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Innervation of pathologies in the lumbar vertebral end plate and intervertebral disc

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Abstract

BACKGROUND CONTEXT: Magnetic resonance imaging (MRI) has limited diagnostic value for chronic low back pain because of the unclear relationship between any anatomic abnormalities on MRI and pain reported by the patient. Assessing the innervation of end plate and disc pathologies—and determining the relationship between these pathologies and any abnormalities seen on MRI—could clarify the sources of back pain and help identify abnormalities with enhanced diagnostic value.

PURPOSE: To quantify innervation in the vertebral end plate and intervertebral disc and to relate variation in innervation to the presence of pathologic features observed by histology and conventional MRI.

STUDY DESIGN/SETTING: A cross-sectional histology and imaging study of vertebral end plates and intervertebral discs harvested from human cadaver spines.

METHODS: We collected 92 end plates and 46 intervertebral discs from seven cadaver spines (ages 51–67 years). Before dissection, the spines were scanned with MRI to grade for Modic changes and high-intensity zones (HIZ). Standard immunohistochemical techniques were used to localize the general nerve marker protein gene product 9.5. We quantified innervation in the following pathologies: fibrovascular end-plate marrow, fatty end-plate marrow, end-plate defects, and annular tears.

RESULTS: Nerves were present in the majority of end plates with fibrovascular marrow, fatty marrow, and defects. Nerve density was significantly higher in fibrovascular end-plate marrow than in normal end-plate marrow ($p<.001$). Of the end plates with fibrovascular and fatty marrow, less than 40% were Modic on MRI. Innervated marrow pathologies collocated with more than 75% of the end plate defects; hence, innervation was significantly higher in end plate defects than in normal end plates ($p<.0001$). In the disc, nerves were observed in only 35% of the annular tears; in particular, innervation in radial tears tended to be higher than in normal discs ($p=.07$). Of the discs with radial tears, less than 13% had HIZ on T2 MRI. Innervation was significantly less in radial tears than in fibrovascular end-plate marrow ($p=.05$) and end-plate defects ($p=.02$).

CONCLUSIONS: These findings indicate that vertebral end-plate pathologies are more innervated than intervertebral disc pathologies and that many innervated end-plate pathologies are not detectable on MRI. Taken together, these findings suggest that improved visualization of end-plate pathologies could enhance the diagnostic value of MRI for chronic low back pain.

Keywords: Innervation; End plate; Modic change; Intervertebral disc; Low back pain

FDA device/drug status: Not applicable.

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Introduction

Chronic low back pain (CLBP) is a spinal condition with a substantial socioeconomic burden [1]. Magnetic resonance imaging (MRI) is a powerful diagnostic tool for many spinal conditions, but MRI findings have limited diagnostic value for CLBP because of the unclear relationship between any anatomic abnormalities seen on MRI and symptoms reported by the patient [2–4]. Although symptoms can have many causes [5], one important cause is thought to be the presence of innervated pathologies of the vertebral end plate and intervertebral disc because nerves in these pathologies may become sensitized by chemical [6] or mechanical [7] stimuli. Assessing the innervation of end plate and disc pathologies—and determining the relationship between these pathologies and any abnormalities seen on MRI—may therefore clarify the tissue sources of back pain and help to identify abnormalities with enhanced diagnostic value.

Innervated pathologies of the end plate and disc are thought to underlie many cases of CLBP. In symptomatic patients, innervation is greater in end plates with cartilage and subchondral bone damage [8,9], perhaps as a chemotactic response to neurotrophin production by disc cells [10] and new blood vessels [11]. Innervation is also greater in painful discs with annulus fissures [12,13], which may provide a chemically and mechanically favorable environment for perivascular nerve growth [12,14]. Although these findings suggest that end plate damage and internal disc disruption can cause pain, the diagnostic value of these observations is limited because it is unknown how end plate and disc pathologies are innervated in general—and whether MRI is capable of detecting features that associate with neoinnervation. Thus, we sought to quantify innervation in the vertebral end plate and intervertebral disc and to relate variation in innervation to the presence of pathologic features observed by histology and conventional MRI.

Methods

Cadaver materials and MRI

Ninety-two vertebral end plates (from T11 to S1) and 46 corresponding intervertebral discs (from T11–T12 to L5–S1) were obtained from seven human thoracolumbar spines (donor ages 51–67 years; two females and five males). All spines were scanned in situ using MRI (GE 3T Signa HDx scanner; GE Healthcare, Waukesha, WI, USA) with sagittal T1- and T2-weighted fast spin-echo sequences. The T1-weighted sequence comprised the following: echo time 15.6 ms, repetition time 516 ms, echo train length 2, acquisition matrix 256×256, slice thickness 3 mm. The T2-weighted sequence comprised the following: echo time 61.6 ms, repetition time 2500 ms, echo train length 8, acquisition matrix 256×256, slice thickness 3 mm.

End plate and disc abnormalities on MRI

After scanning the spines, we rated the images for end plate and disc abnormalities using established criteria. End-plate signal intensity changes, or Modic changes [15], are related to pathologies of the end plate and bone marrow, and have two main types: type 1 changes are hypointense on T1-weighted images and hyperintense on T2-weighted images, and type 2 changes are hyperintense on T1-weighted images and either iso- or hyperintense on T2-weighted images. Both types of Modic changes collocate with end plate damage on histology, but type 1 changes reflect fibrovascular replacement of the normal marrow elements, whereas type 2 changes reflect fatty replacement of the marrow elements [15]. Two raters classified the end plates as normal, Modic type 1, or Modic type 2 (inter-rater reliability, $\kappa=0.89$).

For the disc, we rated the MRI scans for high-intensity zones (HIZ), which are related to internal disc disruption. HIZ appear more hyperintense on T2-weighted images than does the adjacent nucleus pulposus [16,17] and are thought to reflect neovascularized granulation tissue that occurs secondary to an annulus tear [18]. Two raters classified the discs as normal, low intensity, or high intensity (inter-rater reliability, $\kappa=0.67$). Also, we assessed disc degeneration using the Pfirrmann grading scheme [19] (inter-rater reliability, $\kappa=0.74$).

Histology

Complete bone-disc-bone motion segments were prepared from the intact spines and processed for histology. First, the surrounding musculature and posterior elements were removed from the spines. Next, the spines were cut into four, 5- to 7-mm-thick para-sagittal slabs. One medial slab was chosen at random from each spine and was fixed in formalin, radiographed, and then decalcified in a mild ion-exchange decalcifying agent (Biocare Medical, Concord, CA, USA). Radiographic assessment was used to monitor the decalcification process, which typically required 1 week to complete. After decalcification, the slabs were cut transversely to produce motion segments containing one-half of the cranial vertebral body, the intervertebral disc, and one-half of the caudal vertebral body.

The resulting bone-disc-bone motion segments were processed for paraffin histology. Segments were first dehydrated in ethanol baths of ascending concentration, cleared in Clearite, and then infiltrated with paraffin. Next, 7-μm thick sections were cut from the blocks using a microtome (Microm 355 S; Thermo Fisher Scientific, Waltham, MA, USA), mounted on slides, and stained with Heidenhain connective tissue stain that contains aniline blue, orange G, and acid fuchsin. Adjacent slides were immunostained for the general neuronal marker protein gene product 9.5 (PGP 9.5; AbD Serotec, Kidlingdon, United Kingdom) using a polymer detection system (MACH 4 HRP; Biocare Medical). PGP 9.5 is a cytoplasmic C-terminal hydrolase