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LETTER TO THE EDITOR

MRI identifies biochemical alterations of intervertebral discs in patients with low back pain and radiculopathy

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Key Points

- *Molecular intervertebral disc damage was associated with LBP and radiculopathy.*
- *Patients with radiculopathy and LBP demonstrated a depletion of gagCEST values compared with healthy controls.*
- *GagCEST imaging may be a non-invasive tool for investigation of degeneration processes of lumbar intervertebral discs (IVDs). GagCEST imaging may be an imaging biomarker for biochemical IVD alterations.*

Abbreviations

AP	Annulus fibrosus
BMI	Body mass index
CEST	Chemical exchange saturation transfer
GAG	Glycosaminoglycan
GagCEST	Glycosaminoglycan chemical exchange saturation transfer
IVD	Intervertebral disc
LBP	Lower back pain
MRI	Magnetic resonance imaging
NP	Nucleus pulposus
RF	Radiofrequency
ROI	Region of interest
SLR_{asym}	Asymmetric spin-lock ratio
VAS	Visual analogue scale
WASABI	Water Saturation and B1
WHO	World Health Organization

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Introduction

Low back pain (LBP) is the leading cause of years lived with disability in developed and developing countries [1] and can be caused by intervertebral disc (IVD) degeneration [2]. IVD degeneration includes loss of fluid in the nucleus pulposus (NP), loss of disc height, and fissures in the annulus fibrosus (AF) which may cause pain [3]. Glycosaminoglycans (GAGs) are a main component of IVDs, in particular of the NP. They maintain tissue fluid and therefore play a central role in degenerative disc processes prior to the appearance of morphological MR findings [4]. The feasibility of GAG chemical exchange saturation transfer (gagCEST) imaging of the IVDs has been demonstrated and lower GAG values were found in morphologically degenerated discs of healthy volunteers and in patients with LBP.

The aim of our study was to assess the GAG content of lumbar IVDs using gagCEST MRI in patients with chronic LBP and radiculopathy compared with healthy individuals, to figure out a difference between patients with radiculopathy and LBP.

Materials and methods

Study population

This prospective study was approved by the local ethics committee. Written informed consent was obtained from all participants prior to the MRI examination. Exclusion criteria were prior spine surgery and age < 18 years, in addition to whether participants suffer from a systemic disease or

received a systemic therapy. A spine surgeon with 10 years of experience performed the screening and classification of patients. The healthy individuals neither had LBP at the time of the study nor a history of LBP.

MR hardware and sequence protocol

The lumbar spine of all participants was examined in supine position using a clinical whole-body 3-T MR system (Magnetom Trio, A Tim System, Siemens Healthineers). MR protocol included a T2w sequence in sagittal and transversal orientation. Biochemical imaging was performed with a novel gagCEST sequence (using the Spin-Lock technique; CESL) and WASABI (Water Saturation and B1) method for B0 and B1 field inhomogeneity correction [5]. Detailed sequence parameters are given in supplement material.

Data analysis

One board-certified radiologist (6 years of experience in musculoskeletal radiology, C.S.) blinded to the gagCEST values scored all lumbar intervertebral discs according to the Pfirrmann scoring system for morphological IVD classification according to sagittal T2 images. A region-of-interest (ROI) analysis was performed for SLR_{asym} evaluation of the NP and AF to identify the gagCEST effect. SLR_{asym} values were given in percent and were excluded from further analysis.

Statistical analysis

Statistical analysis was performed using MATLAB (MathWorks) and SAS version 9.4 (SAS Institute Inc.). Mean gagCEST values, median, 95% confidence intervals, and standard deviations were calculated for patients with radiculopathy, LBP and healthy controls and for NP and AF, respectively (Fig. 1). In order to investigate mean differences in gagCEST values between patients with radiculopathy versus LBP versus healthy controls and between NP and AF, multivariable statistical analyses were performed using a linear mixed model. p values were significant in cases of $p \leq 0.05$.

Results

Patient population

The study collective consisted of 41 patients: 18 healthy, 13 with LBP, 10 with radiculopathy; 20 females, 21 males; age 41.6 ± 15.2 years; median 34 years; range 23–83 years. Of the 205 lumbar IVDs (L1–S1), all NPs and AFs were successfully imaged with biochemical imaging.

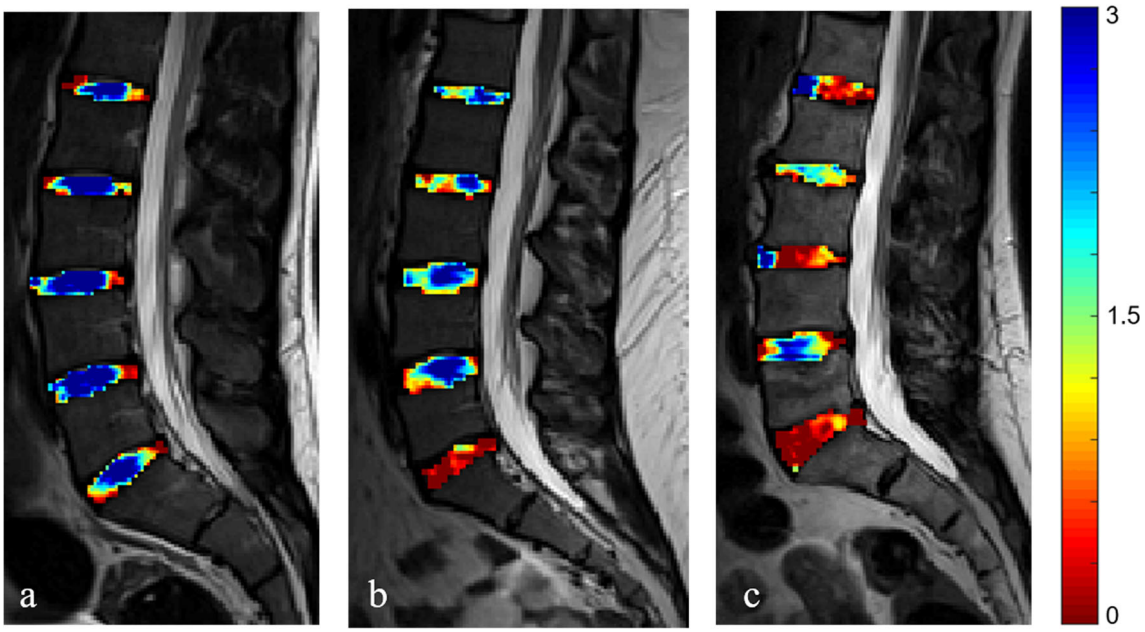

Fig. 1 Color-coded gagCEST map with high GAG content in blue and low GAG content in red of the lumbar spine (L1–S1). Three different participants of our study collective: picture (**a**) showed gagCEST values of a healthy control, picture (**b**) revealed gagCEST effects of a patient with chronic LBP, and picture (**c**) displayed a patient suffering from radiculopathy. Patients with LBP and radiculopathy presented significantly lower GAG content compared with controls, especially in localization of the affected segment L5/S1 of the patient with radiculopathy showed the lowest GAG values that were not significantly lower compared with patients suffering from LBP

Morphological analysis

No significant differences of morphological grading were found between healthy controls and the two patient groups (lumbago/radiculopathy).

gagCEST analysis of patients with radiculopathy or LBP and healthy controls

All ten patients with radiculopathy symptoms corresponded to the L5/S1 level. At level L5/S1, gagCEST values of the NP were significantly lower in patients with radiculopathy and LBP compared with healthy individuals (0.03% ± 0.88% vs. 2.40% ± 1.80%, $p = 0.0001$; and 0.88% ± 1.22% vs. 2.40% ± 1.80%, $p = 0.0056$).

GagCEST values of the NP were 0.03% ± 0.88% in patients with radiculopathy compared with 0.88% ± 1.22% in patients with LBP which did not reach the level of statistical significance ($p = 0.1652$).

Discussion

In this study, we have found significantly lower gagCEST values in patients with radiculopathy and LBP compared with healthy controls, while morphological disc analysis revealed no significant difference. Although not statistically significant, a trend toward lower gagCEST values in patients with radiculopathy compared with LBP patients was found.

Although the etiology of LBP is still not completely understood and is a matter of ongoing research, intervertebral disc degeneration is regarded as one of the multifactorial causes of LBP [6, 7]. Molecular GAG loss has been suspected to be a precursor to early IVD degeneration, especially in the NP [8]. With gagCEST MRI imaging, it is possible to non-invasively analyze the GAG content of IVDs without the application of an intravenous contrast agent [9]. With recent reports about gadolinium deposits in the brain after contrast material–enhanced MRI scans, development and implementation of non-contrast sequences are of great interest [10].

Our study has limitations. Only a small number of patients and healthy individuals were analyzed in our study and 15 patients had to be excluded due to incomplete MRI examinations or motion artifacts. For gagCEST and Pfirrmann classification no intra- and inter-observer agreement was performed.

In conclusion, gagCEST values were significantly lower in patients with radiculopathy and chronic LBP compared with healthy individuals. Thus, gagCEST imaging may be a non-invasive tool for investigation of degeneration processes of IVD. Biochemical imaging with gagCEST may provide an early biomarker for IVD degeneration in patients with low back pain. We found a trend toward lower gagCEST values in patients suffering from radiculopathy compared with patients suffering from LBP, which, however, was not statistically significant in our study but justifies larger studies.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is C. Schleich.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- diagnostic or prognostic study
- performed at one institution

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