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SCIENTIFIC ARTICLE

Can magnetic resonance imaging accurately predict concordant pain provocation during provocative disc injection?

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Abstract
Objective To correlate magnetic resonance (MR) image findings with pain response by provocation discography in patients with discogenic low back pain, with an emphasis on the combination analysis of a high intensity zone (HIZ) and disc contour abnormalities.
Materials and methods Sixty-two patients (aged 17–68 years) with axial low back pain that was likely to be disc related underwent lumbar discography (178 discs tested). The MR images were evaluated for disc degeneration, disc contour abnormalities, HIZ, and endplate abnormalities. Based on the combination of an HIZ and disc contour abnormalities, four classes were determined: (1) normal or bulging disc without HIZ; (2) normal or bulging disc with HIZ; (3) disc protrusion without HIZ; (4) disc protrusion with HIZ. These MR image findings and a new combined MR classification were analyzed in the base of concordant pain determined by discography.
Results Disc protrusion with HIZ [sensitivity 45.5%; specificity 97.8%; positive predictive value (PPV), 87.0%] correlated significantly with concordant pain provocation ($P<0.01$). A normal or bulging disc with HIZ was not associated with reproduction of pain. Disc degeneration (sensitivity 95.4%; specificity 38.8%; PPV 33.9%), disc protrusion (sensitivity 68.2%; specificity 80.6%; PPV 53.6%), and HIZ (sensitivity 56.8%; specificity 83.6%; PPV 53.2%) were not helpful in the identification of a disc with concordant pain.
Conclusion The proposed MR classification is useful to predict a disc with concordant pain. Disc protrusion with HIZ on MR imaging predicted positive discography in patients with discogenic low back pain.

Keywords Discogenic low back pain · High intensity zone · Lumbar intervertebral disc · Magnetic resonance imaging · Discography

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Introduction

Patients complaining of low back pain often have magnetic resonance (MR) images revealing annular bulging, disc protrusions, loss of disc height, and endplate abnormalities [1–4]. Because these structural abnormalities are often identified in individuals without low back or extremity pain [5, 6], provocation discography is often used to help confirm or refute one's clinical impression that a particular disc is the source of a patient's pain [7, 8]. Concordant pain provocation during flow of contrast into radial annular fissures may

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be due to the presence of sensitized nocioceptors that accompany the ingrowth of vascular tissue following injury to the disc annulus [9–11]. Concordant pain provocation during flow of contrast into 'painful' discs remains an active area of research. Most painful discs exhibit radial annular fissures [12]. Furthermore, there is immunohistochemical evidence that a disc which gives positive findings on provocation discography may contain cytokine-sensitized nocioceptors, phagocytic cells, perivascular neo-innervation, (accompanying the ingrowth of granulation tissue), or small free nerve fibers (axonogenesis), not only in the outer annulus, but also extending to the inner annulus and nucleus pulposus [13–18].

Although post-discography computed tomography (CT) scans will conclusively identify radial annular tears, annular disruption can also be non-invasively identified as an area of high signal intensity in the annulus [high intensity zone (HIZ)] visualized on a T2-weighted and gadolinium diethylene triamine penta-acetic acid (Gd-DTPA)-enhanced T1-weighted MR image [4, 19]. Numerous previous studies correlated pain provocation during discography to the presence of an area of high signal intensity located in the annulus fibrosus on T2-weighted images (the HIZ) [9, 11, 14, 20–27]. One study, however, showed no significant correlation between the presence of an HIZ and pain provocation during discography [21]. That study correlated only the presence or absence of an HIZ with a 'positive discography' and did not specifically analyze the combination of an HIZ with other structural abnormalities.

Therefore, our study correlated pain provocation during discography with a variety of MR image findings and, in particular, analyzed the predictive value of the combined presence or absence of an HIZ with disc contour abnormalities (either a normal or bulging disc or disc protrusion)

Materials and methods

From March 2004 to December 2007, 62 consecutive patients (age range 17–68 years; mean age 46 years) were prospectively enrolled in the study. All patients underwent magnetic resonance imaging (MRI) of the lumbar spine followed by provocation discography. Inclusion was based on satisfaction of all the following criteria: 1. Severe low back pain that was likely to be disc related (e.g., pain aggravation with forward bending and pain during prolonged sitting with or without referred leg pain). 2. Failure of an adequate trial of nonsurgical treatment of at least 6 months' duration. 3. Appropriateness of the candidate for spinal fusion or minimally invasive treatment in the case of positive findings at discography. Exclusion criteria were based on MR imaging findings that were considered to be a potential source of nondiscogenic low back pain and included the presence of disc extrusion or sequestration, nerve root compression, neural foraminal or central spinal stenosis, spondylolisthesis, previous lumbar disc surgery, and suspected spinal infection or neoplasm. Institutional review board approval was obtained for the study.

MR imaging was performed with a 1.5-T imager (Magnetom Vision; Siemens Medical Systems, Erlangen, Germany), using a phased array spine coil. The imaging protocol consisted of sagittal and axial T1-weighted (repetition time/echo time 400–600 ms/12–20 ms) and sagittal and axial T2-weighted (repetition time/echo time 3,000–4,000 ms/96–112 ms) turbo spin-echo imaging of the entire lumbar spine.

MR images were assessed by two independent musculoskeletal radiologists (C.H.K., J.H.K) who were unaware of the results of the discography. The evaluated findings of the MR images included the presence of an HIZ, disc contour abnormalities, the presence and grading of disc degeneration, and the presence of endplate abnormalities. HIZ was defined as high signal intensity (fluid-like signal intensity) located in the substance of the posterior annulus fibrosus that was clearly dissociated from the signal of the nucleus pulposus [9]. According to the recommendations of the combined task forces of the North American Spine Society, the American Society of Spine Radiology and the American Society of Neuroradiology [28], the following terms for disc contour abnormalities were used: normal, bulging, and protrusion. Bulging is not a herniation, and a term for describing the extension of a disc beyond the confines of the vertebral endplate must involve more than 50% of the circumference of the disc. Protrusion is a herniation and is present if the greatest distance, in any plane, between the edges of the disc material beyond the disc space is less than the distance between the edges of the base, in the same plane. Protrusion is subcategorized as "focal" or "broad-based" depending on involvement of less than or more than 25%, respectively, of the circumference of the entire disc (Fig. 1). Extrusions including sequestration and migration were excluded. For the combination analysis of an HIZ and disc contour abnormalities, a new classification system was used to classify disc morphology into four grades (Table 1, Figs. 1, 2, 3, 4 and 5).

Disc degeneration was graded on mid-sagittal T2-weighted images according to the grading system of Pfirrmann et al. [29], in which five grades (homogeneous versus inhomogeneous bright nucleus for grades 1 and 2; the possibility of differentiating the annulus and nucleus for grades 3 and 4; the marked collapse of disc space for grade 5). For the purpose of this study, grades 1 and 2 were grouped together as discs without degeneration. Endplates and adjacent bone marrow abnormalities were classified on sagittal MR images according to the definitions of Modic et al. [30] as follows: no abnormality; type I, low signal intensity on T1-weighted images and high signal intensity on T2-weighted images;

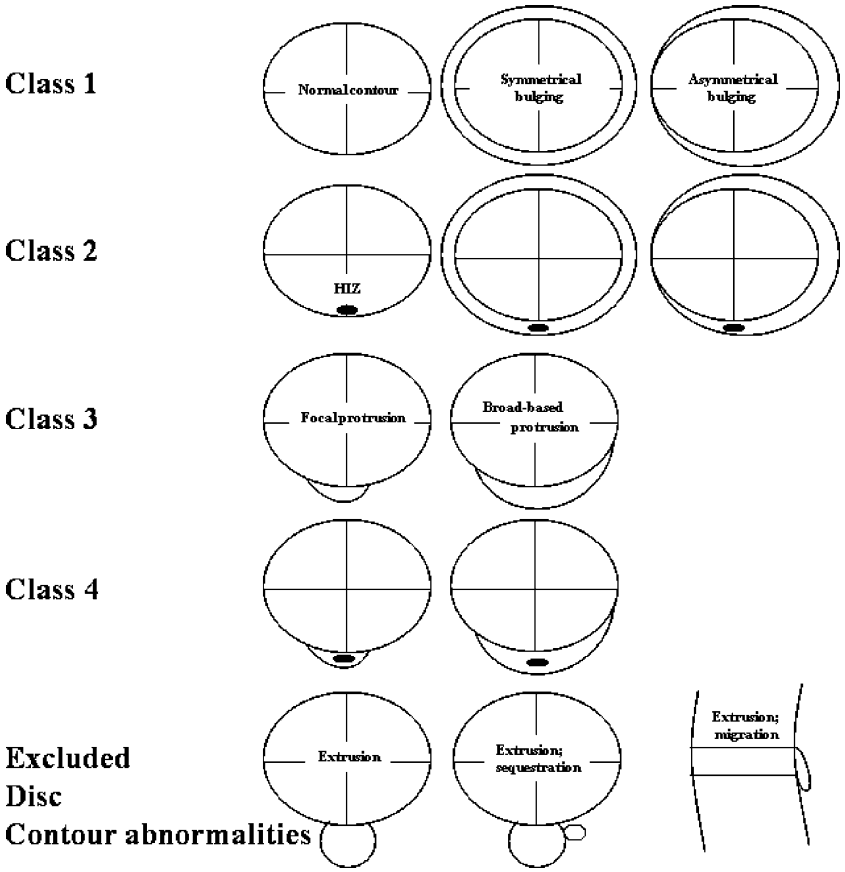

Fig. 1 Schematic illustration shows our MR classification system which is designed from combination of an HIZ and disc contour abnormalities

type II, high signal intensity on both images; type III, low signal intensity on both images.

All 62 patients underwent provocation discography of abnormal lumbar discs, as defined by the radiologists involved in the initial evaluation of the MR images. When patients had symptomatic (concordant pain) discs, we tested adjacent discs with normal appearance or subtle degeneration and determined if these discs were asymptomatic. Where normal-appearing discs existed in the two levels that were L4–L5 and L5–S1 in the patients that showed abnormal discs (diagnosed through MR images), without concordant pain, we also performed discography at the normal-appearing caudal disc, based on our usual clinical practice. Patients were instructed in the use of the numeric rating scale [range 0 (no pain) to 10 (worst pain that could ever be experienced)] for pain intensity responses. One discographer, who had 10 years experience of the procedure, performed discography in a surgical suite under aseptic conditions with the use of C-arm fluoroscopy. Antibiotics (2 g of cephalosporin) were administered intravenously 20 min before the procedure. All patients were premedicated with 0.025 mg/kg of midazolam before the procedure. Discography was performed with a standard posterolateral approach with a 24-gauge spinal needle. The L5–S1 level was also accessed by this one-needle technique. Once accurate placement had been achieved, 1.5–3.5 ml of nonionic contrast medium (iohexol, Omnipaque 300; GE Healthcare, Milwaukee, Wis, USA) mixed with 6 mg/ml of cephalosporin was injected into each disc with a controlled injection syringe. During injection, pain response was recorded into three grades: no pain, unfamiliar pain, and familiar pain, as well as the use of the numeric rating scale. Designation as a disc with concordant pain by discography required the presence of an abnormal disc, a pain response on the numeric rating scale of 6 out of 10 or higher, pain described by the participant as familiar, and a negative control disc. Each discogram was reviewed by the spine clinician (S.H.L) who had performed the discography.

Table 1 MR classification for the combination analysis of an HIZ and disc contour abnormalities

Classification	Description
Class 1	Normal or bulging disc in the absence of an HIZ
Class 2	Normal or bulging disc in the presence of an HIZ
Class 3	Disc protrusion in the absence of an HIZ
Class 4	Disc protrusion in the presence of an HIZ

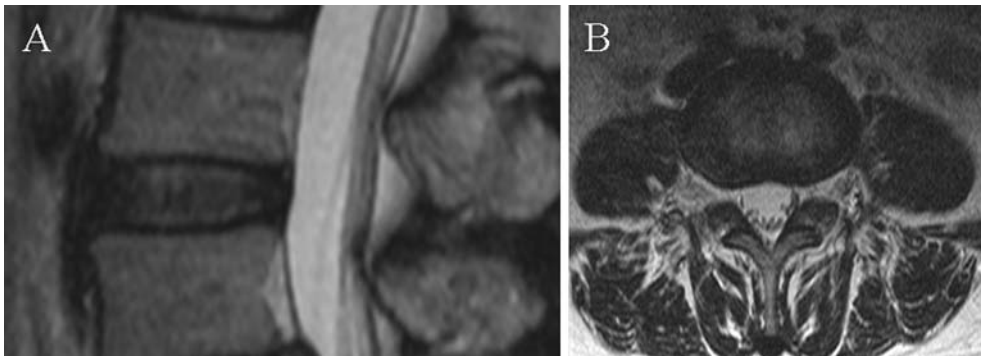

Fig. 2 Class 1 disc. Sagittal (**a**) and axial (**b**) T2-weighted MR images show normal disc contour and grade 3 disc degeneration. No HIZ was present

We classified disc morphologic characteristics, using conventional radiographs and the classification of Adams et al.: type I, cotton ball; type II, lobular; type III, irregular; type IV, fissured; and type V, ruptured [31]. Types I and II were normal discographic findings and were grouped together as discs without degeneration.

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), version 10.0. Chi-square or Fisher's exact test and logistic regression analysis was used to correlate pain response on discography and MR image findings. Discographic findings (according to the classification of Adams et al. [31]) were compared with pain response on discography, using the chi-square test. The patient's gender, age, duration of symptoms, and disc level were also considered in the statistical analysis. The interobserver agreement of the MR classification system was tested using the k coefficient. A kappa value of less than 0.40 indicated poor agreement; 0.40 to 0.59, moderate agreement; 0.60 to 0.74, good agreement; and 0.75 or greater, excellent [32].

Results

Discography was performed on 178 discs in 62 patients at the following levels: one disc at the L1–L2 level, nine discs (5.1%) at the L2–L3 level, 53 discs (29.8%) at the L3–L4 level, 59 discs (33.1%) at the L4–L5 level, and 56 discs (31.5%) at the L5–S1 level. Thirty-six patients (58.1%) had one disc or more that met the criteria for concordant pain response. When analyzed by disc as opposed to by patient, 44 (24.7%) of the 178 discs met the criteria for concordant pain response. No association was found between concordant pain reproduction and the duration of symptoms, and the levels at which discography was performed. The prevalence of MR image findings for the 178 disc levels where discography was done are shown in Table 2. There was good interobserver agreement (k= 0.70; 95% confidence interval 0.56–0.84) for the MR classification system.

Fifty-six (31.5%) of the discs that had undergone discography had a disc protrusion, of which 23 discs had a protrusion with an HIZ, and 33 discs had a protrusion without an HIZ. The presence of disc protrusion was significantly associated with concordant pain reproduction ($P<0.01$). HIZ was present in 47 (26.4%) of discs: an HIZ with protrusion ($n=23$) and an HIZ with a normal or bulging disc ($n=24$). When only the presence or absence of an HIZ was compared with pain response on discography, concordant pain provocation was significantly related to the presence of an HIZ ($P<0.01$). There were 98 (55.1%) class 1 discs, 24 (13.5%) class 2, 33 (18.5%) class 3, and 23 (12.9%) class 4 as classified by the MR classification system (Table 3). Logistic regression analysis in which class 1 was used as the standard showed that class 4 was significantly associated with concordant pain reproduction (Table 4, Fig. 6). No statistically significant association between class 2 and concordant pain reproduction was found.

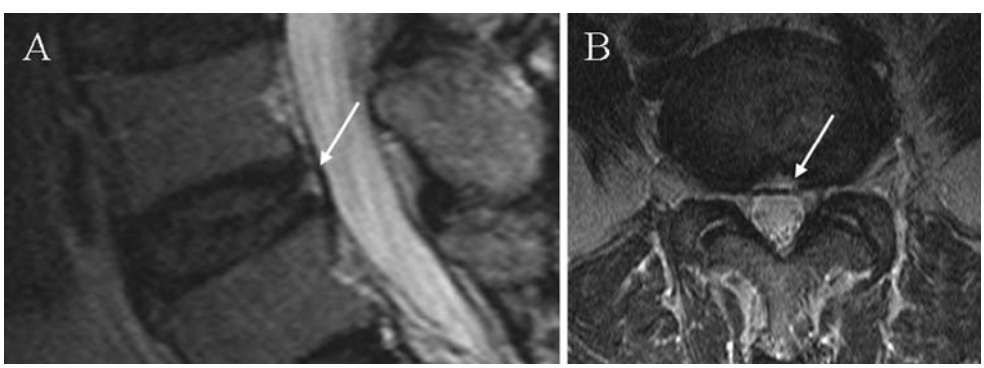

Fig. 3 Class 2 disc. Sagittal (**a**) and axial (**b**) T2-weighted MR images show mild bulging contour of L4–L5 disc with HIZ (*arrows*)

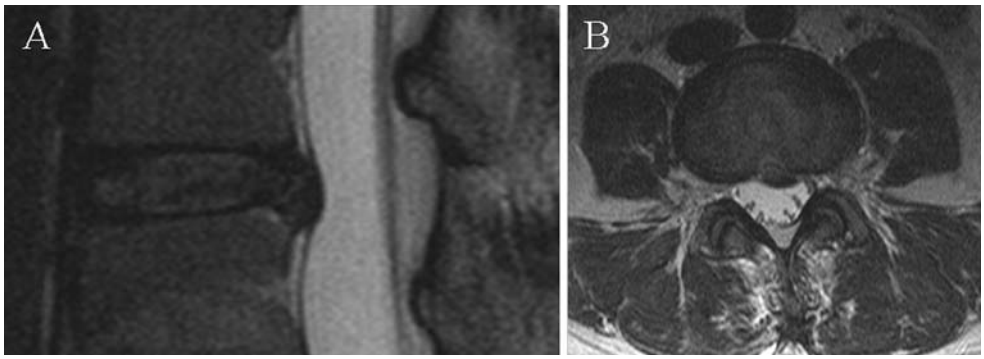

Fig. 4 Class 3 disc. Sagittal (**a**) and axial (**b**) T2-weighted MR image show focal protrusion at L3–L4. No HIZ was present

The following prevalence of disc degeneration was determined by MR imaging: grade 1 or 2 (n=54), grade 3 (n=44), grade 4 (n=67), and grade 5 (n=13). Fifty-four (30.4%) of 178 discs were considered non-degenerated (grades 1 and 2) normal discs without any of the assessed MR abnormalities. All but two normal discs (from a single patient) seen on the MR images correlated with a negative pain provocation test. The negative predictive value (NPV) of a normal disc on MR images in terms of pain provocation was 96.3% (52 of 54 discs). Discs classified as non-degenerated and degenerated showed significant differences for pain reproduction (P<0.05). However, logistic regression analysis showed that there was no statistical difference between non-degenerated discs and each grade of degenerated discs regarding pain provocation. At discography, there were type I or II (n=53), type III (n=19), type IV (n=85), and type V (n=21). No type I or type II disc revealed pain provocation. Concordant pain was significantly more common in the ruptured discs of type V (P<0.05). Endplate abnormalities were observed in 12.9% (23/178) of the cases: Modic type I (n=4), Modic type II (n=16) and Modic type III (n=3). Pain provocation during discography was not associated with the presence of endplate abnormalities.

Sensitivity, specificity, NPV, positive predictive value (PPV), accuracy, and prevalence of MR abnormality are shown in Table 2. Disc degeneration observed on MR images had a high NPV, 96.3 %, but a low specificity, 38.8%, in terms of concordant pain prediction. The presence of an HIZ showed a high specificity, 83.6%, but a low PPV, 53.2%, in terms of concordant pain prediction. Likewise, the presence of a protrusion showed a high specificity, 80.6%, but a low PPV, 53.6%. However, in the presence of both a protrusion and an HIZ, the PPV and specificity of this combination (class 4) were 87.0% and 97.8%, respectively.

Discussion

Ideally, a history and physical examination would consistently diagnose the source of a patient's low back pain, and, if one diagnosed pain secondary to the intervertebral disc, one would be able to identify the exact level or levels involved. In reality, however, the exact source of low back pain is often illusive. Because discogenic pain projects in a somatotropic rather than a dermatomal pattern [20], confirming and localizing a discogenic source, much less the exact level, using clinical findings alone remains unproven [22].

A second best approach might combine the history and physical examination with MR imaging studies, and one would locate discogenic pain in patients with a particular set of signs and symptoms by observing abnormalities associated with chronic low back pain such as disc degeneration, annular tears, endplate abnormality, or a combination of these abnormalities [33–35]. In this respect MRI can, in exquisite detail,

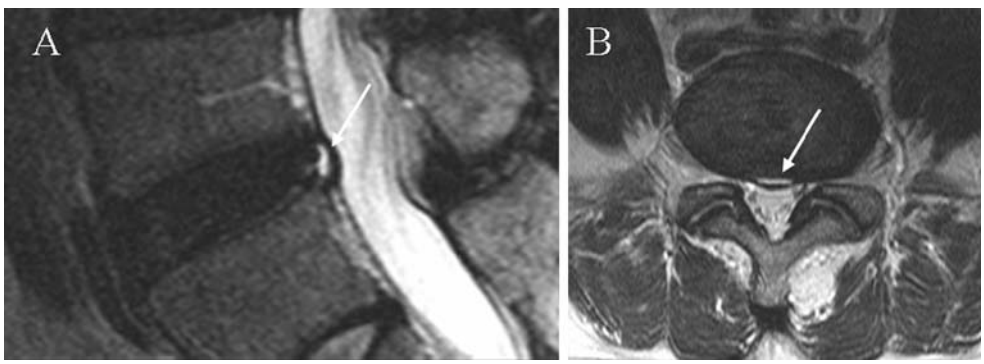

Fig. 5 Class 4 disc. Sagittal (**a**) and axial (**b**) T2-weighted MR images of L4–L5 disc show high signal intensity (*arrows*) in the posterior annulus, as well as the focal extension of disc contour, thus qualifying the lesion as a protrusion with HIZ

Table 2 Diagnostic performance of pain predictors on MRI. Sensitivity, specificity, positive predictive value (*PPV*), negative predictive value (*NPV*), and accuracy were based on a positive prediction of a disc with concordant pain as evidenced by pain response during discography. *Class 2* and *Class 4* indicate combined variables that correspond to a normal or bulging disc in the presence of an HIZ and disc protrusion in the presence of an HIZ, respectively. *Values in parentheses* are percentages

MR abnormalities	Prevalence (n=178)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
HIZ	47 (26.4)	56.8	83.6	53.2	85.5	77.0
Disc protrusion[a]	56 (31.5)	68.2	80.6	53.6	88.5	77.5
Class 2	24 (13.5)	14.2	88.6	25.3	79.2	32.6
Class 4	23 (12.9)	45.5	97.8	87.0	84.5	84.8
Disc degeneration	124 (69.7)	95.4	38.8	33.9	96.3	52.8
Endplate abnormality	23 (12.9)	13.6	87.3	26.1	75.5	69.1

[a] Disc protrusion (n=56) includes both class 3 (disc protrusion in the absence of an HIZ, n=33) and class 4 (n=23)

identify structural abnormalities and is an important part of a detailed search for the source of axial low back pain. However, since many asymptomatic individuals have similar abnormalities [5, 6, 36–38], the definitive diagnosis using MR imaging alone has not been substantiated [7, 39].

Lacking a gold standard for the diagnosis of discogenic pain, coupled with the need to confirm or refute one's hypothesis that a particular disc is or is not a source of pain, many consider provocation discography the criterion standard. Although questioned by some [21, 40] and supported by others [9, 11, 25, 27], pain similarity, location, and reproducibility of pain with repetition are essential elements of discography [41], and studies have focused on the ability of various MR image abnormalities to predict significant concordant pain provocation during discography.

Considered to represent a severe form of combined radial and concentric annular tear [9], an area of HIZ visualized on the T2-weighted MR image was one of the first structural abnormalities that predicted concordant pain provocation during disc stimulation, as first described by Aprill and Bogduk [9]. They correlated the findings with CT discography and found that it was associated with grade 4 fissures, with an 86% PPV for a painful disc on discography. Although similar results were validated by other investigators [11, 25, 27], Ricketson et al. [21] were not able to demonstrate a statistically significant correlation between the presence of an HIZ and concordant pain provocation during disc stimulation with contrast. In addition, Carragee and colleagues [40] questioned the clinical significance of the presence of an HIZ, because the prevalence of an HIZ in asymptomatic individuals with degenerative disc disease was high (25%). In addition, even though Saifuddin et al. [27] found that the presence of an HIZ predicted pain provocation during discography, the clinical significance of an HIZ was limited because of a low 26.7% sensitivity when symptomatic and asymptomatic individuals were compared. However, Bogduk and Modic [42] later noted that a lower intensity zone indicating annular fissures might occur in asymptomatic persons and that these fissures may become painful and assume a higher intensity signal when 'activated'. Failure to differentiate between the two types would lead to misclassification and, thus, to the conclusion that there was no correlation between pain and areas of high signal intensity.

Supporting the concept that an area of high signal intensity represented an area of painful inflammation, Yu et al. [4] correlated the MR finding to the pathological classification of annular tears. These investigators identified three types of annular tears. The concentric tear was a crescentic or oval cavity associated with a rupture of the short transverse fibers connecting the lamellae in the annulus fibrosus. Transverse tears were ruptures of Sharpey's fibers near their attachment to the ring apophysis. The radial tear was a fissure extending from the nucleus to the outermost surface of the annulus. Examining the various tears, the investigators found fluid or mucoid material filling each annular tear and postulated that the presence of fluid indicated inflammation. This inflammation would be represented as an area of bright signal intensity on a T2-weighted MR image.

Table 3 Distribution of pain on discography in relation to MR classifications

Discography	MR classification				
Pain response	Number of discs	Class 1	Class 2	Class 3	Class 4
No or discordant pain	134	89	19	23	3
Concordant pain	44	9	5	10	20

Table 4 Comparison of pain predictors on MRI according to logistic regression (*OR* odds ratio, *95% CI* 95% confidence interval)

Pain predictors on MRI	OR	P^a	95% CI
HIZ	3.91	<0.01[b]	1.60–9.57
Disc protrusion	6.46	<0.01[b]	2.71–15.40
Disc degeneration	6.18	0.02[b]	1.27–30.10
Class 2	1.03	0.96	0.27–3.99
Class 3	2.41	0.11	0.81–7.17
Class 4	36.29	<0.01[b]	8.18–161.09

[a] P <0.05 was considered to indicate statistical significance

[b] P-value is less than 0.05.

The results of our study confirmed the findings on both sides of the controversy. The high PPV (87.0%) and specificity (97.8%) of high signal intensity in the central part of a disc protrusion are consistent with the concept of an 'activated' fissure that is, perhaps, filled with inflammatory fluid. Conversely, our failure to correlate areas of high signal intensity and a positive pain response during discography in discs with normal or bulging contours indicate that these fissure may represent more 'quiescent' fissures that may or may not be later activated. However, our postulation that HIZ without protrusion is a quiescent fissure remains speculative and needs to be studied further.

In the process of correlating HIZ with degrees of annular protrusions, we also accumulated data correlating the frequency of a positive response during discography to the degree of disc degeneration as detected by MRI. This relationship between disc morphology and manifestation of clinically significant discogenic pain is controversial, partly because the frequency of morphologic abnormalities revealed via discography in the back pain population is high and increases with age [21, 24], and such abnormalities can be caused by painless degenerative changes [21]. While Milette et al. [43] found a strong correlation between positive discography and annular tears extending into or beyond the outer annulus in patients with chronic low back pain, loss of disc height and abnormal signal intensity on T2-weighted images, Collins and colleagues [8] found only a 23% positive discographic response in MRI-identified degenerated discs. Poor predictive value of a painful disc in the presence of disc degeneration as seen on MR images is supported by other studies [25, 44, 45]. The results of our study also showed that the presence of a degenerated disc on T2-weighted images was not a reliable marker for a painful disc. Our results were similar to those of Horton and Daftari [44] in regard to discs with normal signal intensity, with or without bulging, having a 95% chance of negative findings on discography. We found that the NPV of a normal disc on MR images in terms of pain provocation was 96.3% (52 of 54 discs). Although, they had small numbers of discs, Horton and Daftari [44] found that a dark nuclear pattern with a torn annulus had a 90–100% chance of being associated with positive findings on a discogram.

In addition to correlating disc degeneration with a positive discography response, we also collected data correlating endplate abnormalities to pain provocation during discography. While moderate to severe endplate abnormalities have been reported to be useful for predicting painful disc derangement in patients with

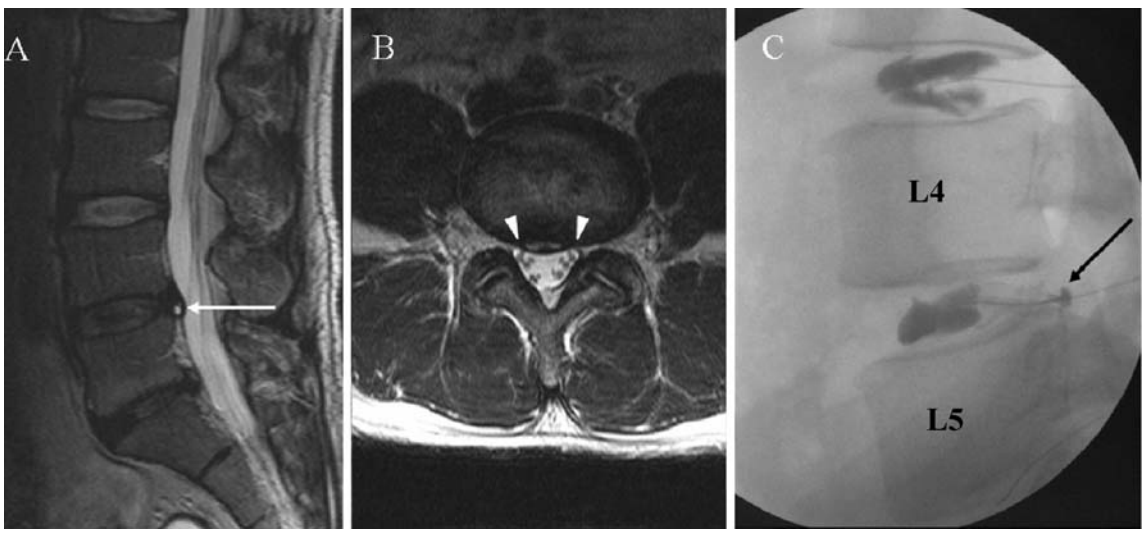

Fig. 6 A 37-year-old man with chronic low back pain. Sagittal T2-weighted image (**a**) shows grade 3 disc degeneration at L4–L5 and grade 5 at L5–S1. A high intensity zone (*arrow*) is present at the L4–L5 intervertebral disc. Axial T2-weighted image (**b**) shows focal protrusion (*arrowheads*) at L4–L5, with a high intensity zone in the protrusion. Lateral discogram (**c**) shows a fissured pattern of type 4 (*arrow*) at L4–L5. The patient had no pain at L3–L4 and had familiar pain at L4–L5 and unfamiliar pain at L5–S1 during discography

symptomatic low back pain [46], pain reproduction was not found to be associated with endplate abnormalities in this study. Endplate abnormalities, of which all were graded as mild or moderate extent, were observed in only 23 (12.9%) of 178 discs for our patients, whereas the previous study observed these abnormalities in 44% of discs [46]. Our results are, however, similar to those of Lim et al. [47], who reported on a retrospective study of 47 patients with chronic low back pain.

Finally, we acknowledge that our study is limited by the relatively small patient population, lack of control group, and a small fraction of discs exhibiting HIZ with protrusion. Since our study included only patients with severely disabling low back pain who underwent discography, we could not assess our new MR classifications for patients without serious low back pain or for healthy subjects. We do remind the reader that HIZ assessed in this study was divided into two groups: HIZ with protrusion and HIZ with normal or bulging disc. Therefore, the results of this study cannot be simply compared with those of other studies on HIZ.

In conclusion, this study correlated pain provocation during discography with a variety of pain predictors on MRI and in particular analyzed the predictive value of the combined presence or absence of an HIZ with disc contour abnormalities. Our results indicate that disc degeneration, disc protrusion and the presence of an HIZ may not be a useful marker in terms of discogenic pain prediction. However, HIZ accompanied with protrusion on MRI appears to be more useful in the prediction of a disc with concordant pain in patients with discogenic low back pain.

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