determined.

Results—T_{1ρ} values of NPs were significantly higher than those of anulus fibrosus at all levels. T_{1ρ} values were significantly lower in women at L3–L4 and L4–L5 discs ($P < 0.05$). T_{1ρ} values

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No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

No funds were received in support of this work.

decreased linearly with degenerative grade. However, nondegenerated discs (Pfirrmann grades 1 and 2) showed a wide range of $T_{1\rho}$ relaxation time. No significant correlation was observed between $T_{1\rho}$ value and BMI.

Conclusion—The data of this study showed a significant difference in IDD onset between sexes. $T_{1\rho}$ values correlate with Pfirrmann degenerative grade in young adults. However, the wide distribution of $T_{1\rho}$ values in healthy intervertebral disc highlights the low sensitivity of Pfirrmann grade to detect the early IDD changes. $T_{1\rho}$ can be potentially used as a clinical tool to identify early IDD and to create a reliable quantitative scale.

Keywords

$T_{1\rho}$; spine; intervertebral disc degeneration; magnetic resonance imaging; healthy young adults

Low back pain (LBP) is a common and important clinical, social, economic, and public health problem affecting the western societies, with an annual prevalence of chronic LBP ranging from 15% to 45%.^{1,2} LBP is already common among children and the prevalence increases with age.^{3,4} It has been suggested that the majority of back pain is caused by intervertebral disc degeneration (IDD).⁵ Although the mechanisms by which IDD may cause LBP are not clear, the severity of IDD is associated with onset of symptoms.⁶ Previous authors have suggested that physiological, that is, nontraumatic changes in the intervertebral discs (IVDs) likely begin as early as the second decade of life and progress until death.⁷ Although a single initiating cause of degeneration has not been identified, early degenerative changes occur in the nucleus pulposus (NP).^{8,9} During the initial phase of IDD, the NP loses proteoglycan (PG) that accounts for up to 70% of the dry weight of the NP in the juvenile and 20% in the mature adult. PG is hydrophilic macromolecule that leads to the hydration of the NP, which accounts for the load-bearing property of the disc.^{10,11} IDD progress results in detrimental changes of disc structures and joint mechanics, which can proceed to multiple spinal disorders, such as spinal stenosis, radiculopathy, disc herniation, and instability.^{5,12} The current focus of spine surgeon is to develop new biological therapies to prevent or to stop the degenerative process of the disc. However, the current diagnostic tools used to detect early degenerative changes are not sensitive. Conventional magnetic resonance imaging (MRI) techniques provide excellent detection for late-stage morphological changes due to IDD. One of the commonly accepted grading systems for the assessment of lumbar IDD is the classification scale described by Pfirrmann *et al*,¹³ which is based on the assessment of structure and loss of the signal intensity on T_2 -weighted MRI images. Among the most accepted grading systems, the Pfirrmann scale has a high clinical feasibility, whereas the Thompson classification scale¹⁴ has more academic than clinical value because it is based on assessing gross morphology of midsagittal sections of human lumbar IVD and cannot be applied on patients.¹⁵ However, the Pfirrmann scale does not provide reliable quantification of the degenerative grade in early IDD stages characterized by a loss of PG in an intact disc.^{16,17} A more sensitive technique is required for the quantitative measurement of biochemical changes to track the progression and regression of IDD. This technique will help evaluate new therapies for the treatment of IDD, such as recombinant growth factors injection, gene therapy, stem cell therapy and tissue engineering strategies.^{18–23}

A potential tool for studying the early stage of IDD is the $T_{1\rho}$ time constant obtained by spin-lock MRI.²⁴ The relaxation that occurs during the application of the spin-lock pulse is referred to as spin-lattice relaxation in the rotating frame, or $T_{1\rho}$ relaxation. The $T_{1\rho}$ time constant is related to slow motional interactions between macromolecules of extracellular matrix and bulk water.²⁵ In articular cartilage, $T_{1\rho}$ is strongly correlated with PG content and has been shown to detect early degenerative changes.^{26–28} Previous studies demonstrated that the $T_{1\rho}$ relaxation time was directly correlated to PG content of human lumbar IVDs *ex vivo*^{29,30} and correlated significantly with disc degeneration *in vivo*³¹ as well as clinical symptoms.^{32–34}

IDD is known to be common among asymptomatic young adults, and few studies on young population cohort demonstrate that degenerative MRI findings are also present in the lumbar spine among young adults.^{7,35} There are no studies to our knowledge that evaluate early degenerative changes in lumbar spine of young adults, using functional MRI techniques sensible to early degenerative changes and the correlation with potential risks for IDD progress such as sex and body mass index (BMI).

The purpose of this study was to evaluate early IDD in the lumbar spine quantified by $T_{1\rho}$ and T_2 -weighted MRI in a population of asymptomatic young adults by correlating $T_{1\rho}$ value with Pfirrmann degenerative grade, sex, and BMI.

MATERIALS AND METHODS

Study Sample

The study was approved by the ethics committee of Campus Bio-Medico University of Rome, and all participants provided written informed consent prior to enrollment. The study population consisted of 63 Italian volunteers (Table 1; 34 men and 29 women; mean age, 22.95 ± 1.8 yr; age range, 19–25 yr). All patients underwent standard clinical and $T_{1\rho}$ MRI of the lumbar spine. Inclusion criteria consisted of age younger than 25 years, no history of chronic back pain, no prior back surgery, no trauma history of the spine, no metabolic disease, no autoimmune disease, no osteoarticular disease, and no morphological alteration. Subjects were excluded if they failed to meet the above criteria or if they had any indicative suggestive of sciatica or neurological symptoms, including leg weakness, numbness, or tingling. BMI of each volunteer was calculated from height and weight. The study evaluated discs segments between L1 and S1 for a total of 315 discs.

MR Image Acquisition

Each participant underwent MRI on a clinical 1.5-T scanner (Siemens Magnetom Avanto 76 × 18; Campus Bio-Medico University Hospital of Rome, Rome, Italy) according to 2 protocols. First, conventional T_1 - and T_2 -weighted images were acquired using a standard spin-echo imaging sequence with the following parameters: T_2 -weighted: field of view (FoV) = 320 mm, slice thickness = 4 mm, acquisition matrix = 514, and time echo time/repetition time (TE/TR) = 83 ms/5560 ms; inversion time (TI) = 150 ms, T_1 -weighted images were acquired TE/TR = 8.1 ms/400 ms, turbo spin echo (TSE), FoV = 400 mm, slice thickness = 4 mm, and matrix = 384. Next, a series of $T_{1\rho}$ -weighted images was acquired

using a TSE pulse sequence with fat suppression, with the following parameters: FoV = 280 mm, slice thickness = 4 mm, acquisition matrix = 358, flip angle = 30°, TE/TR = 5.24 ms/3030.96 ms, and TI = 1700 ms. Spin-lock durations ranged from 15 to 75 ms with a spin-lock pulse amplitude set to correspond to a spin-lock frequency of 400 Hz. Both axial and sagittal images were acquired. Total time for each examination was about 15 minutes each.

Data Processing

The degenerative grade of each lumbar disc (n = 315) was assessed from T₂-weighted images according to the classification system described by Pfirrmann *et al*¹³ scale as grade 1 (normal shape, no horizontal bands, and distinction of annulus fibrosus [AF] and NP is clear), grade 2 (nonhomogeneous shape with horizontal bands and some blurring between NP and AF), grade 3 (nonhomogeneous shape with blurring between NP and AF, AF shape is still recognizable), grade 4 (nonhomogeneous shape with hypointensity, AF shape is not intact and distinction between NP and AF is impossible, and disc height is usually decreased), and grade 5 (same as grade 4 but collapsed disc space). Grading was performed by 3 independent operators: 2 musculoskeletal radiologists (S.B., F.M.M) 1 orthopedic surgeon (G.V.).

T_{1ρ} values were calculated on a pixel-by-pixel basis by a linear regression of intensity data to an exponential decay function:

$$S(\text{TSL})=S_0 e^{-\text{TSL}/T_1\rho}$$

Values were used to create 3-dimensional spatial maps of T_{1ρ} using MATLAB (Mathworks, Cupertino, CA). A circular region of interest of 5-mm diameter was manually positioned by 2 independent investigators in the center of the NP of the map, and mean T_{1ρ} value was computed within that region. Moreover, T_{1ρ} values of the NP and the AF of the IVD were also calculated by manually segmenting the different region of the disc using custom-written software in MATLAB (<http://cmroi.med.upenn.edu/index.php/t1rho-t2-processing>).

Statistic Analysis

We compared median T_{1ρ} values of men and women of both NP and AF according to the anatomic level of each disc, using the MannWhitney test. The Jonckheere-Terpstra test, a nonparametric test for trends in ordered groups, was used to evaluate the decreasing trend in the relationship between NP (and AF) and the level of the discs. Scatter plots were mapped and Spearman rank correlation coefficient was applied to determine relationships between NP and Pfirrmann grade. Two-sided tests were used (except for the Jonckheere-Terpstra test which is 1-tailed). A *P* value of <0.05 was considered statistically significant. Linear regressions between T_{1ρ} values and BMI were performed.

Statistical analyses were done with Stata software, version 10.0 (StataCorp. 2007. Stata Statistical Software: Release 10; StataCorp LP, College Station, TX).

RESULTS

Table 1 shows the characteristics of all analyzed discs sorted by their Pfirrmann degenerative grade. Sagittal T₂-weighted images and corresponding quantitative T_{1ρ}-weighted images were used to evaluate the degenerative grade and the T_{1ρ} value, respectively. Representative sagittal T₂-weighted images and corresponding quantitative T_{1ρ} maps are shown in Figure 1, reporting the degenerative grade as Pfirrmann grading and the T_{1ρ} value. The T_{1ρ} map is a graphical representation of the quantitative T_{1ρ} parameter calculated at each pixel location.

In Table 2, the T_{1ρ} values of both NP and AF are listed according to the anatomic level of each disc and sex. For both sexes, the T_{1ρ} values of the NP were significantly higher compared with the AF values in all levels. T_{1ρ} value decreased as one proceeded caudally down the spinal column (Figure 2).

Evaluation of the sex difference in T_{1ρ} value at different levels showed a significant lower value in the female discs at L3–L4 ($P < 0.01$) and L4–L5 discs ($P < 0.05$) in T_{1ρ} value of the NP and a significant lower value in the female discs at L3–L4 ($P < 0.05$) in T_{1ρ} value of the AF (graph not shown). Figure 3 shows the box plot for NP T_{1ρ} values for men and women at the different lumbar levels. A significant decreasing trend in T_{1ρ} values of both NP and AF, from the upper to the lower lumbar level, was found in men and women (trend P values were < 0.0001 , according to the Jonckheere-Terpstra test).

The box plot for the 2 variables T_{1ρ} values and Pfirrmann grades, as shown in Figure 4, indicates that the 2 variables were inversely and linearly related. The correlation between T_{1ρ} values and Pfirrmann grades was -0.51 ($P < 0.0001$). However, the interquartile range shows the wide heterogeneity distribution of T_{1ρ} value, especially for the nondegenerated disc as evaluated according to the Pfirrmann scale; in fact, the T_{1ρ} value of all the population ranged from 51.7 to 185.5 ms for the 158 discs of grade 1, from 45.0 to 156.9 ms for the 108 discs of grade 2, and from 42.3 to 110.5 ms for the 36 discs of grade 3.

No significant linear association was observed between the T_{1ρ} value of the NP and the BMI of each subject (Figure 5).

DISCUSSION

Restoring PG content during the early stage of IDD is at the basis of new biological strategies for IDD prevention and disc regeneration.³⁶ Translational research in this field will be based on clinical trials where noninvasive quantitative analysis on water and PG content of the disc are required. T_{1ρ}-weighted MRI technique has been shown to be a promising tool for PG detection and early stage of IDD evaluation²⁹; therefore, it might be used for translational research focusing on reversing IDD.

This study evaluated quantitatively the early degenerative grade of the lumbar discs of asymptomatic young adults. T_{1ρ} value measured in this study was lower at caudal lumbar levels in both the NP and the AF, with an increasing trend of T_{1ρ} values proceeding cranially up the spinal column. This finding is in accordance with observations by others with different evaluations techniques.^{7, 35, 37–39} It reflects that mechanical loads are involved in

early PG loss of young discs because upper and midlumbar spine are subjected to lower mechanical loads than the caudal lumbar spine.

$T_{1\rho}$ values resulted higher in NP than in AF. These reflect the different composition of their extracellular matrix. The AF is a multilamellar fibrocartilage with PG precipitates in the interlamellar space that resist the tensile forces generated during bending or twisting, whereas the NP has a more random organization rich in PG that provides the osmotic properties needed for the discs to resist compressive loads.³⁶

A new finding arises by the sex comparison, because the $T_{1\rho}$ values of NP at L3–L4 and L4–L5 discs were significantly lower in women. These results suggest that PG loss of the NP may begin first in women and then in men. A straightforward comparison with earlier research is not possible due to lack of studies that used $T_{1\rho}$ relaxation time as method to evaluate IDD. A cross-sectional MRI study of Takatalo *et al*⁷ investigated the prevalence of degenerative findings of the lumbar spine among young Finnish adults aged 20 to 22 years. These authors reported that women had significantly higher prevalence of annular tears whereas men had significantly higher prevalence of IDD and disc herniations. However, these data were based on Pfirrmann degenerative grade whereas grades 1 to 2 were classified as normal discs, while grades 3 to 5 were defined as degenerated, with 13% prevalence in their cohort.⁷ According to these data, we observed 15% of grade 3 to 5 degenerated discs, while the sex difference evaluation we performed was based on $T_{1\rho}$ values of both normal and degenerated discs. In a cross-sectional cohort study, Kjaer *et al*³⁵ described the associations between lumbar MRI findings and LBP in 13-year-old children. These authors observed differences between sexes; degenerative disc changes in the upper lumbar spine were more strongly associated with LBP in boys, whereas disc abnormalities in the lower lumbar spine (L3–L4, L4–L5, and L5–S1) were more strongly associated with LBP in girls.³⁵ Thus, our findings are in accordance with the results from these Danish population-based cohorts.

Degenerative spondylolisthesis is the only disorder of the adult spine in which a distinct difference between sexes has been reported. It is approximately 4 times more common in women than in men and occurs more frequently at L4–L5.⁴⁰ This reason has not been explained, although factors, such as the lumbosacral junction anatomy (sacral horizontal angle and/or lumbar lordosis angle), facet joint orientation, ligamentous laxity, previous pregnancy, and hormonal factors have been suggested as etiological factors.⁴¹

A number of lifestyle and social demographic factors have been linked with LBP.^{42, 43} BMI has been correlated with LBP of obese people; however, this association has been considered controversial and causal link has not been demonstrated.⁴⁴ Although the population described in this study includes very few obese subjects, a correlation between $T_{1\rho}$ value of the NP and BMI has not been observed.

We observed that $T_{1\rho}$ MRI was linearly correlated to the Pfirrmann degenerative grade. However, nondegenerated discs (Pfirrmann grades 1 and 2) showed a wide range of $T_{1\rho}$ relaxation time (Figure 4). Indeed, the grading system based on T_2 -weighted images assesses disc water content and other morphological features and is able to give information

on biochemical changes that characterize IDD. Sowa *et al*⁴⁵ examined the changes observed during normal aging of the IVD in an animal model and showed modest age-related MRI changes assessed with T₂-weighted images compared with the dramatic histological changes analyzed on the same discs. These data suggested that conventional MRI techniques are relatively insensitive measures of IDD.⁴⁵

T_{1ρ} weighted MRI may have greater utility in demonstrating age- and degeneration-related disc changes that correlate with PG content, and it could provide spatial and quantitative measurements, which may be more closely correlated with biochemical changes in disc. Moreover, Nguyen *et al*³⁰ demonstrated that T_{1ρ} weighted MRI is directly correlated with isometric swelling pressure of cadaveric discs and suggested that it may be a valuable quantitative biomarker of the mechanical function of the NP. Furthermore, Blumenkrantz *et al*³² evaluated the association between T_{1ρ} and clinical finding as quantified by 36-Item Short Form Health Survey and Oswestry Disability Index in 16 patients observing a correlation. Therefore, T_{1ρ} -weighted MRI may be sensitive to early degenerative changes and clinical symptoms in IDD, and it could be used to define a new quantification IDD scale with higher specificity than T₂-weighted MRI-based Pfirrmann scales.

The strength of this study is the large homogeneous asymptomatic population of young adults analyzed with unconventional *versus* standard MRI techniques. Because early IDD changes start by the second decade of an individual's life, this is the first study that used T_{1ρ}-weighted MRI allowing a spatial and quantitative assessment of IDD in such population. Early degenerative changes were quantitatively assessed by T_{1ρ} relaxation time revealing a difference between sexes in the lower disc levels. Moreover, IDD changes assessed by T₂-weighted MRI Pfirrmann grading (grades 3–5) were observed in 15% of the subjects, and the nondegenerated discs (grade 1) were just in the 45.8%. Although IDD is known to be common among asymptomatic patients,^{7, 46} the prevalence of MRI findings among young adults is virtually unknown.

This cross-sectional study is limited by a relatively small sample size due to the complexity of the assessment and the costs of magnetic resonance examination of healthy young volunteers that limited the number of participant enrolled. This study is also limited by the lack of further advanced imaging techniques such as T₂ mapping⁴⁷ to compare with T_{1ρ}

Future T_{1ρ} MRI spine studies will include a large patient population consisting of both symptomatic and asymptomatic subjects and may lead to a better understanding of the pathophysiology of IDD. Prospective studies on subjects with high prevalence of IDD, such as heavy workers, athletes, and obese people, may provide further information on preventive strategies. The use of T_{1ρ} -weighted images in clinical protocols may be a useful guide to enroll and to evaluate the patients who may be treated with emerging technologies developed to treat early IDD, such as stem cell therapy.

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Key Points

- Early IDD was evaluated in asymptomatic young adults with the new $T_{1\rho}$ MRI.
- $T_{1\rho}$ values were significantly lower in women at L3–L4 and L4–L5 discs, showing a difference in IDD onset between sexes.
- The data of the study show that $T_{1\rho}$ value correlates with Pfirrmann degenerative grade highlighting the low sensitivity of Pfirrmann grade to detect the early IDD changes.
- $T_{1\rho}$ can be potentially used as a clinical tool to identify early IDD and to create a reliable quantitative scale.

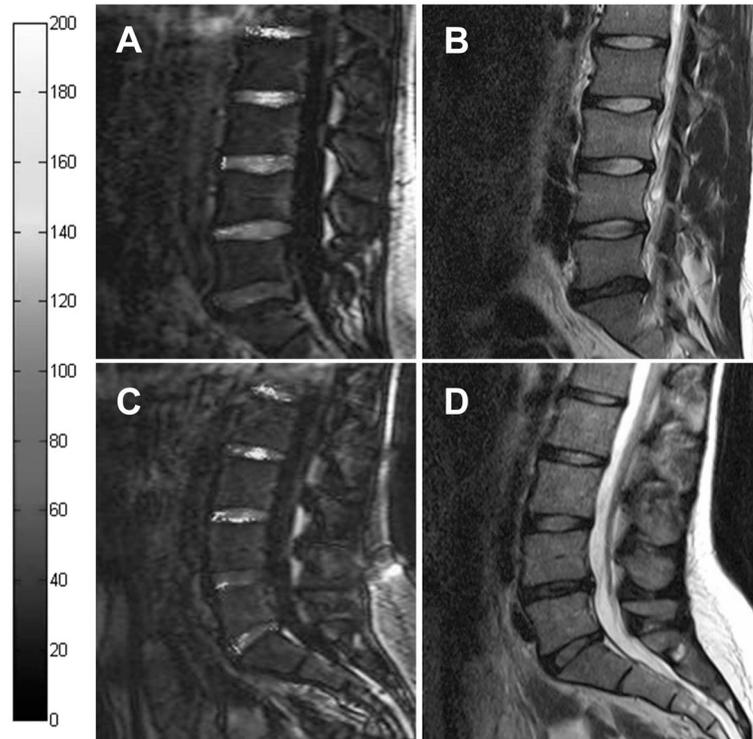


Figure 1.

Representative $T_{1\rho}$ map overlaid on $T_{1\rho}$ image (**A** and **C**) and T_2 -weighted images (**B** and **D**) from a 23-year-old man (**A** and **B**) and a 24-year-old woman (**C** and **D**). The L1–L2 and L2–L3 discs are nondegenerative with relatively high $T_{1\rho}$ relaxation times in both sexes. In contrast, the L3–L4 discs show a normal T_2 -signal intensity on T_2 -weighted images and a significant decrease of $T_{1\rho}$ value in both subjects. The L4 and L5–S1 show a distinct loss of signal intensity on T_2 imaging and a dramatic decrease in $T_{1\rho}$ time in women and men, respectively.

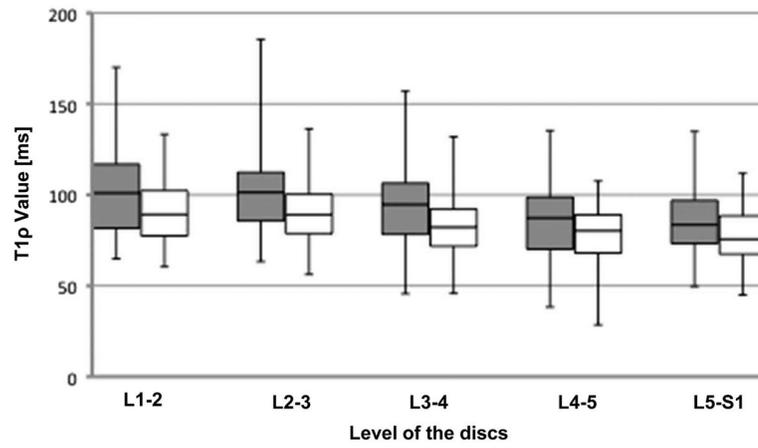


Figure 2. Box plots of $T_{1\rho}$ value of both nucleus pulposus (gray) and annulus fibrosus (white) according to the anatomic level of each disc. The boxes represent the median and the interquartile range, with the vertical lines showing the range.

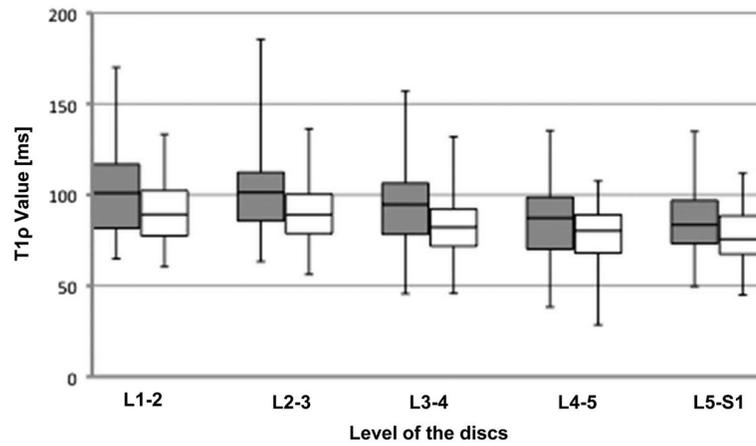


Figure 3.

Box plots of $T_{1\rho}$ value of nucleus pulposus by sex according to the anatomic level of each disc. Gray = Male; white = Female. The boxes represent the median and the interquartile range, with the vertical lines showing the range. The graph shows a significant lower $T_{1\rho}$ value in the female discs at L3–L4 and L4–L5 discs than that in the male discs. * $P < 0.05$.

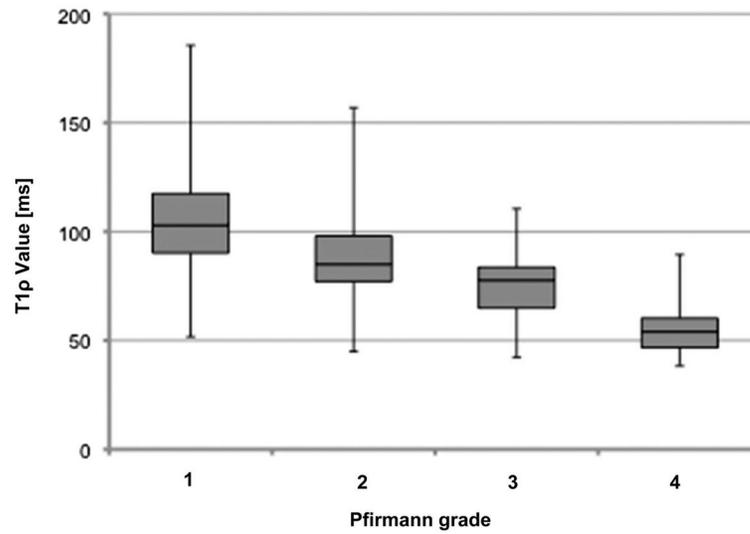


Figure 4. Box plots of $T_{1\rho}$ value of nucleus pulposus according to the grade of Pfirmann. The boxes represent the median and the interquartile range, with the vertical lines showing the range. One case with Pfirmann grade 5 ($T_{1\rho} = 51.7$) was excluded.

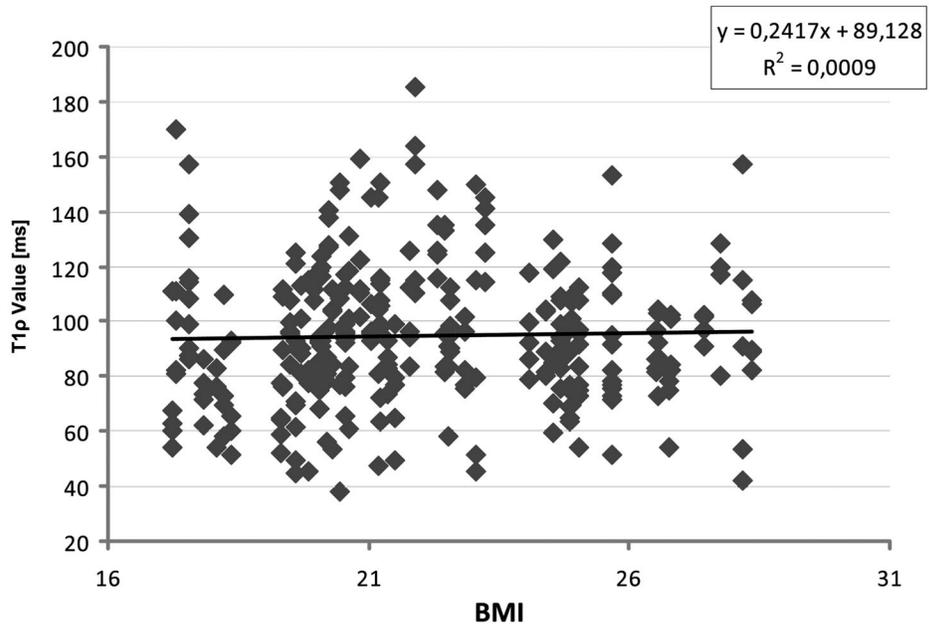


Figure 5. Correlation between $T_{1\rho}$ relaxation time and BMI of all discs was analyzed. No correlation was found. BMI indicates body mass index.

TABLE 1
 Degenerative Grade According to Pfirrmann Scale, Sex, and Disc Level of the Lumbar Intervertebral Discs of Healthy Young Adults Analyzed in Study

Degeneration Grades	Sex		Disc Levels						Total
	Male	Female	L1-L2	L2-L3	L3-L4	L4-L5	L5-S1		
1	87	71	30	30	38	32	28	158	
2	54	54	25	29	20	16	18	108	
3	20	17	8	4	4	9	12	37	
4	8	3	0	0	1	5	5	11	
5	1	0	0	0	0	1	0	1	
Total	170	145	63	63	63	63	63	315	

T_{1ρ} Value of Male and Female Both Nucleus Pulposus (NP) and Annulus Fibrosus (AF) According to the Anatomic Level of Each Disc Expressed as Median and Interquartile Range

TABLE 2

Disc Levels	T _{1ρ} Value [ms] of the NP		P	T _{1ρ} Value [ms] of the AF		P
	Male	Female		Male	Female	
L1-L2	97.6 (81.3–115.7)	107.4 (84.1–116.9)		86.6 (78.7–99.9)	94.3 (77.4–108.0)	
L2-L3	107.8 (90.7–119.4)	98.7 (82.1–110.0)		92.5 (78.7–106.1)	88.4 (83.6–93.4)	
L3-L4	96.7 (86.0–116.2)	86.4 (69.4–98.1)	< 0.01	87.2 (78.4–93.9)	76.7 (64.6–85.5)	< 0.05
L4-L5	91.6 (75.0–104.0)	81.2 (60.0–93.1)	< 0.05	84.8 (71.4–89.0)	78.3 (67.3–81.4)	
L5-S1	83.7 (75.7–103.4)	82.9 (73.0–95.5)		76.5 (69.5–88.8)	75.3 (66.7–84.9)	