The Role of the Vertebral End Plate in Low Back Pain

J. C. Lotz[1] A. J. Fields[1] E. C. Liebenberg[1]

[1] Orthopaedic Bioengineering Laboratory, Department of Orthopaedic Surgery, University of California at San Francisco, California, United States

Global Spine J 2013;3:153–164.

Address for correspondence Jeffrey C. Lotz, PhD, University of California at San Francisco, 513 Parnassus Avenue, S-1157, San Francisco, CA 94143-0514, United States (e-mail: Jeffrey.lotz@ucsf.edu).

Abstract

End plates serve as the interface between rigid vertebral bodies and pliant intervertebral disks. Because the lumbar spine carries significant forces and disks don't have a dedicated blood supply, end plates must balance conflicting requirements of being strong to prevent vertebral fracture and porous to facilitate transport between disk cells and vertebral capillaries. Consequently, end plates are particularly susceptible to damage, which can increase communication between proinflammatory disk constituents and vascularized vertebral bone marrow. Damaged end plate regions can be sites of reactive bone marrow lesions that include proliferating nerves, which are susceptible to chemical sensitization and mechanical stimulation. Although several lines of evidence indicate that innervated end plate damage can be a source of chronic low back pain, its role in patients is likely underappreciated because innervated damage is poorly visualized with diagnostic imaging. This literature review summarizes end plate biophysical function and aspects of pathologic degeneration that can lead to vertebrogenic pain. Areas of future research are identified in the context of unmet clinical needs for patients with chronic low back pain.

Keywords
- end plate
- intervertebral disk
- spine
- low back pain

Chronic low back pain remains a difficult clinical problem, both to diagnose and to treat. Despite significant investments in basic and clinical research, the rates of disability and associated costs continue to escalate.[1] Although the prevailing view is that axial back pain arises from sensitized nociceptors within the annulus fibrosus of degenerating disks (annulogenic pain), there is growing evidence that the end plates are richly innervated and that innervated end plate damage may represent a common painful pathology (vertebrogenic pain).[2,3] Properly identifying the pain generator is requisite for optimal treatment, so distinguishing between these forms of pain will likely be important for improving patient outcomes. The goal of this review is to summarize data regarding normal end plate anatomy, physiologic age-related end plate changes, and evidence for the role of pathologic changes as a source of chronic low back pain. In an effort to cover these topics within a clinical context, we have focused our summary on the end plates in the human spine. We refer the reader to the literature for a detailed comparison of end plate anatomy and biochemistry between humans and animals.[4,5] Related, we acknowledge that it remains open for debate whether the end plate belongs to the vertebral body or to the intervertebral disk. Rather than presenting a specific viewpoint, we consider topics that are relevant to both its bony and cartilaginous components.[6]

Structure

The end plate is a bilayer of cartilage and bone that separates the intervertebral disks from the adjacent vertebrae (►**Fig. 1A** to **C**). During prenatal development, the future vertebra starts as a cartilage anlagen that arises from chondrification centers of the sclerotomes during the sixth embryonic week (►**Fig. 2**).[7] The anlagen begins ossification at its

received
December 13, 2012
accepted after revision
April 9, 2013
published online
May 23, 2013

DOI http://dx.doi.org/10.1055/s-0033-1347298.
ISSN 2192-5682.

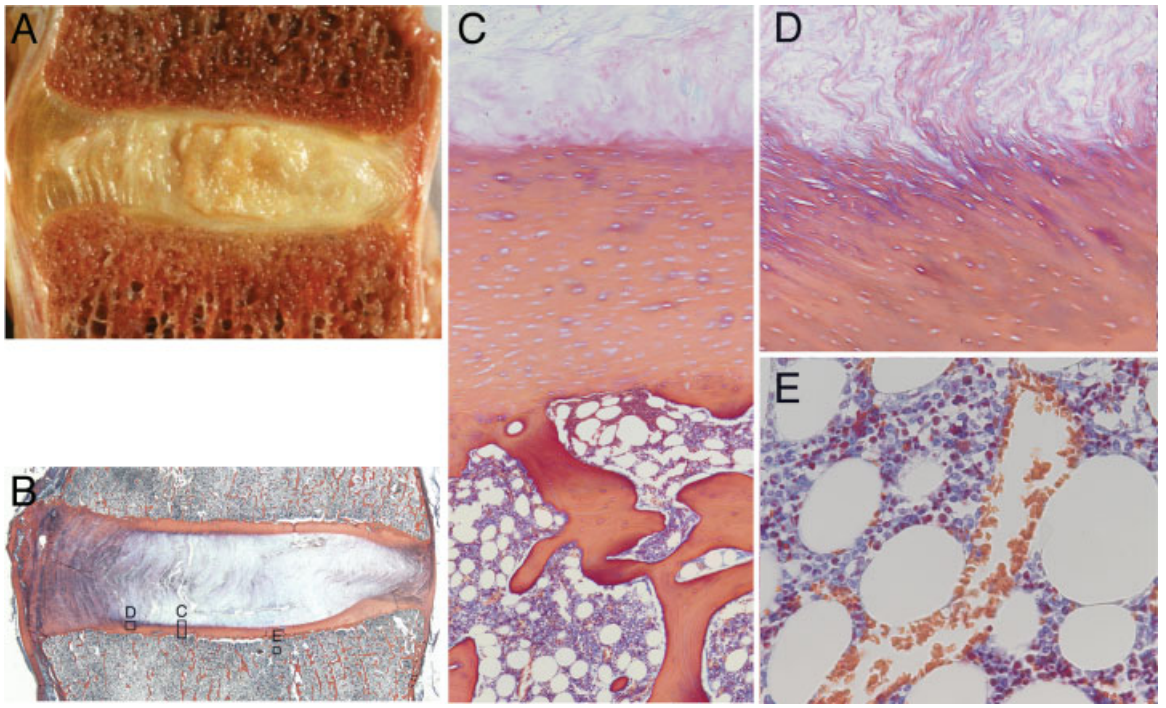

Fig. 1 (A) Gross morphology of the lumbar intervertebral joint. (B) Histology section showing regions of interest for panels C, D, and E. (C) End plate detail showing cartilaginous and bony components with hematopoietic marrow elements. (D) Insertion of annular fibers into the end plate cartilage at the inner annulus junction. (E) Vascular sinusoids in the marrow space adjacent to the end plate. Note for panels A and B, left side is anterior.

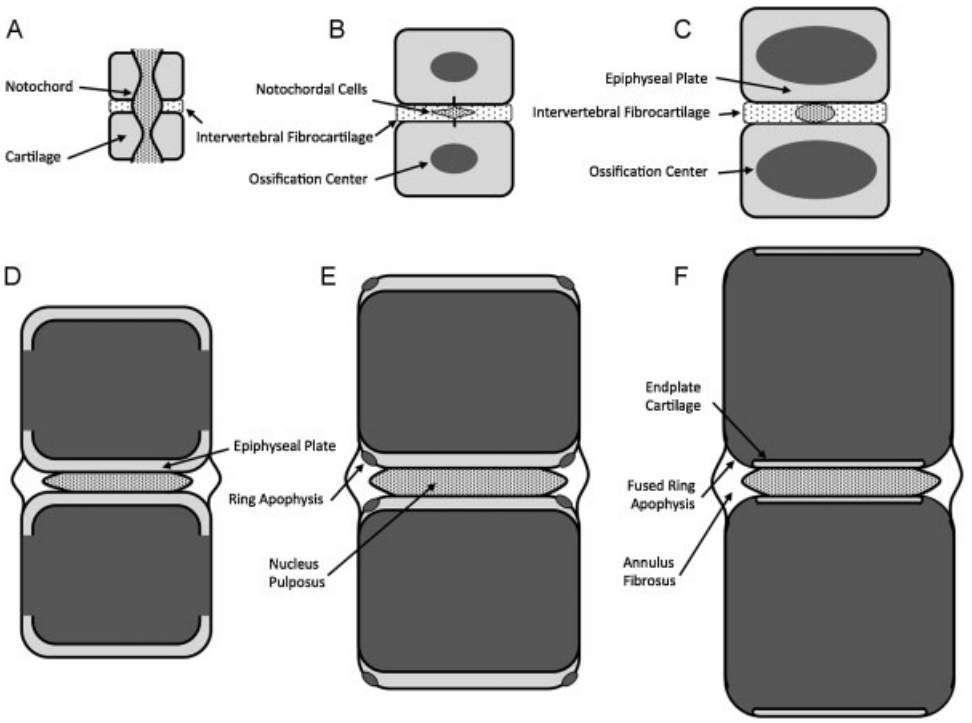

Fig. 2 Schematic representation of vertebral end plate development. (A) At embryonic week 6, the sclerotome begins to segment around the notochord to form periodic cartilaginous and fibrocartilaginous precursors to the vertebra and disks, respectively. (B) By embryonic week 15, the notochord atrophies within the vertebra, and ossification begins at the vertebral centers. (C) At embryonic week 25, the ossification centers expand as the vertebrae lengthen. Columnar cartilage develops at the vertebral ends to form the epiphyseal plates. (D) By age 5 years, the ossified portions of the vertebra extend to the lateral margins and the epiphyseal cartilage begins to thin. (E) By age 13 years, peripheral ossification centers outside the epiphyseal plate form the ring apophysis. (F) By age 18 years, the ring apophysis begins to fuse to the osseous mass of the vertebral body.

centrum around invading blood vessels.[8] This trabecular centrum is separated from the forming disk by an epiphyseal plate of columnar cartilage that progressively thins as the vertebra lengthens. Peripheral to the epiphyseal plate is a ring apophysis that doesn't participate in longitudinal growth, but is rather a traction apophysis by virtue of annular fiber insertion.[9] Yet, the ends of the vertebrae are completely covered by the same end plate cartilage. By age 18, the epiphyseal cartilage has thinned and a subchondral bone plate has formed, thus creating the adult end plate bilayer. Simultaneously, the ring apophysis fuses to the vertebral body.

Like articular cartilage, the end plate cartilage consists of chondrocytes interspersed throughout an extracellular matrix of proteoglycans, collagen (types I and II), and water (►**Fig. 1C**). However, the end plate cartilage differs from articular cartilage in its collagen fiber organization. Although healthy articular cartilage has zones of differing collagen orientation, end plate cartilage has collagen fibers aligned horizontally (parallel to the ends of the vertebrae).[10] In the young disk, the end plate cartilage proteoglycan content is ~300 μg/mg, with water and type I collagen contents being 78% and 0.9 ng/mg, respectively.[11] The cartilage end plate is typically between 0.1 and 2.0 mm thick[12,13]; however, its thickness is known to vary with position and level, being thinner centrally and in the upper levels of the spine than peripherally and in the lower levels of the spine.[13] The nature of the structural integration between the end plate and the surrounding tissues also varies with position. Peripherally, the collagen fibers in the lamellae of the annulus fibrosus are continuous with the collagen fibers in the end plate (►**Fig. 1D**), whereas centrally, the integration between collagen fibers in the nucleus pulposus and the end plate is more convoluted.[13,14] The collagen fibers of the cartilaginous and bony components of the end plate are completely separate.[13]

The bony component of the end plate has a structure not unlike that of the vertebral cortex and resembles a thickened, porous layer of fused trabecular bone with osteocytes entombed within saucer-shaped lamellar packets.[15] Like the end plate cartilage, the bony end plate thickness varies depending on spinal level and location and is generally between 0.2 and 0.8 mm thick.[16–19] At a given lumbar level, the bony end plates are thinner centrally than peripherally; also, the end plate cranial to a particular disk is thicker and has higher bone mineral density than does the end plate caudal to it.[18,20] In some individuals, a second, dense layer of bone exists below the superficial layer.[16,19]

The bone marrow compartment adjacent to the bony end plate consists of hematopoietic cells, fat cells, sinusoids (thin-walled capillaries), and nerves. The vertebral capillaries and nerves enter via the basivertebral foramen at the posterior vertebral cortex and small pores in the cortical shell, form an "arterial grid" at the vertebral centrum, then branch and terminate just adjacent to the cartilage end plates.[21–23] These sinusoids and nerves provide a continuous bed across the bone–disk interface (►**Fig. 1E**).[21] Importantly for the disk, there is an intimate relationship between the effective perfusion of these sinusoids and marrow cellularity type. For example, perfusion decreases as thicker-walled capillaries replace the sinusoids, which can occur when the hematopoietic marrow converts to fat.[24,25] The cause of this marrow conversion is unclear, but the increase in bone marrow adiposity may be related to declining bone mass,[26–30] vascularity,[29,31] temperature,[25] or reduced bone loading.[32]

End plate subchondral bone is innervated by basivertebral nerve, the fibers of which reach the bone marrow along with nutrient arteries that enter the vertebra through the posterior basivertebral foramen.[21,33–35] End plate innervation is comparable to that of the peripheral annulus,[2,3,36] and it is increased in areas of bone damage (►**Figs. 3** and **4**).[37]

Biophysical Function

The structure of the end plate facilitates important biomechanical and nutritional functions. Biomechanically, the end plate is subjected to significant loads during activities of daily living as the trunk muscles contract to stabilize posture. Lumbar compression forces can be in the range of 800 N while standing upright to over 3,000 N during active lifting.[38] The nucleus becomes pressurized in response to these forces, the values of which have been measured to vary from 0.4 MPa while lying, to 1.5 MPa while standing and sitting, to 2.3 MPa while lifting.[39–41] The end plate distributes these intradiscal pressures onto the adjacent vertebrae and prevents the pressurized disk nucleus from bulging into the underlying trabecular bone.[42–44]

During spinal compression, the pressurized nucleus causes the end plate to be stretched, like a drumhead.[45] Consequently, the end plate is most prone to fail in tension. Ultimately, thickness, porosity, and curvature are important structural determinants of end plate biomechanical function: thick, dense end plates with a high degree of curvature are stronger than thin, porous, and flat end plates.[18,46–49]

Nutritionally, the end plate is the primary pathway for transport between vertebral capillaries and cells within the disk nucleus.[50,51] Blood vessels and marrow spaces abut the

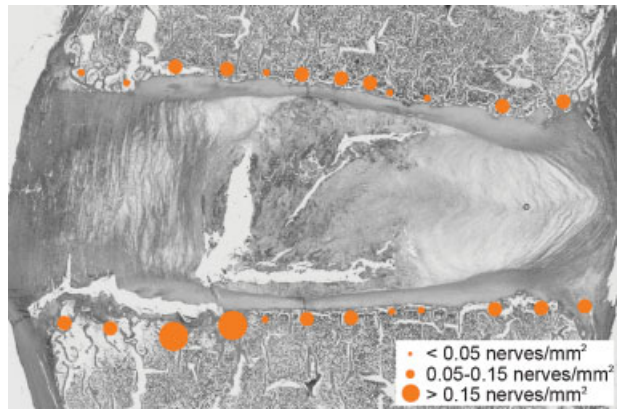

Fig. 3 Distribution of protein gene product 9.5 (PGP 9.5)-positive nerve fibers across the end plates (63-year-old woman, L5–S1). Compared with the density of nerves in normal end plate regions, nerve density is higher in end plate regions with damage. Nerve fibers in this disk were observed in the inferoposterior outer annulus. Note: left side is anterior.

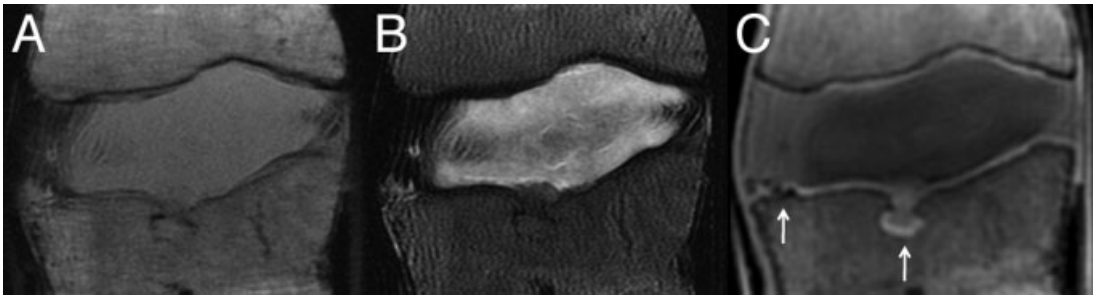

Fig. 4 Midsagittal T1-weighted (A) and T2-weighted (B) magnetic resonance (MR) images of an L1–L2 motion segment with poor end plate signal. (C) Corresponding ultrashort time-to-echo (UTE) MR image showing enhanced end plate signal. Arrows indicate end plate defects shown in ►**Fig. 5A** and **5B**. (UTE imaging courtesy of Drs. Roland Krug and Misung Han, Department of Radiology, University of California, San Francisco.)

cartilage layer (►**Fig. 1C, E**) and provide channels for glucose and oxygen to enter the disk and for waste products to exit the disk. Permeability across the cartilage end plate correlates with the amount of direct contact between the end plate and vertebral marrow or vascular buds.[50] The typical marrow contact area (or effective exchange area) is between 10 and 40%,[52–54] with the central end plate (adjacent the nucleus) being more permeable than at the periphery.[50] The density of these vascular channels is higher adjacent to the disk nucleus than the annulus.[13,50,55]

Once nutrients reach the end plate, movement of small solutes (glucose, lactate, and oxygen) pass through disk matrix primarily by diffusion.[56,57] Larger solutes may also be influenced by convective fluid flow created by mechanical disk compression and recovery. Diffusion into the disk is driven by the concentration gradient between the blood plasma and tissue matrix and represents a balance between supply (capillary density) and demand (disk cell density and metabolic rate).

Consequently, the end plate must balance conflicting biophysical demands. It must be strong to resist mechanical failure but must also be porous to facilitate chemical transport. Thin, porous end plates may favor disk health and thick, impermeable end plates favor vertebral integrity.[18,58] Recent data indicate that double-layer end plates may provide a more optimal balance between end plate strength and porosity,[15] thereby protecting against damage while supporting improved transport to and from adjacent disks.

Physiologic Degeneration

During aging, the cartilage end plate experiences changes in proteoglycan and collagen, resulting in gradual thinning and calcification.[11,13,59,60] Proteoglycan content decreases from 300 µg/mg at age 2 to 150 µm/mg by age 80. Simultaneously, water and type I collagen decrease from 78 to 67% and from 0.9 ng/mg to 0.25 ng/mg, respectively.[11] Although the specific mechanisms responsible for the compositional deterioration are unclear, these age-related changes coincide with degeneration in the adjacent disk and are generally consistent with markers of chondrocyte hypertrophy (e.g., elevated expression of type X collagen).[11,61] Hence, it may be that factors such as diminished hydrostatic pressure play a role in end plate deterioration because hydrostatic pressure is a potent regulator of chondrocyte function.[62,63]

When the spine is compressed, the bony end plate is subjected to high tensile strains as it deforms into the underlying trabecular bone.[42–45,64] Several factors influence the susceptibility of the end plate to damage, including the nature of the mechanical loading, the local morphology of the end plate structure, the tissue material properties, and the condition of the intervertebral disk. End plates at the cranial vertebral aspect may be more susceptible to damage than caudal end plates because they are thinner and supported by less dense trabecular bone.[18] Likewise, damage often occurs to the central end plate, the thinnest and weakest region.[18,65] Accumulation of end plate damage can cause focal weak points that progress to circumferential fissures.[44,66,67] This potential is exacerbated with age as the central region of the bony end plate becomes more porous (~60%) and consequently less stiff and weaker as the adjacent disks degenerate.[12,19,68,69] These deleterious structural changes may be the result of adaptive remodeling to decreased disk proteoglycan content and pressure.[70,71] However, disk degeneration also diverts a greater proportion of the compressive load to the end plate periphery and vertebral rim,[72,73] thereby reducing tensile and shear strains in the central end plate.[45,74]

End plate disruptions upset the uniformity of disk stress distributions.[75,76] This, in turn, is thought to precipitate alterations in disk structure and matrix composition that typify disk degeneration because abnormal pressures can inhibit disk cell metabolism and accelerate matrix degradation.[77–80] End plate disruption may also impede nutrient transport to the cells within the nucleus of the disk or incite inflammatory responses in the disk or vertebra.[50,81–84]

Pathologic Degeneration

A theoretical requirement for discogenic pain is pathologic innervation.[85,86] In the normal disk, innervation is restricted to the outer layers of the annulus.[87] By contrast, vertebrae are well innervated: the periosteum is the most densely innervated bone component, but when the total tissue volume is considered, the bone marrow receives the greatest number of sensory fibers.[36,88] This extensive network of nerves may modulate hemopoiesis and bone metabolism.[89] Marrow

sensory and sympathetic fibers are frequently associated with blood vessels and consist of both fast myelinated fibers (group III or A-delta fibers with diameters ranging from 1 to 5 μm) that transmit sharp pain and slow unmyelinated fibers (group IV or C-fibers with diameters ranging from of 0.5 to 2 μm) that transmit dull or aching pain. Nearly all marrow pain fibers express calcitonin gene-related peptide (CGRP) and coexpress TrkA and p74 receptors that are sensitized by nerve growth factor (NGF).[90] These marrow fibers are the first to encounter and presumably become excited by pathologic processes occurring in the bone space. Consequently, patients can experience bone pain from elevated interosseous pressures even when the pathology is confined to the marrow,[23] and this pain can be ameliorated when bone innervation is ablated, such as after vertebroplasty.[91]

Provocation diskography (PD) is considered by many as the gold standard for diagnosing discogenic pain.[92] The procedure consists of injecting a contrast agent into disks of a lightly sedated patient while monitoring the injected volume, pressure, contrast distribution pattern, and patient's pain response.[93] A positive test is based on pain intensity, concordance (similarity to pain before the procedure), degree of annular disruption, and presence of a negative adjacent control disk.[94] This test can reveal internal disk disruption and also identify which disks are painful and may be appropriate for treatment. Although not without controversy regarding its usefulness and safety,[95–97] PD results can be quite accurate (specificity of 0.94 and a false-positive rate of 6%) if performed using low-pressure technique.[93]

The theoretical basis for PD-provoked pain is mechanical stimulation of chemically sensitized nociceptors.[98] Sensitized nociceptors within the outer annulus of the disk can be stretched by nucleus pressurization if the annulus is weakened by fissures. Nociceptors in the end plate may be similarly perturbed if the end plate is weakened by damage.[99] For example, the end plates can deflect comparably to the annulus during diskography (0.3 mm versus 0.5 mm, respectively, at 75 to 100 psi),[99,100] and end plate deflection can increase in the presence of bone microdamage.[101] In support of this concept are the observations that increased vertebral interosseous pressures: (1) occur during PD as pressures are transmitted to adjacent disks;[102] (2) can cause pain;[23,103] and (3) are elevated in chronic low back pain (CLBP) patients.[104] Further, end plates removed from patients with chronic back pain show proliferation of blood vessels and CGRP-positive nerve fibers in the subchondral bone that predominates in areas of end plate damage and are sensitive to direct mechanical stimulation.[37,105,106]

Perhaps the best evidence for the role of end plates in CLBP is the association between PD-confirmed discogenic pain and vertebral bone marrow abnormalities. Three types of vertebral bone marrow lesions (BML) noted on magnetic resonance imaging (MRI) were first described by Modic et al in 1988.[107] Type I changes (fibrovascular replacement) show decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. Histopathology of type I changes shows an active inflammatory stage that coincides with disruption and fissuring of the end plate and vascularized granulation tissue within the marrow. Type II changes show increased signal intensity on T1-weighted images and an iso- or slightly hyperintense signal on T2-weighted images. Type II changes correlate with fatty marrow replacement. Both types of Modic changes are dynamic in that type I changes can convert to type II or back to normal marrow, and similarly, type II can convert back to type I.[108–110] Type III changes are represented by decreased signal intensity on both T1- and T2-weighted images that correlate with dense woven bone (sclerosis).

Data from multiple independent studies suggest that Modic type I and II changes adjacent to the end plate are among the most specific of all MRI observations for predicting concordant PD-induced pain (►**Table 1**). In one prospective study, moderate to severe Modic type I or II end plate abnormalities correlated 100% of the time with positive concordant pain at the adjacent disk.[116] Recently, increased end plate innervation has also been reported for end plates with Modic changes.[117,118] However, the presence of Modic changes are not very sensitive (15 to 65%) to PD-confirmed disk pain.[111–115] Poor sensitivity may reflect the categorical and subjective techniques used to classify BML,[119] rather than ones that are quantitative and objective. It may also be that innervated end plate damage is not well visualized using standard MRI techniques, because the end plate has a short T2 that shows little signal with pulse sequences that have long

Table 1 Summary of incidence and diagnostic values of Modic changes for diskography-concordant CLBP

Study	Subjects	Age (y), range (mean)	Modic incidence, % (*n*)[a]	Sensitivity (%)	Specificity (%)	PPV (%)	NPV %
Braithwaite et al[111]	58	21–63 (42)	10.7 (31/290)	23.3	96.8	91.3	46.5
Ito et al[112]	39	21–57 (37)	8.9 (9/101)	21.7	94.9	55.5	80.4
Kokkonen et al[113]	36	20–58 (40)	37.9 (39/103)	40.5	63.6	42.9	61.4
O'Neill et al[114]	143	21–71 (43)	8.0 (37/460)	13.8	98.2	89.2	51.3
Thompson et al[115]	736	22–78 (43)	12.3 (302/2,457)	25.5	94.8	72.5	70.1
Weishaupt et al[116]	50	28–50 (42)	22.4 (26/116)	47.9	95.6	88.5	72.2

Abbreviations: CLBP, chronic low back pain; NPV, negative predictive value; PPV, positive predictive value.
[a]Incidence refers to the number of levels studied.

echo times. Newer imaging sequences with ultrashort echo times may therefore help discriminate between patients with and without end plate pathologies (►**Fig. 4**).

The precise etiology of BML is not well understood, but it appears to involve autoimmune and inflammatory responses to chemicals produced by disk cells. Crock first proposed that vertebral BML result from inflammatory constituents that diffuse from the adjacent disks,[120] because disk tissue can trigger an autoimmune response due to secretion of proinflammatory and neurogenic factors such as interleukin-1, -6, and -8; tumor necrosis factor-α, prostaglandin E_2, monocyte chemotactic protein-1, and NGF.[121–125] These nucleus-derived chemicals can both sensitize existing nerves and promote new nerve growth.[126–128] Additionally, end plate nerves can be irritated via accumulated by-products of disk cell anaerobic metabolism, such as lactic acid.[129]

A predisposing factor for enhanced communication between the nucleus and vertebral marrow is end plate damage. For example, end plate damage has been qualitatively related to BML that contain pain fibers,[105,117] and more directly, end plate damage significantly increases diffusion between the vertebra and nucleus.[82,130] Not surprisingly, therefore, various forms of end plate defects have been clinically associated with disk degeneration and axial back pain.[131–134] These include Schmorl nodes, fractures, avulsions/erosions, and calcifications (►**Fig. 5**). Small end plate defects are difficult to observe radiographically,[58,101] and they are thought to be a common component of normal aging.[135] Schmorl nodes are large, focal end plate indentations that represent herniations of nucleus into adjacent vertebrae and are significantly associated with disk degeneration severity.[136] Because it can be challenging to distinguish between nodes that arise prior to skeletal maturity (e.g., at sites of cartilage defects that remain after notochord regression and growth plate closure) and nodes that form traumatically secondary to age-related subchondral weakening,[137–140] the results from clinical studies relating Schmorl nodes to symptoms are mixed. For example, Schmorl nodes are relatively common in asymptomatic individuals.[136,141] However, in cases where the nodes associate with CLBP, MRI shows evidence of BML and fibrovascular bone marrow changes,[142,143] which suggests a traumatic etiology. A recent cadaveric study relating different types of end plate defects to back pain history demonstrated a clear dose effect: larger lesions were associated with more severe degeneration and more frequent back pain (odds ratio = 17.88).[144]

The finding that certain types of end plate defects predominate at distinct levels and locations in the spine suggests that end plate defects have unique etiologies (►**Fig. 6**). Node-like defects are more common in the central end plates of the upper lumbar and thoracolumbar spine,[131] where trabecular bone density is lower,[145] end plates are less strong,[146] and subchondral softening is more severe.[145,147] In contrast, avulsions/erosions and calcifications are more common at the vertebral rim in the lower lumbar spine,[148–151] where the greater range of motion in flexion and extension could lead to increased traction at the junction of the annulus and end plate cartilage.[152] Calcification and sclerosis at the vertebral rim of the lower lumbar levels may be a consequence of repeated compressive trauma.

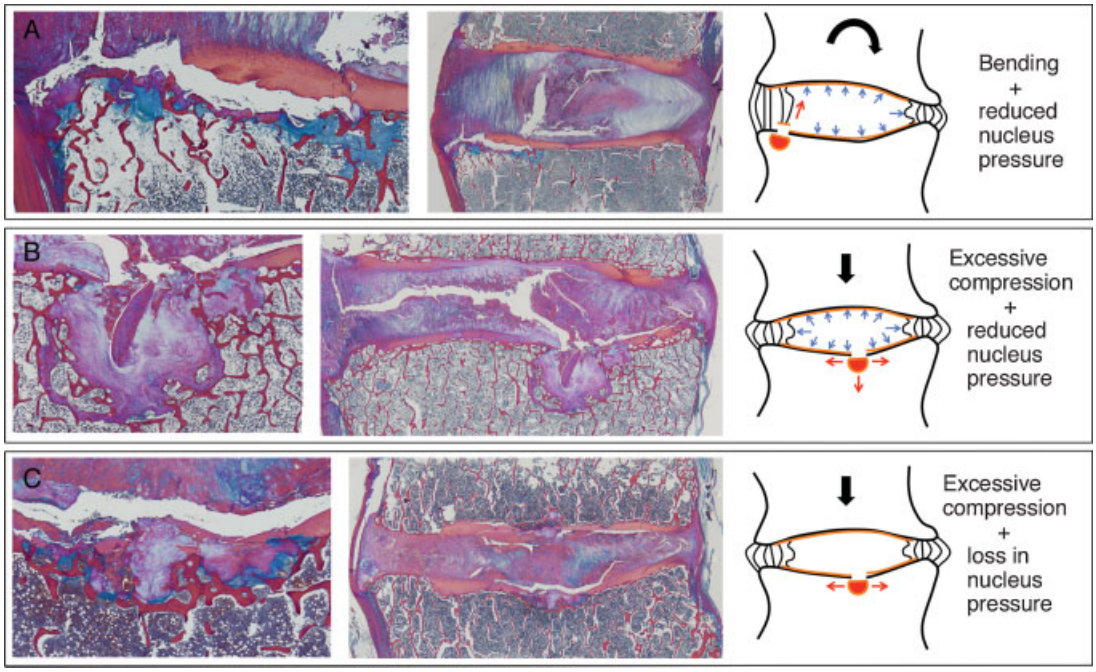

Fig. 5 Various end plate defects with hypothesized etiologies. (A) End plate cartilage avulsion resulting from bending motion that causes traction at the interface between the end plate and inner annulus. (B) Traumatic node with end plate fragment resulting from excessive compression with a healthy, gel-like nucleus pulposus. (C) Central end plate fracture with exposed trabeculae resulting from excessive compression with a degenerate, fibrous nucleus pulposus.

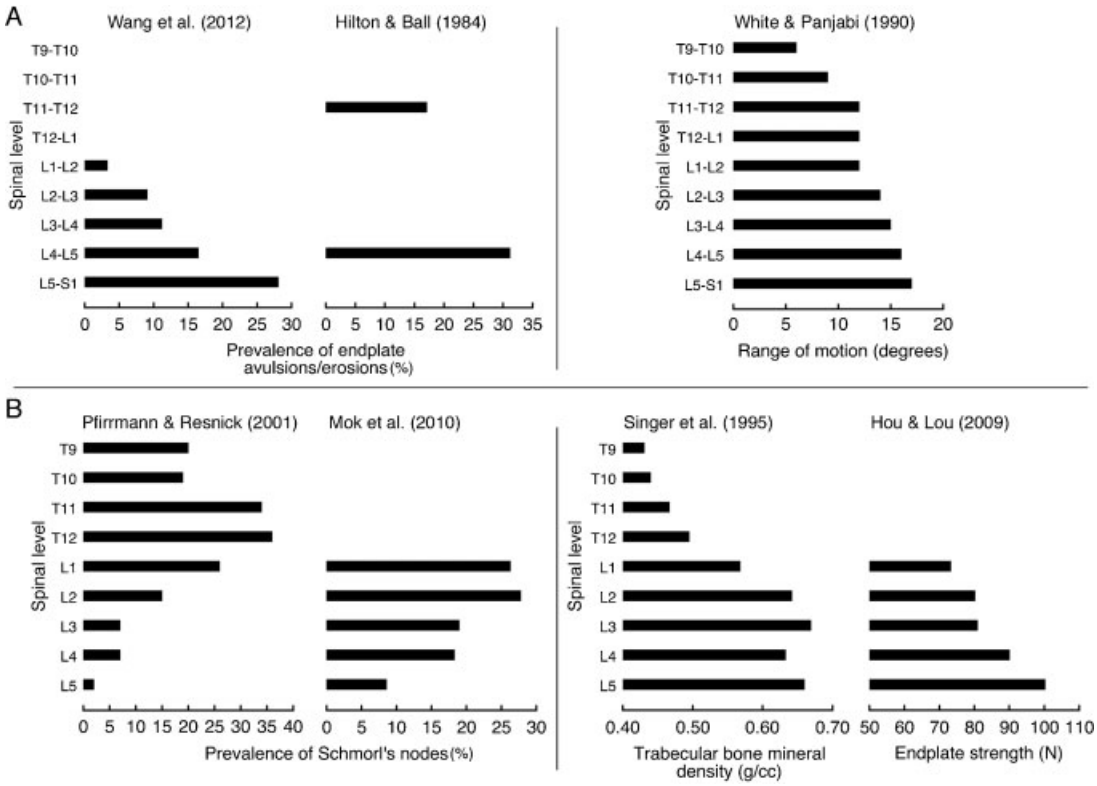

Fig. 6 Prevalence of end plate pathologies in different regions may arise from distinct biomechanical conditions. (A) In the lower lumbar spine, the prevalence of end plate cartilage avulsions and erosions increases caudally,[148–150] mirroring the increase in range of motion (combined flexion/extension data are shown).[152] (B) In the upper lumbar spine, Schmorl nodes increase cranially,[131] mirroring the decrease in trabecular bone mineral density[145] and end plate strength.[146]

End Plates and Disk Regeneration

There is growing interest in developing novel technologies to repair or regenerate the degenerated intervertebral disk. These approaches consist of increasing the signals for cell matrix synthesis (gene or growth factor therapy) in attempts to reestablish nuclear swelling.[153] Because the disk is relatively acellular (typically 4,000 cells/mm^3 in the nucleus),[12] it may also be critical to augment these approaches by introducing cells.

It is unclear whether end plate permeability and vascularity in degenerated disks is sufficient to support increases in cell density and metabolism (because poor nutrition may have led to the degeneration in the first place). These uncertainties may ultimately limit or prevent the successful extrapolation of disk repair technologies from small animals to man. Importantly, if it proves true that disk cell density and ultimately disk degeneration are tightly coupled to end plate permeability, then by definition, disk cellularity cannot be enhanced without commensurate increases in end plate permeability and vascularity (by yet undetermined methods). Similarly, efforts to increase synthesis rates of existing cells (by gene or growth factor therapy) may create excessive demands on a tenuous nutrition supply and thereby promote cell death.

Summary and Future Directions

End plates play a central role in maintaining disk and vertebral health. Their structure and composition reflect a balance between competing requirements for porosity and strength. As a result, end plates are particularly vulnerable to damage. End plate regions weakened by damage facilitate communication between the disk nucleus and vertebral marrow, which can cause an adverse combination of end plate nerve proliferation plus chemical sensitization and mechanical stimulation.

Unfortunately, current diagnostic tools do not depict subtle end plate damage that associates with neoinnervation, and consequently, the clinical significance of end plate damage may be underappreciated. Therefore, more research is needed to clarify the role of end plates in accelerated disk degeneration and discogenic pain. Three areas are of particular importance. First, more data are needed to define the dependence of disk cell function on the quality of end plate vascularity and end plate permeability. This information will help establish individual risk factors that associate with disk degeneration severity. Second, disk/vertebra structural models with improved fidelity of end plate architecture and composition are needed to define mechanisms of increased end plate damage risk. This information may guide development of new diagnostic tools that stratify injury risk. Third, the biological basis for BML and end plate neoinnervation is unknown. Studies are needed to identify the chemical factors and cellular participants in the development of innervated, fibrovascular bone marrow. Ultimately, strong links between clinical observations in back pain patients and scientific studies on disk

cells and tissues are a necessity given the lack of validated animal models of discogenic pain.

Funding Sources
National Institutes of Health Grant AR052811 Relievant Medsystems.

Disclosures
J. C. Lotz, Consultant, Research Support, Stock/Options: Relievant Medsystems, Nocimed LLC
A. J. Fields, None
E. C. Liebenberg, None

References

1 Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. Arch Intern Med 2009;169:251–258
2 Fagan A, Moore R, Vernon Roberts B, Blumbergs P, Fraser R. ISSLS prize winner: The innervation of the intervertebral disc: a quantitative analysis. Spine 2003;28:2570–2576
3 van Dieën JH, Weinans H, Toussaint HM. Fractures of the lumbar vertebral endplate in the etiology of low back pain: a hypothesis on the causative role of spinal compression in aspecific low back pain. Med Hypotheses 1999;53:246–252
4 Roberts S, Menage J, Duance V, Wotton S, Ayad S. 1991 Volvo Award in basic sciences. Collagen types around the cells of the intervertebral disc and cartilage end plate: an immunolocalization study. Spine 1991;16:1030–1038
5 Lotz JC. Animal models of intervertebral disc degeneration: lessons learned. Spine 2004;29:2742–2750
6 Moore RJ. The vertebral end-plate: what do we know? Eur Spine J 2000;9:92–96
7 Dias MS. Normal and abnormal development of the spine. Neurosurg Clin N Am 2007;18:415–429
8 Bick EM, Copel JW. Longitudinal growth of the human vertebra; a contribution to human osteogeny. J Bone Joint Surg Am 1950;32 (A:04)803–814
9 Bick EM, Copel JW. The ring apophysis of the human vertebra; contribution to human osteogeny. II. J Bone Joint Surg Am 1951;33-A:783–787
10 Aspden RM, Hickey DS, Hukins DW. Determination of collagen fibril orientation in the cartilage of vertebral end plate. Connect Tissue Res 1981;9:83–87
11 Antoniou J, Goudsouzian NM, Heathfield TF, et al. The human lumbar endplate. Evidence of changes in biosynthesis and denaturation of the extracellular matrix with growth, maturation, aging, and degeneration. Spine 1996;21:1153–1161
12 Rodriguez AG, Slichter CK, Acosta FL, et al. Human disc nucleus properties and vertebral endplate permeability. Spine 2011;36: 512–520
13 Roberts S, Menage J, Urban JP. Biochemical and structural properties of the cartilage end-plate and its relation to the intervertebral disc. Spine 1989;14:166–174
14 Wade KR, Robertson PA, Broom ND. A fresh look at the nucleus-endplate region: new evidence for significant structural integration. Eur Spine J 2011;20:1225–1232
15 Fields AJ, Sahli F, Rodriguez AG, Lotz JC. Seeing double: a comparison of microstructure, biomechanical function, and adjacent disc health between double- and single-layer vertebral endplates. Spine 2012;37:E1310–E1317
16 Edwards WT, Zheng Y, Ferrara LA, Yuan HA. Structural features and thickness of the vertebral cortex in the thoracolumbar spine. Spine 2001;26:218–225
17 Silva MJ, Wang C, Keaveny TM, Hayes WC. Direct and computed tomography thickness measurements of the human, lumbar vertebral shell and endplate. Bone 1994;15:409–414
18 Zhao FD, Pollintine P, Hole BD, Adams MA, Dolan P. Vertebral fractures usually affect the cranial endplate because it is thinner and supported by less-dense trabecular bone. Bone 2009;44: 372–379
19 Rodriguez AG, Rodriguez-Soto AE, Burghardt AJ, et al. Morphology of the human vertebral endplate. J Orthop Res 2012;30:280–287
20 Wang Y, Battié MC, Boyd SK, Videman T. The osseous endplates in lumbar vertebrae: thickness, bone mineral density and their associations with age and disk degeneration. Bone 2011;48: 804–809
21 Bailey JF, Liebenberg E, Degmetich S, Lotz JC. Innervation patterns of PGP 9.5-positive nerve fibers within the human lumbar vertebra. J Anat 2011;218:263–270
22 Crock HV, Yoshizawa H. The blood supply of the lumbar vertebral column. Clin Orthop Relat Res 1976;(115):6–21
23 Laroche M. Intraosseous circulation from physiology to disease. Joint Bone Spine 2002;69:262–269
24 Montazel JL, Divine M, Lepage E, Kobeiter H, Breil S, Rahmouni A. Normal spinal bone marrow in adults: dynamic gadolinium-enhanced MR imaging. Radiology 2003;229:703–709
25 Kricun ME. Red-yellow marrow conversion: its effect on the location of some solitary bone lesions. Skeletal Radiol 1985; 14:10–19
26 Meunier P, Aaron J, Edouard C, Vignon G. Osteoporosis and the replacement of cell populations of the marrow by adipose tissue. A quantitative study of 84 iliac bone biopsies. Clin Orthop Relat Res 1971;(80):147–154
27 Crock HV, Goldwasser M, Yoshizawa H. Vascular anatomy related to the intervertebral disc. In: The Biology of the Intervertebral Disc. Boca Raton, FL: CRC Press; 1988
28 Lips P, van Ginkel FC, Netelenbos JC. Bone marrow and bone remodeling. Bone 1985;6:343–344
29 Schnitzler CM, Mesquita J. Bone marrow composition and bone microarchitecture and turnover in blacks and whites. J Bone Miner Res 1998;13:1300–1307
30 Burkhardt R, Kettner G, Böhm W, et al. Changes in trabecular bone, hematopoiesis and bone marrow vessels in aplastic anemia, primary osteoporosis, and old age: a comparative histomorphometric study. Bone 1987;8:157–164
31 Tornvig L, Mosekilde LI, Justesen J, Falk E, Kassem M. Troglitazone treatment increases bone marrow adipose tissue volume but does not affect trabecular bone volume in mice. Calcif Tissue Int 2001;69:46–50
32 Trudel G, Payne M, Mädler B, et al. Bone marrow fat accumulation after 60 days of bed rest persisted 1 year after activities were resumed along with hemopoietic stimulation: the Women International Space Simulation for Exploration study. J Appl Physiol 2009;107:540–548
33 Sherman MS. The nerves of bone. J Bone Joint Surg Am 1963;45:522–528
34 Antonacci MD, Mody DR, Heggeness MH. Innervation of the human vertebral body: a histologic study. J Spinal Disord 1998; 11:526–531
35 Bogduk N, Tynan W, Wilson AS. The nerve supply to the human lumbar intervertebral discs. J Anat 1981;132(Pt 1):39–56
36 Mach DB, Rogers SD, Sabino MC, et al. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. Neuroscience 2002;113:155–166
37 Antonacci MD, Mody DR, Rutz K, Weilbaecher D, Heggeness MH. A histologic study of fractured human vertebral bodies. J Spinal Disord Tech 2002;15:118–126
38 Arjmand N, Plamondon A, Shirazi-Adl A, Parnianpour M, Larivière C. Predictive equations for lumbar spine loads in load-dependent asymmetric one- and two-handed lifting activities. Clin Biomech (Bristol, Avon) 2012;27:537–544

39 Quinnell RC, Stockdale HR, Willis DS. Observations of pressures within normal discs in the lumbar spine. Spine 1983;8:166–169
40 Wilke HJ, Neef P, Caimi M, Hoogland T, Claes LE. New in vivo measurements of pressures in the intervertebral disc in daily life. Spine 1999;24:755–762
41 Sato K, Kikuchi S, Yonezawa T. In vivo intradiscal pressure measurement in healthy individuals and in patients with ongoing back problems. Spine 1999;24:2468–2474
42 Brinckmann P, Frobin W, Hierholzer E, Horst M. Deformation of the vertebral end-plate under axial loading of the spine. Spine 1983;8:851–856
43 Rolander SD, Blair WE. Deformation and fracture of the lumbar vertebral end plate. Orthop Clin North Am 1975;6:75–81
44 Yoganandan N, Maiman DJ, Pintar F, et al. Microtrauma in the lumbar spine: a cause of low back pain. Neurosurgery 1988; 23:162–168
45 Fields AJ, Lee GL, Keaveny TM. Mechanisms of initial endplate failure in the human vertebral body. J Biomech 2010;43:3126–3131
46 Hulme PA, Boyd SK, Ferguson SJ. Regional variation in vertebral bone morphology and its contribution to vertebral fracture strength. Bone 2007;41:946–957
47 Fields AJ, et al. Effects of endplate microstructure on biomechanical integrity. Presented at: New Horizons in Intervertebral Disc Research. Philadelphia, PA; 2011
48 Langrana NA, Kale SP, Edwards WT, Lee CK, Kopacz KJ. Measurement and analyses of the effects of adjacent end plate curvatures on vertebral stresses. Spine J 2006;6:267–278
49 Nekkanty S, Yerramshetty J, Kim DG, et al. Stiffness of the endplate boundary layer and endplate surface topography are associated with brittleness of human whole vertebral bodies. Bone 2010;47:783–789
50 Nachemson A, Lewin T, Maroudas A, Freeman MA. In vitro diffusion of dye through the end-plates and the annulus fibrosus of human lumbar inter-vertebral discs. Acta Orthop Scand 1970;41:589–607
51 Urban JP, Holm S, Maroudas A, Nachemson A. Nutrition of the intervertebral disk. An in vivo study of solute transport. Clin Orthop Relat Res 1977;(129):101–114
52 Roberts S, Menage J, Urban JPG. Biochemical and structural properties of the cartilage end-plate and its relation to the intervertebral disc. Spine 1989;14:166–174
53 Holm S, Maroudas A, Urban JP, Selstam G, Nachemson A. Nutrition of the intervertebral disc: solute transport and metabolism. Connect Tissue Res 1981;8:101–119
54 Maroudas A, Stockwell RA, Nachemson A, Urban J. Factors involved in the nutrition of the human lumbar intervertebral disc: cellularity and diffusion of glucose in vitro. J Anat 1975;120(Pt 1):113–130
55 Roberts S, Urban JP, Evans H, Eisenstein SM. Transport properties of the human cartilage endplate in relation to its composition and calcification. Spine 1996;21:415–420
56 Urban MR, Fairbank JC, Etherington PJ, Loh FRCA L, Winlove CP, Urban JP. Electrochemical measurement of transport into scoliotic intervertebral discs in vivo using nitrous oxide as a tracer. Spine 2001;26:984–990
57 Bartels EM, Fairbank JC, Winlove CP, Urban JP. Oxygen and lactate concentrations measured in vivo in the intervertebral discs of patients with scoliosis and back pain. Spine 1998;23:1–7, discussion 8
58 Benneker LM, Heini PF, Alini M, Anderson SE, Ito K. 2004 Young Investigator Award Winner: vertebral endplate marrow contact channel occlusions and intervertebral disc degeneration. Spine 2005;30:167–173
59 Bernick S, Cailliet R. Vertebral end-plate changes with aging of human vertebrae. Spine 1982;7:97–102
60 Bishop PB, Pearce RH. The proteoglycans of the cartilaginous endplate of the human intervertebral disc change after maturity. J Orthop Res 1993;11:324–331
61 Aigner T, Gresk-otter KR, Fairbank JC, von der Mark K, Urban JP. Variation with age in the pattern of type X collagen expression in normal and scoliotic human intervertebral discs. Calcif Tissue Int 1998;63:263–268
62 Adams MA, McNally DS, Dolan P. "Stress" distributions inside intervertebral discs. The effects of age and degeneration. J Bone Joint Surg Br 1996;78:965–972
63 Wong M, Siegrist M, Goodwin K. Cyclic tensile strain and cyclic hydrostatic pressure differentially regulate expression of hypertrophic markers in primary chondrocytes. Bone 2003;33: 685–693
64 Hulme PA, Ferguson SJ, Boyd SK. Determination of vertebral endplate deformation under load using micro-computed tomography. J Biomech 2008;41:78–85
65 Grant JP, Oxland TR, Dvorak MF. Mapping the structural properties of the lumbosacral vertebral endplates. Spine 2001;26: 889–896
66 Smith FP. Experimental biomechanics of intervertebral disc rupture through a vertebral body. J Neurosurg 1969;30: 134–139
67 Vernon-Roberts B, Pirie CJ. Healing trabecular microfractures in the bodies of lumbar vertebrae. Ann Rheum Dis 1973;32:406–412
68 Grant JP, Oxland TR, Dvorak MF, Fisher CG. The effects of bone density and disc degeneration on the structural property distributions in the lower lumbar vertebral endplates. J Orthop Res 2002;20:1115–1120
69 Keller TS, Ziv I, Moeljanto E, Spengler DM. Interdependence of lumbar disc and subdiscal bone properties: a report of the normal and degenerated spine. J Spinal Disord 1993;6:106–113
70 Aoki J, Yamamoto I, Kitamura N, et al. End plate of the discovertebral joint: degenerative change in the elderly adult. Radiology 1987;164:411–414
71 Simpson EK, Parkinson IH, Manthey B, Fazzalari NL. Intervertebral disc disorganization is related to trabecular bone architecture in the lumbar spine. J Bone Miner Res 2001;16:681–687
72 Homminga J, Weinans H, Gowin W, Felsenberg D, Huiskes R. Osteoporosis changes the amount of vertebral trabecular bone at risk of fracture but not the vertebral load distribution. Spine 2001;26:1555–1561
73 Kurowski P, Kubo A. The relationship of degeneration of the intervertebral disc to mechanical loading conditions on lumbar vertebrae. Spine 1986;11:726–731
74 Shirazi-Adl SA, Shrivastava SC, Ahmed AM. Stress analysis of the lumbar disc-body unit in compression. A three-dimensional nonlinear finite element study. Spine 1984;9:120–134
75 Adams MA, Freeman BJ, Morrison HP, Nelson IW, Dolan P. Mechanical initiation of intervertebral disc degeneration. Spine 2000;25:1625–1636
76 Adams MA, McNally DS, Wagstaff J, Goodship AE. Abnormal stress concentrations in lumbar intervertebral discs following damage to the vertebral bodies: a cause of disc failure? Eur Spine J 1993;1:214–221
77 Handa T, Ishihara H, Ohshima H, Osada R, Tsuji H, Obata K. Effects of hydrostatic pressure on matrix synthesis and matrix metalloproteinase production in the human lumbar intervertebral disc. Spine 1997;22:1085–1091
78 Ishihara H, McNally DS, Urban JP, Hall AC. Effects of hydrostatic pressure on matrix synthesis in different regions of the intervertebral disk. J Appl Physiol 1996;80:839–846
79 Lotz JC, Chin JR. Intervertebral disc cell death is dependent on the magnitude and duration of spinal loading. Spine 2000;25: 1477–1483
80 Walsh AJ, Lotz JC. Biological response of the intervertebral disc to dynamic loading. J Biomech 2004;37:329–337
81 Maroudas A, Stockwell RA, Nachemson A, Urban J. Factors involved in the nutrition of the human lumbar intervertebral disc: cellularity and diffusion of glucose in vitro. J Anat 1975;120(Pt 1): 113–130

82 Rajasekaran S, Babu JN, Arun R, Armstrong BR, Shetty AP, Murugan S. ISSLS prize winner: a study of diffusion in human lumbar discs: a serial magnetic resonance imaging study documenting the influence of the endplate on diffusion in normal and degenerate discs. Spine 2004;29:2654–2667

83 Bisla RS, Marchisello PJ, Lockshin MD, Hart DM, Marcus RE, Granda J. Auto-immunological basis of disk degeneration. Clin Orthop Relat Res 1976;(121):205–211

84 Crock HV. Internal disc disruption. A challenge to disc prolapse fifty years on. Spine 1986;11:650–653

85 Coppes MH, Marani E, Thomeer RT, Groen GJ. Innervation of "painful" lumbar discs. Spine 1997;22:2342–2349, discussion 2349–2350

86 Peng B, Hao J, Hou S, et al. Possible pathogenesis of painful intervertebral disc degeneration. Spine 2006;31:560–566

87 Jackson HC II, Winkelmann RK, Bickel WH. Nerve endings in the human lumbar spinal column and related structures. J Bone Joint Surg Am 1966;48:1272–1281

88 Serre CM, Farlay D, Delmas PD, Chenu C. Evidence for a dense and intimate innervation of the bone tissue, including glutamate-containing fibers. Bone 1999;25:623–629

89 Artico M, Bosco S, Cavallotti C, et al. Noradrenergic and cholinergic innervation of the bone marrow. Int J Mol Med 2002;10:77–80

90 Halvorson KG, Kubota K, Sevcik MA, et al. A blocking antibody to nerve growth factor attenuates skeletal pain induced by prostate tumor cells growing in bone. Cancer Res 2005;65:9426–9435

91 Niv D, Gofeld M, Devor M. Causes of pain in degenerative bone and joint disease: a lesson from vertebroplasty. Pain 2003;105: 387–392

92 Fraser RD. The North American Spine Society (NASS) on lumbar discography. Spine 1996;21:1274–1276

93 Wolfer LR, Derby R, Lee JE, Lee SH. Systematic review of lumbar provocation discography in asymptomatic subjects with a meta-analysis of false-positive rates. Pain Physician 2008;11:513–538

94 Walsh TR, Weinstein JN, Spratt KF, Lehmann TR, Aprill C, Sayre H. Lumbar discography in normal subjects. A controlled, prospective study. J Bone Joint Surg Am 1990;72:1081–1088

95 Carragee EJ, Don AS, Hurwitz EL, Cuellar JM, Carrino JA, Herzog R. 2009 ISSLS Prize Winner: Does discography cause accelerated progression of degeneration changes in the lumbar disc: a ten-year matched cohort study. Spine 2009;34:2338–2345

96 Carragee EJ, Alamin TF. Discography. A review. Spine J 2001;1: 364–372

97 Carragee EJ, Lincoln T, Parmar VS, Alamin T. A gold standard evaluation of the "discogenic pain" diagnosis as determined by provocative discography. Spine 2006;31:2115–2123

98 Weinstein J, Claverie W, Gibson S. The pain of discography. Spine 1988;13:1344–1348

99 Peng B, Chen J, Kuang Z, Li D, Pang X, Zhang X. Diagnosis and surgical treatment of back pain originating from endplate. Eur Spine J 2009;18:1035–1040

100 Heggeness MH, Doherty BJ. Discography causes end plate deflection. Spine 1993;18:1050–1053

101 Yoganandan N, Larson SJ, Pintar FA, Gallagher M, Reinartz J, Droese K. Intravertebral pressure changes caused by spinal microtrauma. Neurosurgery 1994;35:415–421, discussion 421

102 Hebelka H, Gaulitz A, Nilsson A, Holm S, Hansson T. The transfer of disc pressure to adjacent discs in discography: a specificity problem? Spine 2010;35:E1025–E1029

103 Esses SI, Moro JK. Intraosseous vertebral body pressures. Spine 1992;17(6, Suppl):S155–S159

104 Arnoldi CC. Intraosseous hypertension. A possible cause of low back pain? Clin Orthop Relat Res 1976;(115):30–34

105 Brown MF, Hukkanen MV, McCarthy ID, et al. Sensory and sympathetic innervation of the vertebral endplate in patients with degenerative disc disease. J Bone Joint Surg Br 1997;79: 147–153

106 Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica: a report of pain response to tissue stimulation during operations on the lumbar spine using local anesthesia. Orthop Clin North Am 1991;22:181–187

107 Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology 1988;166(1 Pt 1):193–199

108 Kuisma M, Karppinen J, Niinimäki J, et al. A three-year follow-up of lumbar spine endplate (Modic) changes. Spine 2006;31:1714–1718

109 Vital JM, Gille O, Pointillart V, et al. Course of Modic 1 six months after lumbar posterior osteosynthesis. Spine 2003;28:715–720, discussion 721

110 Marshman LA, Trewhella M, Friesem T, Bhatia CK, Krishna M. Reverse transformation of Modic type 2 changes to Modic type 1 changes during sustained chronic low-back pain severity. Report of two cases and review of the literature. J Neurosurg Spine 2007;6:152–155

111 Braithwaite I, White J, Saifuddin A, Renton P, Taylor BA. Vertebral end-plate (Modic) changes on lumbar spine MRI: correlation with pain reproduction at lumbar discography. Eur Spine J 1998;7: 363–368

112 Ito M, Incorvaia KM, Yu SF, Fredrickson BE, Yuan HA, Rosenbaum AE. Predictive signs of discogenic lumbar pain on magnetic resonance imaging with discography correlation. Spine 1998;23:1252–1258, discussion 1259–1260

113 Kokkonen SM, Kurunlahti M, Tervonen O, et al. Endplate degeneration observed on magnetic resonance imaging of the lumbar spine: correlation with pain provocation and disc changes observed on computed tomography diskography. Spine (Phila Pa 1976) 2002;27:2274–2278

114 O'Neill C, Kurgansky M, Kaiser J, et al. Accuracy of MRI for diagnosis of discogenic pain. Pain Physician 2008;11:311–326

115 Thompson KJ, Dagher AP, Eckel TS, Clark M, Reinig JW. Modic changes on MR images as studied with provocative diskography: clinical relevance—a retrospective study of 2457 disks. Radiology 2009;250:849–855

116 Weishaupt D, Zanetti M, Hodler J, et al. Painful lumbar disk derangement: relevance of endplate abnormalities at MR imaging. Radiology 2001;218:420–427

117 Ohtori S, Inoue G, Ito T, et al. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back Pain and Modic Type 1 or Type 2 changes on MRI. Spine 2006;31:1026–1031

118 Yamauchi K, Ohtori S, Inoue G, et al. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplate of patients with vertebral endplates of patients with discogenic low back pain and Modic Type 1 or Type 2 changes on MRI. Presented at: 33rd Annual Meeting of the International Society for the Study of the Lumbar Spine; Bergen, Norway; 2006

119 Rahme R, Moussa R. The modic vertebral endplate and marrow changes: pathologic significance and relation to low back pain and segmental instability of the lumbar spine. AJNR Am J Neuroradiol 2008;29:838–842

120 Crock HV. Internal disc disruption. A challenge to disc prolapse fifty years on. Spine 1986;11:650–653

121 Ma XL, Ma JX, Wang T, Tian P, Han C. Possible role of autoimmune reaction in Modic Type I changes. Med Hypotheses 2011;76: 692–694

122 Miyamoto H, Saura R, Harada T, Doita M, Mizuno K. The role of cyclooxygenase-2 and inflammatory cytokines in pain induction of herniated lumbar intervertebral disc. Kobe J Med Sci 2000; 46:13–28

123 Ahn SH, Cho YW, Ahn MW, Jang SH, Sohn YK, Kim HS. mRNA expression of cytokines and chemokines in herniated lumbar intervertebral discs. Spine 2002;27:911–917

124 Olmarker K, Larsson K. Tumor necrosis factor alpha and nucleus-pulposus-induced nerve root injury. Spine 1998;23:2538–2544

125 Weiler C, Nerlich AG, Bachmeier BE, Boos N. Expression and distribution of tumor necrosis factor alpha in human lumbar intervertebral discs: a study in surgical specimen and autopsy controls. Spine 2005;30:44–53, discussion 54
126 García-Cosamalón J, del Valle ME, Calavia MG, et al. Intervertebral disc, sensory nerves and neurotrophins: who is who in discogenic pain? J Anat 2010;217:1–15
127 Olmarker K, Blomquist J, Strömberg J, Nannmark U, Thomsen P, Rydevik B. Inflammatogenic properties of nucleus pulposus. Spine 1995;20:665–669
128 Cavanaugh JM. Neural mechanism of idiopathic low back pain. In: Weinstein JN, Gordon S eds. Low Back Pain: A Scientific and Clinical Overview. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1996
129 Keshari KR, Lotz JC, Link TM, Hu S, Majumdar S, Kurhanewicz J. Lactic acid and proteoglycans as metabolic markers for discogenic back pain. Spine 2008;33:312–317
130 Niinimäki J, Korkiakoski A, Parviainen O, et al. Association of lumbar artery narrowing, degenerative changes in disc and endplate and apparent diffusion in disc on postcontrast enhancement of lumbar intervertebral disc. MAGMA 2009;22:101–109
131 Pfirrmann CW, Resnick D. Schmorl nodes of the thoracic and lumbar spine: radiographic-pathologic study of prevalence, characterization, and correlation with degenerative changes of 1,650 spinal levels in 100 cadavers. Radiology 2001;219:368–374
132 Katz ME, Teitelbaum SL, Gilula LA, Resnick D, Katz SJ. Radiologic and pathologic patterns of end-plate-based vertebral sclerosis. Invest Radiol 1988;23:447–454
133 Stäbler A, Bellan M, Weiss M, Gärtner C, Brossmann J, Reiser MF. MR imaging of enhancing intraosseous disk herniation (Schmorl's nodes). AJR Am J Roentgenol 1997;168:933–938
134 Cheung KM, Samartzis D, Karppinen J, Luk KD. Are "patterns" of lumbar disc degeneration associated with low back pain?: new insights based on skipped level disc pathology Spine 2012;37: E430–E438
135 Coventry MB, Ghormley RK, Kernohan JW. The intervertebral disc: its microscopic anatomy and pathology. J Bone Joint Surg Br 1945;27:460–474
136 Mok FP, Samartzis D, Karppinen J, Luk KD, Fong DY, Cheung KM. ISSLS prize winner: prevalence, determinants, and association of Schmorl nodes of the lumbar spine with disc degeneration: a population-based study of 2449 individuals. Spine 2010;35: 1944–1952
137 Hassler O. The human intervertebral disc. A micro-angiographical study on its vascular supply at various ages. Acta Orthop Scand 1969;40:765–772
138 Hirsch C, Schajowicz F. Studies on structural changes in the lumbar annulus fibrosus. Acta Orthop Scand 1952;22:184–231
139 Hilton RC, Ball J, Benn RT. Vertebral end-plate lesions (Schmorl's nodes) in the dorsolumbar spine. Ann Rheum Dis 1976;35:127–132
140 Wagner AL, Murtagh FR, Arrington JA, Stallworth D. Relationship of Schmorl's nodes to vertebral body endplate fractures and acute endplate disk extrusions. AJNR Am J Neuroradiol 2000;21: 276–281
141 Wang Y, Videman T, Battié MC. Lumbar vertebral endplate lesions: prevalence, classification, and association with age. Spine 2012;37:1432–1439
142 Takahashi K, Miyazaki T, Ohnari H, Takino T, Tomita K. Schmorl's nodes and low-back pain. Analysis of magnetic resonance imaging findings in symptomatic and asymptomatic individuals. Eur Spine J 1995;4:56–59
143 Peng B, Wu W, Hou S, Shang W, Wang X, Yang Y. The pathogenesis of Schmorl's nodes. J Bone Joint Surg Br 2003;85:879–882
144 Wang Y, Videman T, Battié MC. ISSLS prize winner: Lumbar vertebral endplate lesions: associations with disc degeneration and back pain history. Spine 2012;37:1490–1496
145 Singer K, Edmondston S, Day R, Breidahl P, Price R. Prediction of thoracic and lumbar vertebral body compressive strength: correlations with bone mineral density and vertebral region. Bone 1995;17:167–174
146 Hou Y, Luo Z. A study on the structural properties of the lumbar endplate: histological structure, the effect of bone density, and spinal level. Spine 2009;34:E427–E433
147 Hansson T, Roos B. The relation between bone mineral content, experimental compression fractures, and disc degeneration in lumbar vertebrae. Spine 1981;6:147–153
148 Wang Y, Battié MC, Videman T. A morphological study of lumbar vertebral endplates: radiographic, visual and digital measurements. Eur Spine J 2012;21:2316–2323
149 Hilton RC, Ball J. Vertebral rim lesions in the dorsolumbar spine. Ann Rheum Dis 1984;43:302–307
150 Vernon-Roberts B, Pirie CJ. Degenerative changes in the intervertebral discs of the lumbar spine and their sequelae. Rheumatol Rehabil 1977;16:13–21
151 Grignon B, Grignon Y, Mainard D, et al. The structure of the cartilaginous end-plates in elder people. Surg Radiol Anat 2000;22:13–19
152 White AA, Panjabi MM. Clinical Biomechanics of the Spine. 2nd ed. Philadelphia, PA: J.B. Lippincott Co; 1990
153 Lotz JC, Haughton V, Boden SD, et al. New treatments and imaging strategies in degenerative disease of the intervertebral disks. Radiology 2012;264:6–19