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MUSCULOSKELETAL IMAGING

ORIGINAL ARTICLE

Lumbar vertebral T2-relaxation time investigated with T2-mapping at multiple time points in a day demonstrate large individual variations

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PURPOSE
The increasing interest of endplate and Modic changes as potential pain generators in low back pain (LBP), along with advancement of functional quantitative magnetic resonance imaging (MRI) techniques, makes it important to characterize the vertebral dynamic behavior in detail. This study aims to perform characterization of the dynamic behavior of the vertebral bodies (VB) by investigating the VB diurnal variation in T2-relaxation time in a cross-sectional asymptomatic group of individuals.

METHODS
T2-mapping of 30 VBs (L1-L5) in six healthy volunteers (mean age, 40 years; range, 29-65 years) was performed with a 1.5 Tesla MRI at three time points over the day (7 am, 12 am, 5 pm). Volumetric regions of interest were segmented manually to determine VB T2-relaxation time, which was compared between the three time points.

RESULTS
On a group level only small and not significant diurnal VB variation was detected (all $P > .10$), with median T2 (ms) (quartiles; Q1, Q3) at the three time points 88.7 (84.1, 99.1), 87.3 (85.0, 96.1) and 87.8 (84.4, 99.2). However, in some VBs up to 7% increase respectively 9% decrease in T2-relaxation time was found during the day. Further, there was a relatively large variation between the individuals in absolute VB T2-relaxation times (range 73.2-108.3 ms), but small differences between the VBs within an individual.

CONCLUSION
This first T2-mapping study of the VB signal dynamics, in repeated investigations during one day, display variation in T2-relaxation time in specific individual VBs but were negligible on a group level. The result may be of importance when evaluating patients with spinal pathologies and suggest further examinations of dynamic changes not only of the disc but also vertebrae.

In the search for improved diagnostic methods to separate different conditions causing low back pain (LBP), quantitative magnetic resonance imaging (MRI) techniques, with assessment of both objective spinal and functional measures, are promising. For example, T2-mapping enables detailed tissue characterization of the intervertebral disc (IVD) and the vertebrae, which in addition to provide objective measure of IVD degeneration has been shown to display differences between patients and controls in both the IVD and the vertebrae.[1-5] Quantitative MRI techniques have also been used to demonstrate relation between the IVD and the vertebrae, for example significant association between vertebral fat content and biochemical changes in the adjacent IVD was reported using a combined $T_{1\rho}$ and T2-mapping pulse sequence.[6]

With such quantitative MRI methods, diurnal changes within the IVD have been demonstrated,[7-10] interpreted as water displacement between IVD sub-regions, potentially also due to displacement to adjacent structures, during the day. Spinal loading during the day induces a convective flux in the vertebral segment, a pumping mechanism that facilitates nutrient supply to and metabolite removal from the avascular IVD.[11] In this process, the vertebral endplate represents a dominant flow path.[11-13] Contrary to the relatively well-studied diurnal behavior of the IVD, the dynamic behavior of the vertebrae is less established. Even though Boos et al.[14] already in 1993 reported a significant increase in vertebral T2-weighted signal over the day in 10 volunteers, studies replicating their findings are lacking. Moreover, there

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are no studies investigating the diurnal vertebral behavior using modern quantitative MRI techniques, such as T2-mapping.[14]

The increased interest of endplate and vertebral changes as potential pain generators, along with advancement of quantitative MRI techniques, makes it interesting to characterize the vertebral dynamic behavior in detail. Dynamic tissue behavior might be related to vertebral phenotype, and could be of importance when evaluating patients with spinal pathologies. For example, an asymmetric loading of spinal segments has been suggested as initiator of vertebral tissue changes, including Modic changes,[15] most probably also influenced by genetics and several other factors. There are also other highly controversial theories of involvement of bacteria in vertebrae with Modic changes, which yielded several studies with opposing results.[15-18] Detailed characterization of the vertebral tissue with MRI is important in order to deepen the understanding of normal changes seen with quantitative MRI, as well as to understand the pathophysiology behind LBP, and may contribute to standardize quantitative MRI examinations. The aim of this study was therefore to perform detailed characterization of the vertebral dynamic behavior by investigating the diurnal variation in T2-relaxation time in the vertebral body (VB) in a healthy population.

Methods

Participants

In this study, 30 lumbar VBs were examined (L1–L5) in six healthy volunteers, including four men (mean age, 40 years; range, 29–65 years) and two women (mean age, 39 years; range, 31–48 years). The participants were initially recruited for a study investigating the diurnal variation in T2-relaxation time in the IVD both during conventional supine MRI and axial loading during MRI.[19] The participants were enrolled during the first six months of 2017, with aim to largely reflect a LBP cohort in terms of age and IVD degeneration. This is a secondary analysis of the cohort, focusing on the diurnal vertebral T2-relaxation time at conventional supine MRI. The reason for not including the sequences acquired during loading of the spine in this first T2-mapping study of the VB diurnal behavior was avoidance to introduce too many parameters to analyze, considering the known inter-individual variance in the VB, affected by many factors.[20,21] All participants were asymptomatic and without any history of spine disease or back pain. The study was conducted according to the Declaration of Helsinki. Ethical approval was given by the regional ethics review board (Dnr;888-14). Oral and written informed consent was obtained from all participants.

Main points

- This first T2-mapping study of the vertebral signal dynamics display variation in T2-relaxation time in specific individual vertebrae.
- The vertebral signal variation during the day was, however, negligible on a group level.
- These results may be of importance when evaluating patients with spinal pathologies and suggest further examinations of dynamic quantitative changes not only of the disc but also vertebrae.

Image collection and protocol

All participants were examined with T2-mapping of the lumbar spine using conventional supine MRI at three different time points over one day (7 am, 12 am, and 5 pm). The images were acquired with a Siemens Magnetom Aera 1.5 T scanner. The scan protocol consisted of a sagittal T1- and T2-weighted turbo spin echo sequence and an axial T2-weighted turbo spin echo sequence (Table 1). Each scan session was approximately 20 minutes, including a sagittal multi-echo spin echo incorporated at the end of the protocol, enabling reconstruction of high-quality standardized T2-maps (T2-mapping). With the T2-mapping last in the protocol, the T2-maps were acquired after approximately 15 minutes bedrest. No other activity restrictions were imposed before or between sessions since we wanted to investigate potential diurnal variation during normal variation in activity.

Image analysis

Multiplanar reconstructions were used to generate volumetric analysis of the VBs. A 10 mm midsagittal T1-weighted image was fused with the corresponding sagittal T2-map, using a dedicated software (Syngovia, Siemens Healthcare). For T2-relaxation time determination, the VBs were segmented manually in the sagittal plane at the three most central fused midsagittal images using the volumetric polygonal region of interest (ROI) (Figure 1). The diurnal mean T2-relaxation time and the standard deviation (SD) were measured for the entire VB and compared between the three time points. All measurements were performed by a radiology resident after a training period, supervised by a senior consultant radiologist. Blinded intra-observer variability was assesses by repeating the measurements at the three time points, in 50% of the individuals. Inter-observer variability has previously been demonstrated to be excellent for the applied method.[22] Three repeated scans (with maximum 12 minutes between initiation of each scan) were further performed on one volunteer during the same session, in order to test the robustness of the scanning.

Statistical analysis

Continuous variables are presented as median and quartiles. For comparison of T2-relaxation times between time points, the Wilcoxon signed rank test was used

Table 1. MRI parameters for T1-weighted, T2-weighted, and T2-map imaging

	T1W (TSE)	T2W (TSE)	T2W (TSE)	T2-map
Imaging plane	Sagittal	Sagittal	Axial	Sagittal
Repetition time (ms)	480	3500	4862	1400
Echo time (ms)	9	95	97	8 echos; 11.1, 22.2, 33.3, 44.4, 55.5, 66.6, 77.7, 88.8
Slice thickness (mm)	3.5	3.5	3.5	3.5
Slice gap (mm)	0.7	0.7	0.4	0.7
Pixel bandwidth (Hz)	235	180	195	220
Flip angle (degree)	150	150	150	180
Acquisition matrix	320x224	384×288	320×256	256×256
Reconstruction matrix	320×320	384×384	320x320	256×256
Field of view (mm^2)	300×300	300×300	200x200	220×220

MRI, magnetic resonance imaging, T1W, T1-weighted; T2W, T2-weighted; TSE, turbo spin echo.

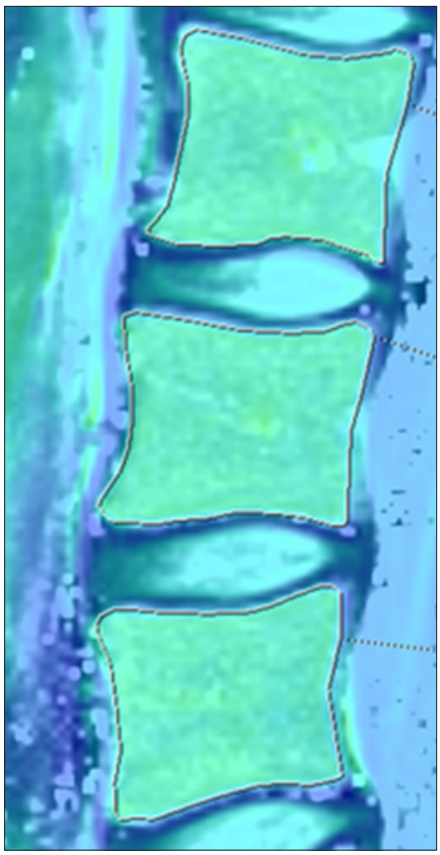

Figure 1. Fused T1-weighted and T2-weighted maps over midsagittal L2-L4 of one individual, illustrating the vertebral body segmentation.

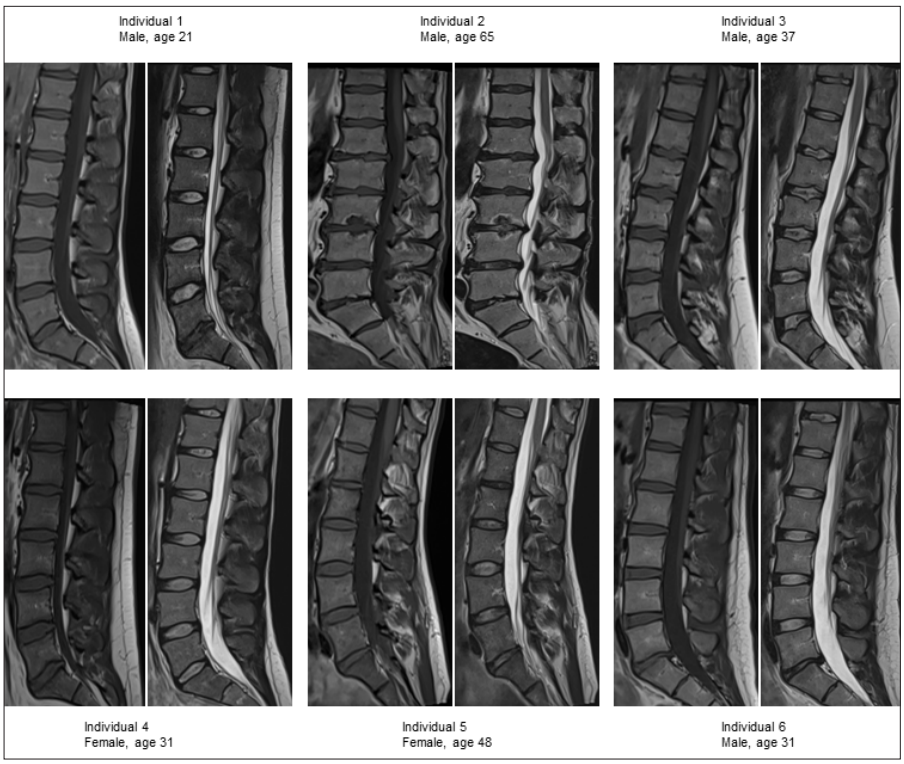

Figure 2. Midsagittal T1-weighted and T2-weighted sagittal images and demographic data of each individual.

at a group level analysis. A mixed model was used to adjust for intra-individual dependency. Reliability of quantitative measurements for inter-rater agreement was performed using intraclass correlation coefficients (ICC) with 95% confidence intervals. ICC model 2 was used with single measurement to determine consistency in the agreement. ICC values less than 0.4 represent poor agreement, values between 0.4 to 0.75 represent fair to good agreement, and values exceeding 0.75 indicate excellent reliability.[23] All tests were two-tailed and conducted at $P < .05$ significance level. All analyses were performed by using SAS software version 9.4 (SAS Institute Inc.).

The study was designed to evaluate the short term VB T2-relaxation time variation in healthy individuals and to determine statistical group difference between time points. Lack of previous studies investigating the diurnal VB behavior with quantitative MRI techniques made adequate sample size calculation precarious. The sample size was chosen in accordance with a previous study, investigating diurnal behavior in IVDs with quantitative technique.[8]

Results

Demographics as well as an overview of morphology features of the lumbar spine are displayed in Figure 2 and Figure 3.

On a group level only small and nonsignificant diurnal VB variations were detected, with median T2 (ms) (quartiles; Q1, Q3) at the three time points 88.7 (84.1, 99.1), 87.3 (85.0, 96.1) and 87.8 (84.4, 99.2) (Table 2).

However, some VBs displayed more pronounced dynamics with a higher magnitude of T2 variation over the day (Figure 4). In Individual 3, the T2-relaxation time varied in several VBs. For example, in L2 the T2-relaxation time increased with mean 6.2 ms between 7 am and 12 am whereas a 8.3 ms decline was registered between 12 am and 5 pm (Figure 4). This individual displayed endplate (Schmorls nodules) changes at multiple levels (Figure 2). Further, in Individual 6 mean T2 in L2 decreased with 5.2 ms between the first two time points followed by an 4.4 ms increase at 5 pm, without any obvious VB or endplate changes displayed. No obvious relation between specific morphological VB features and T2 variation was detected and the study was not designed for statistical analysis at single levels intra-individually.

There was a wide inter-individual variation in absolute VB T2-relaxation times with a range of 73.2-108.3 ms. The intra-individual VB T2-relaxation times, however, did display a relatively low variation. The highest VB T2-relaxation times were noted in the oldest individual (Individual 2), who displayed quite extensive degenerative spinal changes (Figure 2 and Figure 4), but also in one of the younger individuals with a nondegenerated spine (Individual 6), except a degenerated IVD L5/S1 (Figure 2 and Figure 4). The lowest VB T2-relaxation times appeared in a middle-aged individual without apparent VB changes and two slightly dehydrated IVDs (Individual 5) (Figure 2 and Figure 4).

Intra-observer measurements displayed high agreement with an ICC of 0.99 (95% CI 0.98-0.99). Repetitive scans on the same volunteer demonstrated robustness of the scanning with only minor T2-value variations (range, 0.8-2 ms; 1%-2.6%) between the three repeated scans.

Discussion

This study, applying T2-mapping in healthy individuals at three different time

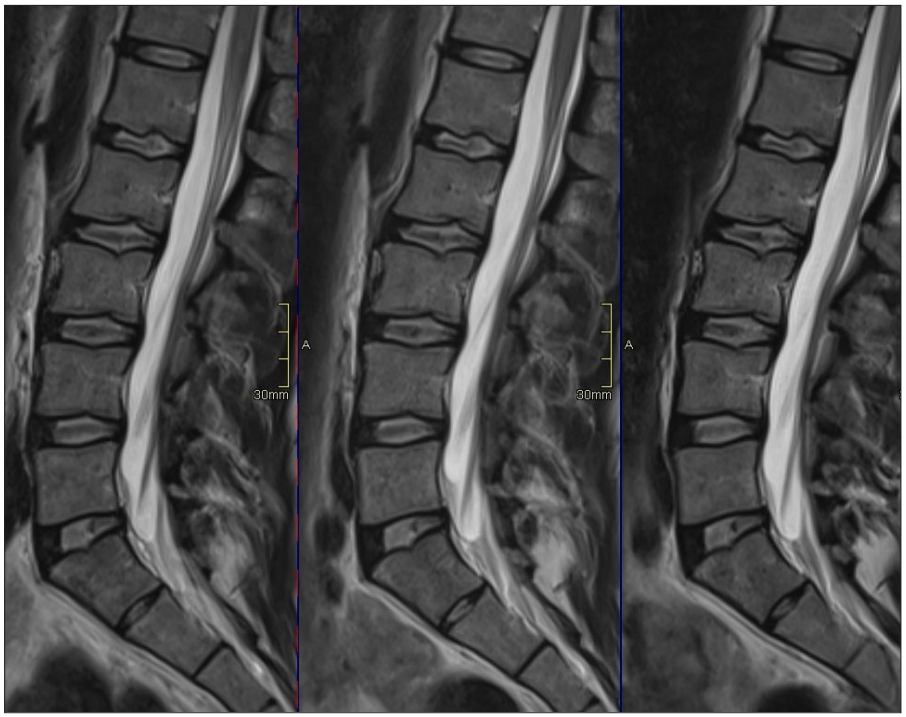

Figure 3. Example of an individual´s T2-weighted sagittal images at the three time points (Individual 3).

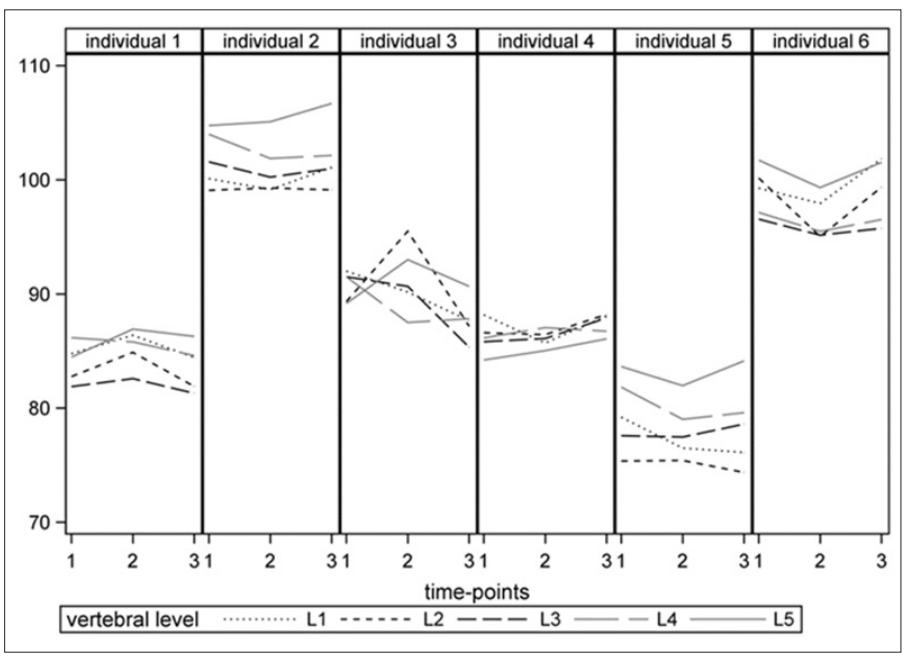

Figure 4. Vertebral body T2-relaxation time (ms) variation at each time-point (1-3) in each individual. The vertebral body relaxation time (ms) is displayed on the y-axis, for the three time points, 7 am, 12 am, 5 pm (x-axis) for each individual.

points over the day, show small and insignificant diurnal T2 variations in the VB. Even though the diurnal variation was negligible on a group level, awareness should exist that there may be a dynamic behavior, with wide variation in T2-relaxation time, in individual VBs.

The magnitude of the T2-relaxation time change over the day was low, declining with mean 1.7 ms between 7 am and 5 pm. Thus, this study could not confirm the findings by Boos et al.,[14] reporting an increase in VB T2-weighted signal over the day. The current method, using T2-mapping and including the entire VB in the analysis, likely reflect a more true diurnal behavior of the VB as compared to previous studies analyzing only small parts of the VB with conventional T2-weighted sequences.

Table 2. Median vertebral body T2-relaxation time (ms) at all time points

T2-relaxation time (ms)		
Time point (TP)	Median Quartiles	Within group *P*
TP1	88.7	
	84.1, 99.1	
TP2	87.3	
	85.0, 96.1	
TP3	87.8	
	84.4, 99.2	
TP1-2	0.6	0.139
	(-)0.7, 1.9	
TP1-3	0.5	0.323
	(-)1.1, 1.6	
TP2-3	(-) 0.5	0.658
	(-)1.8, 1.2	

Table 3. Median intervertebral disc T2-relaxation time (ms) at all time points

T2-relaxation time IVD (ms)	
Time point (TP)	Median (Quartiles; Q1,Q3)
TP1	84.5 (55.5, 99.5)
TP2	78.4 (56.8. 94.0)
TP3	75.0 (50.5, 92.8)

Early diurnal IVD studies, using only one image slice and one region of interest, reported a T2-signal variation of the IVD with decline, interpreted as loss of water, over the day.[9,14,24] Later studies, based on subregional IVD analysis, display that at least part of this diurnal "dehydration" is due to redistribution from nucleus to annulus.[8] Since fluid exchange between the VB and the IVD mainly occurs via the EP,[12,13,25] it would seem logical that over the day water molecules are, through load, forced from the nucleus to not only the annulus but also to surrounding structures like the VB. This study was not designed to enable statistical analysis regarding any potential diurnal interplay between the VB and the IVD. In the preceding study investigating the diurnal IVD behaviour on the same population,[19] no significant diurnal alterations were found, neither for the entire IVD nor for separate

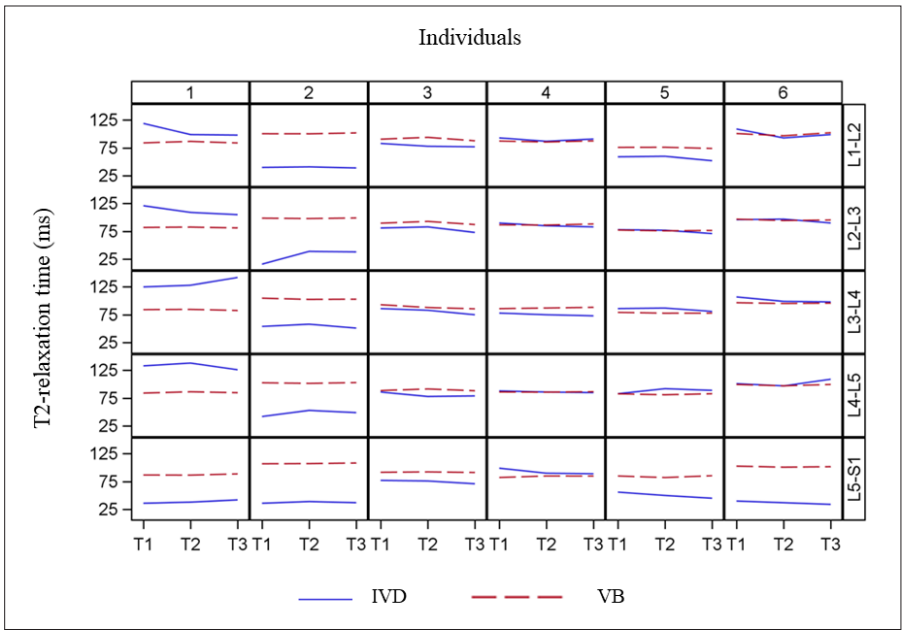

Figure 5. T2-relaxation time (ms) at each time-point (1-3) in each individual for each intervertebral disc (IVD) and adjacent vertebral body (VB). Since each IVD is bordered by two adjacent VBs, the mean T2 value of the caudal 50% of the cranial adjacent VB and the cranial 50% of the caudal adjacent VB was calculated.

subregions. An overview of the relation between the T2 time of each IVD and adjacent VBs are displayed in Figure 5 with median IVD T2-values displayed in Table 3. No obvious relation between dynamic VB behavior and corresponding IVD behavior could be detected.

In some VBs the T2 fluctuated quite extensively over the day, ranging from 6.2 ms increase to 8.3 ms decrease, representing a change with relatively high magnitude (7% respectively 9%). This deviant behavior both inter-individually as well as intra-individually (Figure 4) is likely a reflection of the close, and complex interplay between the IVD and the VB,[6] in which a number of different factors such as endplate function/permeability, vertebral vascularization, IVD degeneration grade, loading forces due to activity (e.g., lordosis angle, BMI) may impact.

The diurnal T2 change in one of the individuals (Individual 3) with distinct endplate lesions is interesting. One may hypothesize that the impaired border between the IVD and the VB increase the flux of molecules between the tissues. Rajasekaran et al.[25] reported such behavior in their MRI study of diffusion characteristics in human lumbar IVDs over 24 hours in healthy volunteers and LBP patients. They found altered diffusion characteristics, with more intense contrast enhancement, also at an earlier stage, within segments with impairment in the endplate.[25] Disrupted endplates might make the VB more prone to display short-term variation in signal secondary to the alteration of the diffusion/perfusion pattern between the IVD and the VB.[26] Hypothetically, the combination of non-degenerated IVDs and endplate changes (Individual 3) makes the spinal segments more prone to large molecular flux during daily activities, displayed as fluctuating VB T2-relaxation times compared with more stable T2 in Individual 2, who displayed endplate changes and severely dehydrated IVDs. How such functional properties of the spinal segments relate to phenotype of the IVD, endplate, and VB needs to be further investigated since such behavior may be of importance when evaluating patients with spinal pathologies.

The wide variation in VB T2-relaxation times among individuals (73-108 ms) is within the same range as previous VB T2-mapping studies.[5] This wide inter-individual VB T2 variation was expected since the VB marrow is a dynamic organ, continuously changing with age, hematopoietic need and the influence of environmental factors and morphology.[20,21,27]

Quantitative MRI techniques have a broad application and have long been used to phenotype bone marrow.[6,27] For example, T2*, magnetic resonance spectroscopy (MRS) and Dixon imaging have been demonstrated to differentiate between VB fractures of acute benign or malignant origin.[27-29] Further, MRS has been used to demonstrate an age- and gender-related increase of VB marrow signal-weighted fat fraction.[30] However, also within subjects of a given age, the MRI VB signal display a large variation with less signal variation among each VB of the same subject.[31] This was confirmed by the present study. With few exceptions, all lumbar segments within the same subject displayed similar T2 value variation at the three time points (Figure 4).

It needs to be highlighted that even though the studied group was well representative for a LBP cohort, with a wide range in both age and heterogeneous spinal phenotypes, they were asymptomatic individuals. Higher VB and endplate T2 values in patients compared to controls have been reported, indicating that endplates and VBs in patients have altered biodynamical characteristics compared to controls.[5,6] This study of VB dynamic behavior constitute a base for future research and calls for further investigations on how short-term VB T2 behavior is related to VB phenotype and IVD composition, since such quantitative dynamic tissue behavior may be of importance when evaluating patients with spinal pathologies.

The small study group limits the conclusions that can be drawn. It cannot be excluded that the lack of significant changes on a group level can be caused by the low number of observations. T2-mapping acquisition is known to be complex, depending on the scan technique. Since the fitting curve was optimized to account for both IVD and VB signal, it cannot be excluded that a fitting curve optimized for only the VB would slightly alter the absolute T2-values, but if so it would unlikely impact the diurnal effect. Further, whether data from a machine with higher field strength, i.e., a 3T machine, would reveal additional findings on this specific topic is unknown.

The purpose of this study was to characterize "normal" dynamic VB behavior over the day, therefore, neither the participants' activity level, nor the effect of age or bone density, was controlled for. This could be considered a limitation; however, considering previous lack of detailed characterization of diurnal VB T2-relaxation time data in the literature, this study provides a base for future research regarding quantitative dynamic VB behavior.

In conclusion, this first T2-mapping study of the VB signal dynamics in repeated investigations during one day display variation in T2-relaxation time in specific individual VBs but were negligible on a group level. The result may be of importance when evaluating patients with spinal pathologies and suggests further examinations of dynamic changes not only of the disc but also vertebrae.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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