Title
Contribution of the Endplates to Disc Degeneration

Journal
Current Molecular Biology Reports, 4(4)

ISSN
2198-6428

Authors
Fields, Aaron J
Ballatori, Alexander
Liebenberg, Ellen C
et al.

Publication Date
2018-12-01

DOI
10.1007/s40610-018-0105-y

Peer reviewed

HHS Public Access

Author manuscript

Curr Mol Biol Rep. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

Curr Mol Biol Rep. 2018 December ; 4(4): 151–160. doi:10.1007/s40610-018-0105-y.

Contribution of the endplates to disc degeneration

Aaron J. Fields, Ph.D.[*], **Alexander Ballatori, B.S.**, **Ellen C. Liebenberg, B.S.**, and **Jeffrey C. Lotz, Ph.D.**[*]

Department of Orthopaedic Surgery, University of California, San Francisco, CA

Abstract

Purpose of review: The endplates form the interface between the rigid vertebral bodies and compliant intervertebral discs. Proper endplate function involves a balance between conflicting biomechanical and nutritional demands. This review summarizes recent data that highlight the importance of proper endplate function and the relationships between endplate dysfunction, adjacent disc degeneration, and axial low back pain.

Recent findings: Changes to endplate morphology and composition that impair its permeability associate with disc degeneration. Endplate damage also associates with disc degeneration, and the progression of degeneration may be accelerated and the chronicity of symptoms heightened when damage coincides with evidence of adjacent bone marrow lesions.

Summary: The endplate plays a key role in the development of disc degeneration and low back pain. Clarification of the mechanisms governing endplate degeneration and developments in clinical imaging that enable precise evaluation of endplate function and dysfunction will distinguish the correlative *vs.* causative nature of endplate damage and motivate new treatments that target pathologic endplate function.

Keywords

endplate; intervertebral disc degeneration; back pain; Modic change; endplate bone marrow lesion; spine

1. Introduction

Low back pain represents the leading cause of disability and healthcare expenditures in adults worldwide. In the United States, low back pain is the most common, non-cancer reason for opioid prescription [1]. Low back pain is closely linked with intervertebral disc

[*]**Co-corresponding authors:** Aaron J. Fields, Ph.D., 513 Parnassus Avenue, S-1161, University of California, San Francisco, CA 94143-0514, USA, (415) 476-0960, fax (415) 476-1128, aaron.fields@ucsf.edu. Jeffrey C. Lotz, Ph.D., 513 Parnassus Avenue, S-1157, University of California, San Francisco, CA 94143-0514, USA, (415) 476-7881, fax (415) 476-1128, jeffrey.lotz@ucsf.edu.

Conflict of Interest

Alexander Ballatori and Ellen C. Liebenberg each declare no potential conflicts of interest.

Jeffrey C. Lotz is co-founder and has shares in Relievant Mesystems.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Papers of particular interest, published 2015–2018, have been highlighted as:

• Of importance

•• Of major importance

degeneration; in fact, even in asymptomatic individuals, disc degeneration severity predicts future first-time low back pain episodes [2]. The factors leading to disc degeneration are complex, and commonly involve synergistic interactions between physical and biological mechanisms [3, 4]. Because degeneration seen on clinical imaging is most visible in the nucleus pulposus — *e.g.* height loss, herniation, and loss of nucleus pulposus signal intensity — the nucleus pulposus is considered to be the key malefactor. Indeed, disc cell death and matrix catabolism first occur in the innermost disc tissues [5, 6], which has led to the notion that disc degeneration progresses from the inside-out. However, the critical role of the vertebral endplate in disc health and degeneration is becoming increasingly apparent. The purpose of this review is to summarize recent data that highlight the importance of proper vertebral endplate function and the relationships between endplate dysfunction, adjacent disc degeneration, and axial low back pain.

2. Anatomy

The intervertebral disc consists of three distinct structures: the central gelatinous nucleus pulposus (NP), the collagenous annulus fibrosus (AF), which surrounds the NP circumferentially, and the cartilage endplates (CEP), which separate the AF and NP from the vertebral bodies [7]. The endplates are layered composites of semi-porous thickened cancellous bone (0.6 – 1 mm)[8–12] and hyaline cartilage (0.2–0.8 mm) [7, 13]. The bony endplate (BEP) is approximately 40% porous in the central region, with a hydraulic permeability in the range of 30×10^{-10} m^4/N-s [9, 14]. The cartilage endplate is composed primarily of proteoglycan (100 ug/mg dry weight), type II collagen (550 ug/mg dry weight), and water (40–60% by weight) [15, 16, 7, 17], and its hydraulic permeability is significantly lower than that of the adjacent BEP (approximately 1.2×10^{-10} m^4/N-s) [14]. The porosity of the CEP (66% by volume, on average) is significantly higher in the central region adjacent to the NP compared to the anterior and posterior regions [18]. Unlike the depth-dependent zones of varying collagen alignment found in articular cartilage, the collagen fibers of the CEP are mainly aligned parallel to the vertebral surface [19, 20].

The endplate has a more complex structure where it integrates with the annulus fibrosus. The collagen fibers in the lamellae of the inner annulus fibrosus are continuous with the collagen fibers in the endplate, whereas the integration between collagen fibers in the nucleus pulposus and the CEP is more convoluted [7, 21]. The CEP is not structurally anchored into the BEP, and consequently the interface is easily separated: the tensile failure strength of the CEP/BEP interface is approximately 0.4 MPa where it integrates with the annulus [22]. The relatively low separation strength may reflect the loading environment at this location: in a healthy disc, the CEP/BEP interface predominately experiences compression.

At the outer annulus, the vertebral interface is formed by an enthesis – a fibrocartilaginous composite where the annular fibers are embedded into a zone of calcified cartilage that is anchored to the subchondral bone via a complex, geometric interdigitation [22]. The complex morphology and graded material properties minimize stress concentrations during complex loading that includes tension, compression, and shear forces [23, 24].

The bone marrow compartment adjacent to the BEP 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 via small pores in the cortical shell. Inside the centrum, the capillaries and nerves form an ‘arterial grid’, which then branches and terminates just adjacent to the CEP [25–27]. These vessels and sinusoids provide a continuous bed across the bone-disc interface [25, 27].

The nerve supply to a healthy disc is restricted to about the three outermost lamellae of the AF and to the central part of the endplate [28, 29]. Endplate innervation is comparable to that of the peripheral annulus [30, 31] and is increased in areas of endplate damage [32, 33]. Ninety percent of the nerves are sympathetic afferent and belong to the sinus vertebral nerves. These nerves are capable of sending nociceptive information to the sympathetic nervous system, which can cause a form of visceral pain similar to enteric structure.

3. Function

Biotransport

The disc is the biggest avascular structure in the human body, and cells in the center of an adult lumbar disc must survive 6–8 mm from their nearest blood supply. Therefore, nutrient and metabolite exchange with the vascular network adjacent to the bony endplate and outer AF is critical. Whereas the cells in the outer annulus mainly receive nutrients from peri-annular routes [34, 35], nucleus pulposus cells rely almost exclusively on nutrients supplied by the vertebral capillary bed adjacent to the endplate [36, 37, 35]. These capillaries terminate at the CEP and provide a continuous bed across the interface between the CEP and BEP [38, 27]. Once nutrients reach the CEP, smaller solutes (glucose, lactate, sulfate and oxygen) are believed to reach the disc cells primarily by diffusion [36, 39, 40], while convection is thought to play an important role for larger solutes [41, 36, 39, 40]. Nevertheless, there remains uncertainty about how any convection (fluid flow) induced by dynamic loading aids transport compared to diffusion from static load. A recent study in rabbits, which have much thinner CEPs and thicker bony endplates compared to humans, suggests that any benefits of dynamic loading depend on loading rate: gadolinium enhancement in the disc was maximal (16.8% vs. unloaded controls) for slow loading rates (0.5 Hz) [42]. Transport depends on a number of other factors too, including solute charge, concentration gradient (coupled to solute supply and cellular demand), and tissue permeability (related to pore size and hydration). Solute diffusivities in the CEP are also region- and strain-dependent: glucose diffusivity ($26.8 \pm 9.3\ \mu m^2/s$) and lactate diffusivity ($45.2 \pm 14.7\ \mu m^2/s$) in the healthy CEP are reported to be highest in the central region and lowest peripherally and when the CEP is under higher magnitudes of mechanical strain [18]. Related to this strain-dependency, compression of the compliant CEP against the stiff BEP may result in a greater resistance to fluid outflow from the disc than fluid inflow [43]. In that regard, the CEP functions like a one-way valve to prevent rapid fluid loss from the disc during loading.

Biomechanics

The endplate serves as the hard/soft tissue interface between the disc and vertebra, transmitting complex and multiaxial loads between the disc and vertebra in order to ensure proper range-of-motion. The highly hydrated NP contains large quantities of the proteoglycan aggrecan, which has a negative fixed charge on its sulfated glycosaminoglycans. This creates high interstitial swelling pressures and osmotic pressures when the disc is loaded. The endplate uniformly distributes these intradiscal pressures over the surface of the adjacent vertebrae and prevents the pressurized NP from bulging into the underlying trabecular centrum [44–46] (Fig. 1A). Ultimately, thickness, porosity, and curvature are important structural determinants of endplate biomechanical function: thick and dense endplates with a high degree of curvature (greater volume) are stronger than thin, porous, and flat endplates [47, 48, 12, 49].

In addition to resisting hydrostatic pressures, the central endplate also experiences appreciable levels of transverse shear and tensile stress [50, 51]. For example, structural integration between the NP and the CEP [21] results in transverse shear stress at this interface when the NP bulges laterally under axial compression [50]. Additionally, the EP stretches like a drumhead [51] because the trabecular centrum can compress elastically. Whereas the relative amount of collagen fibers plays an important role in how the CEP resists these tensile stresses [52, 15], the collagen fibers appear to play little role in confined compression [52].

Peripherally, the resistance of the endplate to tensile loading may be especially important for preventing disc herniation. The collagen fibers in the lamellae of the inner AF are continuous with the collagen fibers of the CEP, and the strength of the interconnection between these two tissues (as well as the loading rate [53]) influences failure strength and location [22, 54]. Under slow loading rates, disc pressurization leads to localized stretching and failure of the AF [53]. When the disc is loaded rapidly, the AF fibers have little time to stretch, leading to annular displacements over the full disc height, including at the junction between the AF and CEP. This may strip or avulse the CEP from the underlying bone when there is poor structural integration between those two tissues [22] (Fig. 1H). Indeed, herniated disc materials contain CEP material alone [55] and with the BEP [56], and examination of surgically excised disc protrusions containing CEP revealed that the plane of cleavage is in most cases at the junction of the CEP and BEP and in a few cases within the CEP [57].

4. Endplate pathology and relations to disc degeneration

Impaired transport

Changes to the structure and composition of the endplate alter nutrient availability to the disc, thereby contributing to disc degeneration. With increasing age, the bone-cartilage interface may become partially calcified [58, 59] (Fig. 1G). The calcified zone is virtually impermeable, which severely limits diffusion [36, 37]. This could explain why several anatomic studies have found disc degeneration is associated with changes in the bony endplate, including microfracture and sclerosis [58, 60, 37, 61]. Specifically, Benneker *et al.*

found that increased occlusion of the bony endplate correlates with low nucleus GAG content [61], an effect that may be countered by double endplates [9].

While much emphasis has been placed on the BEP, the data are conflicting about its etiologic role in disc degeneration. For example, using 96 endplate samples from 14 subjects ranging from 35–85 years of age, Rodriguez *et al.* showed that bony endplate sclerosis *decreased* — not increased — with age and degeneration [10], which suggests that sclerosis may be less important than previously thought. In contrast, changes in the CEP may be more influential. Compared to the hydraulic permeability of the BEP, the hydraulic permeability of the CEP is an order of magnitude lower, and is the main factor influencing their combined permeability ($p < 0.0001$, $r = 0.96$) [14].

With age and degeneration, CEP composition undergoes several compositional changes that could reduce permeability and limit nutrient transport (Fig. 1D). Grant *et al.* measured higher calcium content (Ca^{2+}) in CEP tissues adjacent to more severely degenerated human discs, and increasing levels of Ca^{2+} diminished collagen and proteoglycan synthesis in cultured human CEP cells through activation of the extracellular calcium-sensing receptor. Ca^{2+} also enhanced the cleavage of aggrecan by ADAMTS5, suggesting that higher Ca^{2+} levels may promote CEP degeneration by increasing the activity of this aggrecanase [62]. These findings are important since increased calcification and decreased proteoglycan content adversely impact tissue hydration and may therefore impede solute diffusion.

In addition to aggrecan quantity, changes in aggrecan composition may play a role. Bishop *et al.* showed that the ratio of keratan sulfate to chondroitin sulfate in the CEP increases with age from 1:1 to 3:1 [63], which is important because keratan sulfate is less negatively charged than chondroitin sulfate, and so the net hydrophilic charge decreases. This, in turn, coincides with decreased water content. Besides fixed charge density, water content also depends on the quantity and integrity of collagen fibers, which resist swelling. Antoniou *et al.* found that large reductions in the percentage of denatured collagen in the CEP occur with aging and are greatest in the early stages of disc degeneration, which could further lower water content [64]. Collectively, these changes may underlie the decrease in CEP permeability observed with ageing [52].

Impaired solute transport is believed to promote NP cell death and disc degeneration because of nutrient deprivation, mainly oxygen and glucose, and accumulation of metabolic waste, mainly lactic acid. Specifically, if glucose concentration falls below 0.5 mmol/L for more than 3 days, NP cells will die [6]. NP cell death also occurs under acidic conditions (pH < 6.3) resulting from lactic acid accumulation [65], as NP cells mainly produce energy by converting glucose to lactic acid [66, 67]. Less acidic conditions, although not detrimental to viability, may still be harmful because they lower matrix production and lead to an imbalance between production and degradation that favors catabolism [68]. Oxygen tension in the NP is as low as 1% [69] and its deprivation also leads to a higher synthesis rate and accumulation of lactic acid, and consequently to a drop in pH [70]. In short, NP cells are maximally active at pH 6.9 – 7.2 but below pH 6.8 their activity is suppressed and they fail to retain a biomechanically sound extracellular matrix.

Impaired nutrient supply

The marrow space of the bony endplate and of underlying trabecular bone is a rich source of nutrients, and depletion of this nutrient reservoir may independently contribute to disc degeneration. For example, atherosclerosis of the arteries that supply the lumbar spine is associated with disc degeneration [71, 72], as are disorders that compromise microcirculation [73]. Likewise, extrinsic factors that lower circulation like vibration exposure and vasoactive substance use can also restrict nutrient transport into discs [74–76]. Aging appears to reduce endplate vascularity too. For example, vertebral hematopoietic (red) marrow undergoes conversion to fatty (yellow) marrow with aging (~6% per decade) [77], which decreases capillary density [78] and blood flow [79]. Animal models of disc degeneration meant to recapitulate the reductions in nutrient supply support the importance of these changes. In rabbits and rhesus macaques, for example, injection of vessel narrowing agents into the subchondral bone of the lumbar endplates caused progressive disc degeneration that mimicked the onset of disc degeneration in humans, including gradual disc height loss and increased matrix catabolism and disorganization [80, 81].

Depletion of the vertebral nutrient supply and reduced nutrient transport through the endplate may also impact the efficacy of disc regenerative therapies. Regenerative therapies have focused on transplanting new cells to produce disc matrix lost during degeneration, or by injecting genes, growth factors, or other small molecules to stimulate matrix synthesis or reduce catabolism and inflammation. However, all of these therapies require a rich nutrient environment to support higher metabolic demands and to ensure cell survival and proliferation. Since preclinical models used for development and testing do not mimic the nutrition limitations of a degenerated human disc, it remains unclear if these therapies can be successfully translated to the clinic.

Endplate damage

Structural damage to the endplate appears as morphologic irregularities on clinical imaging modalities such as X-ray radiographs and magnetic resonance (MR) images. Forms of damage have been described as fractures (Fig. 1E), erosions, Schmorl’s nodes, avulsions, calcification, and rim degeneration [33, 82, 83]. Depending on the imaging technique, the prevalence varies between nodes and erosions being most prevalent (22% and 14%) (Fig. 1C) to avulsions and rim degeneration (35% and 50%). In a recent histopathology study, Berg-Johansen *et al.* reported that ninety percent of avulsions were subclassified as “tidemark avulsions,” a form of endplate irregularity wherein the outer annulus separates from the vertebra at the enthesis tidemark [83] (Fig. 1B).

Morphological abnormalities of the endplate coincide with increasing severity of disc degeneration in the general population, supporting the belief that endplate damage has a causative role. In the TwinsUK cohort, total endplate damage score assigned to each disc on sagittal T2-weighted MR images was strongly and independently associated with degeneration (Pfirrmann grade) at every lumbar level [84]. The probability of having disc degeneration was significantly increased for individuals with the highest damage scores. Similarly, an earlier study by Feng *et al.* reported that the presence and size of endplate defects was associated with lower disc signal intensity, shorter disc height, and increased

disc bulging [85]. The magnitude of the association between endplate damage and disc degeneration appears to depend on the type of damage, being strongest for endplate erosions and weakest for Schmorl's nodes [86]. The same holds for associations between different types of endplate damage and pain [86], and together these findings suggest that different types of damage have different pathogenic origins and clinical effects [87].

Endplate damage may negatively affect disc health in a number of ways. Focal damage weakens the endplate and allows greater disc bulge into the vertebral body [88]. This increases the volume of space available to nucleus and decreases its pressure, which is sensitive to small changes in volume [89, 90]. To compensate for nucleus decompression, load bearing shifts from the NP to the AF and peak stresses in the outer AF increase [91]. The inner AF may also collapse inward [91] (Fig 1F) and thereby contribute to delamination and separation of the lamellae. Biologically, decompression is believed to hamper the maintenance of matrix homeostasis since abnormal pressures inhibit disc cell metabolism and accelerate matrix degradation [92–97]. In an *in vivo* pig model, endplate damage triggered structural and biological degenerative changes, including reductions in nucleus pressure and proteoglycan content and increases in annular delamination [98, 99]. In a rabbit disc explant model, endplate damage promoted lower anabolic gene expression (aggrecan) and higher catabolic (MMP-1, -3, -13) and pro-inflammatory gene expression (TNF-α, IL-6) [100]. Endplate damage could also compromise disc health by impairing solute transport into the disc. For example, using gadodiamide-enhanced MRI, Rajasekaran *et al.* noted non-uniform diffusion patterns in discs with breaks in the CEP and BEP [101], which suggests that focal breaks may shunt transport to regions of the disc that neighbor endplate damage while starving the more remote zones.

The relationship between endplate damage and disc health is complex and likely involves interplay between mechanical and biological factors. The use of advanced, non-invasive imaging techniques for evaluating endplate integrity may clarify the nature of these relationships. For example, conventional MR sequences used in the spine are unable to show the CEP because the cartilage has short T2 values, and thus, its signal is not captured by conventional sequences with long echo times. Newer sequences may overcome this limitation [102, 17, 103]. In particular, sequences with an ultra-short echo time (UTE) provide a clearer means of identifying and discriminating between different types of CEP defects.

Modic Changes

Endplate bone marrow lesions present on MRI as signal intensity changes, often referred to as Modic changes (MC). Modic *et al.* [104] and de Roos *et al.* [105] classified these changes based on the signal intensity of the bone marrow on sagittal T1-weighted and T2-weighted MR images. Endplate lesions with active inflammation and fibrovascular replacement of the hematopoietic marrow appear hyperintense on T2-weighted images and hypointense on T1-weighted images (type 1 changes; MC1); lesions with fatty replacement of the marrow appear hyperintense on both T2- and T1-weighted images (type 2 changes; MC2); lesions with sclerotic subchondral bone appear hypointense on both T2- and T1-weighted images (type 3 changes; MC3).

MC are highly associated with adjacent endplate damage [33, 85, 106]. For example, in a cohort of low back pain patients, Kerttula *et al.* noted 96% of MC1 were associated with adjacent endplate damage [106]. Although the precise etiology remains unclear, bone marrow lesions are believed to result from inflammatory constituents that diffuse from the adjacent discs [107, 108], which may be promoted at sites of endplate damage. Endplate damage compromises the immune privilege of the healthy disc, and allows comingling of disc material and the quiescent bone marrow. This mixing is amplified by hydraulic pressures induced by cyclic disc loading from activities of daily living.

Cell culture studies demonstrate that cross-talk between the nucleus pulposus and the bone marrow triggers a pro-inflammatory immune response, with the expression of pro-inflammatory (IL-1, -6, -10) and neurotrophic factors (TRK-A)[109]. When nucleus is transplanted into healthy vertebrae, T cells are recruited and bone marrow lesions develop [109]. Biopsies from MC regions of patients with low back pain show pro-osteoclastic and fibrogenic changes, dysregulated myelopoiesis and upregulation of neurotrophic factors [110]. Correlated fibrogenic and pro-inflammatory gene expression between MC bone marrow and adjacent discs further supports the concept that vertebra/disc crosstalk is an etiologic factor in the development of endplate bone marrow lesions. Along with fibrovascular bone marrow conversion adjacent to endplate damage, there is also increased osteoclastic activity and high bone turnover [111], which likely triggers endplate erosion and progression.

In addition to the immunologic basis for endplate bone marrow lesions, another possible etiology is occult discitis, in particular with *Proprionibacterium acnes*. *P. acnes* is thought to enter the disc from the vasculature at sites of endplate damage. Once inside, *P. acnes* can proliferate within the disc, induce degeneration, and cause fibrovascular changes in the adjacent bone marrow that appear as MC1 [112–114].

MC are significantly associated with chronic low back pain [115]. MC1 appear to be especially painful and correlate with persistence of symptoms [116–121]. This is likely because fibrovascular marrow is richly innervated by nociceptive fibers [122, 33, 123], which may be sensitized by inflammatory agents and stress concentrations present at these sites.

Endplate bone marrow changes also associate with accelerated disc degeneration [106, 124, 125]. In a longitudinal study with a follow-up of 11–18 months, unstable MC1 coincided with accelerated adjacent disc degeneration including decrease in disc height, change in signal intensity of the NP, and deformation of the bony endplates. By comparison, disc degeneration in the absence of MC 1 was slower [106]. Another study with over 4 years follow-up, showed that presence of more severe endplate erosions at baseline was significantly associated with progression of disc degeneration (OR = 2.32; CI = 1.07–5.01, $p = 0.03$). Although presence of baseline MC anticipated progression of disc degeneration (OR = 2.59; CI = 0.93–7.26, $p = 0.07$), MC progression was more significantly associated with disc degeneration progression (OR = 12.25; CI = 1.49–100.6, $p = 0.02$) [125].

5. Summary

The endplate must balance opposing mechanical and biological functions, and failure of either of these functions associates with disc degeneration. Yet, it remains unclear if endplate damage and degeneration (calcification, water loss, *etc.*) causes physiologic, age-related disc degeneration or results from it. As a result, a recent trend in endplate research is evaluation of longitudinal clinical data using grading schemes that focus on endplate damage and its association with changes in disc height, NP signal intensity, and Modic changes. Growing evidence from these studies indicates that endplate damage can cause pathologic changes to the adjacent vertebrae and discs, including bone marrow lesions and accelerated disc degeneration, respectively. Developments in clinical imaging that enable accessible, quantitative, and more precise evaluation of endplate mechanical integrity and adjacent bone marrow composition may clarify the correlative *vs.* causative nature of endplate damage, and importantly, facilitate longitudinal measurements that can be related to symptom progression. These developments will also be important for designing and testing new treatments that target degeneration mechanisms and pain sources arising from pathologic endplate function. Finally, additional work is also required to determine the molecular and mechanical mechanisms governing endplate damage and degeneration; their impact on the progression of bone marrow lesions and disc degeneration; and their implications for disc regenerative therapies and for therapies that target endplate-related endplate pain.

Acknowledgements

This work was supported by the National Institutes of Health (AJF: AR070198; JCL: R01 AR063705).

Aaron J. Fields reports a grant from the National Institutes of Health (NIH/NIAMS R01 AR070198).

References

1. Ringwalt C, Gugelmann H, Garrettson M, Dasgupta N, Chung AE, Proescholdbell SK et al. Differential prescribing of opioid analgesics according to physician specialty for Medicaid patients with chronic noncancer pain diagnoses. Pain Res Manag 2014;19(4):179–85. [PubMed: 24809067]
2. Chou D, Samartzis D, Bellabarba C, Patel A, Luk KD, Kisser JM et al. Degenerative magnetic resonance imaging changes in patients with chronic low back pain: a systematic review. Spine 2011;36(21 Suppl):S43–53. [PubMed: 21952189]
3. Setton LA, Chen J. Mechanobiology of the intervertebral disc and relevance to disc degeneration. J Bone Joint Surg Am 2006;88 Suppl 2:52–7. [PubMed: 16595444]
4. Lotz JC. Animal models of intervertebral disc degeneration: lessons learned. Spine (Phila Pa 1976) 2004;29(23):2742–50. [PubMed: 15564923]
5. Adams MA, Dolan P, Hutton WC. The stages of disc degeneration as revealed by discograms. J Bone Joint Surg Br 1986;68(1):36–41. [PubMed: 3941139]
6. Horner HA, Urban JP. 2001 Volvo Award Winner in Basic Science Studies: Effect of nutrient supply on the viability of cells from the nucleus pulposus of the intervertebral disc. Spine 2001;26(23): 25439.
7. 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(2):166–74. [PubMed: 2922637]
8. Edwards WT, Zheng YG, Ferrara LA, Yuan HA. Structural features and thickness of the vertebral cortex in the thoracolumbar spine. Spine 2001;26(2):218–25. [PubMed: 11154545]

9. Fields AJ, Sahli Costabal 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(21):E1310–7. [PubMed: 22781006]
10. Rodriguez AG, Rodriguez-Soto AE, Burghardt AJ, Berven S, Majumdar S, Lotz JC. Morphology of the human vertebral endplate. J Orthop Res 2011.
11. Silva MJ, Wang C, Keaveny TM, Hayes WC. Direct and computed-tomography thickness measurements of the human lumbar vertebral shell and end-plate. Bone 1994;15(4):409–14. [PubMed: 7917579]
12. 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(2):372–9. [PubMed: 19049912]
13. Berg-Johansen B, Han M, Fields AJ, Liebenberg EC, Lim BJ, Larson PE et al. Cartilage Endplate Thickness Variation Measured by Ultrashort Echo-Time MRI Is Associated With Adjacent Disc Degeneration. Spine (Phila Pa 1976) 2018;43(10):E592–E600. [PubMed: 28984733]
14. Rodriguez AG, Slichter CK, Acosta FL, Rodriguez-Soto AE, Burghardt AJ, Majumdar S et al. Human disc nucleus properties and vertebral endplate permeability. Spine 2011;36(7):512–20. [PubMed: 21240044]
15. Fields AJ, Rodriguez D, Gary KN, Liebenberg EC, Lotz JC. Influence of biochemical composition on endplate cartilage tensile properties in the human lumbar spine. J Orthop Res 2014;32(2):245–52. [PubMed: 24273192]
16. 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(9):1030–8. [PubMed: 1948394]
17 •. Fields AJ, Han M, Krug R, Lotz JC. Cartilaginous end plates: quantitative MR imaging with very short echo times-orientation dependence and correlation with biochemical composition. Radiology 2015;274(2):482–9. This study demonstrated that T2* relaxation times of human CEP tissue were highly correlated with glycosaminoglycan content, the ratio of collagen:glycosaminoglycan contents, and water content. Owing to magic angle effects, the accuracy of T2*-based estimates of biochemical composition depended on the orientation of the CEPs; accuracy was greatest at ~55°, which approximates the orientation of the L4-S1 CEPs. [PubMed: 25302832]
18 •. Wu Y, Cisewski SE, Wegner N, Zhao S, Pellegrini VD, Jr., Slate EH et al. Region and straindependent diffusivities of glucose and lactate in healthy human cartilage endplate. J Biomech 2016;49(13):2756–62. This study reported that the diffusivities of glucose and lactate in the human CEP were significantly correlated with matrix porosity. The highest diffusivities were measured in CEP tissues belonging to the central region adjacent to the NP and under lower compressive strains. [PubMed: 27338525]
19. Paietta RC, Burger E, Ferguson VL. Mineralization and collagen orientation throughout aging at the vertebral endplate in the human lumbar spine. J Struct Biol 2013.
20. Reiser KM, Bratton C, Yankelevich DR, Knoesen A, Rocha-Mendoza I, Lotz J. Quantitative analysis of structural disorder in intervertebral disks using second harmonic generation imaging: comparison with morphometric analysis. J Biomed Opt 2007;12(6):064019. [PubMed: 18163835]
21. 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(8):1225–32. [PubMed: 21327814]
22 •. Berg-Johansen B, Fields AJ, Liebenberg EC, Li A, Lotz JC. Structure-function relationships at the human spinal disc-vertebra interface. J Orthop Res 2018;36(1):192–201. This study used excised bone-annulus-bone samples and observed a high proportion of structural failures at the CEP-bone interface in the inner annulus region, which coincided with poor integration between the CEP and bone. After initial failure at the CEP-bone interface, the failure surface propagated to the outer annulus region, where secondary failures were observed within the annulus or bone. Firm anchoring between the annulus and bone in the outer annulus region was believed to explain the shift from interface failure to tissue substance failure. These failure mechanisms may be important for clarifying factors that are predictive of herniation risk. [PubMed: 28590060]

23. Benjamin M, Toumi H, Ralphs JR, Bydder G, Best TM, Milz S. Where tendons and ligaments meet bone: attachment sites ('entheses') in relation to exercise and/or mechanical load. J Anat 2006;208(4):471–90. [PubMed: 16637873]
24. Locke RC, Peloquin JM, Lemmon EA, Szostek A, Elliott DM, Killian ML. Strain Distribution of Intact Rat Rotator Cuff Tendon-to-Bone Attachments and Attachments With Defects. J Biomech Eng 2017;139(11).
25. 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(3):263–70. [PubMed: 21223256]
26. Crock HV, Yoshizawa H. The blood supply of the lumbar vertebral column. Clinical orthopaedics and related research 1976(115):6–21.
27. Oki S, Matsuda Y, Itoh T, Shibata T, Okumura H, Desaki J. Scanning electron microscopic observations of the vascular structure of vertebral end-plates in rabbits. J Orthop Res 1994;12(3): 447–9. [PubMed: 8207599]
28. Edgar MA. The nerve supply of the lumbar intervertebral disc. J Bone Joint Surg Br 2007;89(9): 1135–9. [PubMed: 17905946]
29. Bogduk N, Tynan W, Wilson AS. The nerve supply to the human lumbar intervertebral discs. J Anat 1981;132(Pt 1):39–56. [PubMed: 7275791]
30. 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(23):2570–6. [PubMed: 14652473]
31. 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(3):246–52. [PubMed: 10580532]
32. Antonacci MD, Mody DR, Heggeness MH. Innervation of the human vertebral body: a histologic study. J Spinal Disord 1998;11(6):526–31. [PubMed: 9884299]
33. Fields AJ, Liebenberg EC, Lotz JC. Innervation of pathologies in the lumbar vertebral end plate and intervertebral disc. Spine J 2014;14(3):513–21. [PubMed: 24139753]
34. Ohshima H, Tsuji H, Hirano N, Ishihara H, Katoh Y, Yamada H. Water diffusion pathway, swelling pressure, and biomechanical properties of the intervertebral disc during compression load. Spine 1989;14(11):1234–44. [PubMed: 2603057]
35. Urban JP, Holm S, Maroudas A, Nachemson A. Nutrition of the intervertebral disk. An in vivo study of solute transport. Clinical orthopaedics and related research 1977(129):101–14.
36. 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(1):113–30. [PubMed: 1184452]
37. 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(6):589607.
38. Crock HV, Goldwasser M. Anatomic studies of the circulation in the region of the vertebral end-plate in adult Greyhound dogs. Spine 1984;9(7):702–6. [PubMed: 6505840]
39. Urban JP, Holm S, Maroudas A, Nachemson A. Nutrition of the intervertebral disc: effect of fluid flow on solute transport. Clinical orthopaedics and related research 1982(170):296–302.
40. Katz MM, Hargens AR, Garfin SR. Intervertebral disc nutrition. Diffusion versus convection. Clinical orthopaedics and related research 1986(210):243–5.
41. Ferguson SJ, Ito K, Nolte LP. Fluid flow and convective transport of solutes within the intervertebral disc. J Biomech 2004;37(2):213–21. [PubMed: 14706324]
42. Gullbrand SE, Peterson J, Ahlborn J, Mastropolo R, Fricker A, Roberts TT et al. Dynamic LoadingInduced Convective Transport Enhances Intervertebral Disc Nutrition. Spine 2015;40(15): 1158–64. [PubMed: 26222661]
43. Ayotte DC, Ito K, Tepic S. Direction-dependent resistance to flow in the endplate of the intervertebral disc: an ex vivo study. J Orthop Res 2001;19(6):1073–7. [PubMed: 11781007]
44. Brinckmann P, Frobin W, Hierholzer E, Horst M. Deformation of the vertebral end-plate under axial loading of the spine. Spine 1983;8(8):851–6. [PubMed: 6670020]

45. Rolander SD, Blair WE. Deformation and fracture of the lumbar vertebral end plate. Orthop Clin North Am 1975;6(1):75–81. [PubMed: 1113982]

46. Yoganandan N, Maiman DJ, Pintar F, Ray G, Myklebust JB, Sances A, Jr. et al. Microtrauma in the lumbar spine: a cause of low back pain. Neurosurgery 1988;23(2):162–8. [PubMed: 2972940]

47. Hulme PA, Boyd SK, Ferguson SJ. Regional variation in vertebral bone morphology and its contribution to vertebral fracture strength. Bone 2007;41(6):946–57. [PubMed: 17913613]

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(3):267–78. [PubMed: 16651220]

49. Dudli S, Enns-Bray W, Pauchard Y, Rommeler A, Fields AJ, Ferguson SJ et al. Larger vertebral endplate concavities cause higher failure load and work at failure under high-rate impact loading of rabbit spinal explants. J Mech Behav Biomed Mater 2018;80:104–10. [PubMed: 29414464]

50. O'Connell GD, Johannessen W, Vresilovic EJ, Elliott DM. Human internal disc strains in axial compression measured noninvasively using magnetic resonance imaging. Spine 2007;32(25): 2860–8. [PubMed: 18246009]

51. Fields AJ, Lee GL, Keaveny TM. Mechanisms of initial endplate failure in the human vertebral body. J Biomech 2010;43:3126–31. [PubMed: 20817162]

52 •. DeLucca JF, Cortes DH, Jacobs NT, Vresilovic EJ, Duncan RL, Elliott DM. Human cartilage endplate permeability varies with degeneration and intervertebral disc site. J Biomech 2016;49(4):550–7. This study is important since it observed 50–60% reductions in human CEP permeability with disc degeneration. The authors also reported that collagen fiber reinforcement of the CEP tissue may play important roles in its biomechanical and transport properties. [PubMed: 26874969]

53. Veres SP, Robertson PA, Broom ND. ISSLS prize winner: how loading rate influences disc failure mechanics: a microstructural assessment of internal disruption. Spine 2010;35(21):1897–908. [PubMed: 20838275]

54. Rodrigues SA, Wade KR, Thambyah A, Broom ND. Micromechanics of annulus-end plate integration in the intervertebral disc. Spine J 2012;12(2):143–50. [PubMed: 22326995]

55. Tanaka M, Nakahara S, Inoue H. A pathologic study of discs in the elderly. Separation between the cartilaginous endplate and the vertebral body. Spine 1993;18(11):1456–62. [PubMed: 8235816]

56. Rajasekaran S, Bajaj N, Tubaki V, Kanna RM, Shetty AP. ISSLS Prize Winner: The Anatomy of Failure in Lumbar Disc Herniation: An In Vivo, Multimodal, Prospective Study of 181 Subjects. Spine 2013;38(17):1491–500. [PubMed: 23680832]

57. Vernon-Roberts B, Moore RJ, Fraser RD. The natural history of age-related disc degeneration: the pathology and sequelae of tears. Spine 2007;32(25):2797–804. [PubMed: 18246000]

58. Aoki J, Yamamoto I, Kitamura N, Sone T, Itoh H, Torizuka K et al. End plate of the discovertebral joint: degenerative change in the elderly adult. Radiology 1987;164(2):411–4. [PubMed: 3602378]

59. Bernick S, Cailliet R. Vertebral end-plate changes with aging of human vertebrae. Spine 1982;7(2): 97–102. [PubMed: 7089697]

60. Boos N, Weissbach S, Rohrbach H, Weiler C, Spratt KF, Nerlich AG. Classification of age-related changes in lumbar intervertebral discs: 2002 Volvo Award in basic science. Spine 2002;27(23): 263144.

61. 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(2):167–73. [PubMed: 15644751]

62 ••. Grant MP, Epure LM, Bokhari R, Roughley P, Antoniou J, Mwale F. Human cartilaginous endplate degeneration is induced by calcium and the extracellular calcium-sensing receptor in the intervertebral disc. Eur Cell Mater 2016;32:137–51. This study showed that calcium content was significantly higher in CEP tissues adjacent to more severely degenerated discs. Importantly, increasing the concentration of calcium caused reductions in the secretion and accumulation of collagens and proteoglycan in cultured human CEP cells. Calcium supplementation reduced glucose diffusion and induced disc degeneration in a bovine organ culture model. [PubMed: 27452962]

63. Bishop PB, Pearce RH. The proteoglycans of the cartilaginous end-plate of the human intervertebral disc change after maturity. J Orthop Res 1993;11(3):324–31. [PubMed: 8326438]
64. Antoniou J, Goudsouzian NM, Heathfield TF, Winterbottom N, Steffen T, Poole AR 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(10):1153–61. [PubMed: 8727189]
65. Bibby SR, Urban JP. Effect of nutrient deprivation on the viability of intervertebral disc cells. Eur Spine J 2004;13(8):695–701. [PubMed: 15048560]
66. Holm S, Maroudas A, Urban JP, Selstam G, Nachemson A. Nutrition of the intervertebral disc: solute transport and metabolism. Connect Tissue Res 1981;8(2):101–19. [PubMed: 6453689]
67. Ishihara H, Urban JP. Effects of low oxygen concentrations and metabolic inhibitors on proteoglycan and protein synthesis rates in the intervertebral disc. J Orthop Res 1999;17(6):829–35. [PubMed: 10632449]
68. Razaq S, Wilkins RJ, Urban JP. The effect of extracellular pH on matrix turnover by cells of the bovine nucleus pulposus. Eur Spine J 2003;12(4):341–9. [PubMed: 12883962]
69. Urban JP, Smith S, Fairbank JC. Nutrition of the intervertebral disc. Spine 2004;29(23):2700–9. [PubMed: 15564919]
70. Shirazi-Adl A, Taheri M, Urban JP. Analysis of cell viability in intervertebral disc: Effect of endplate permeability on cell population. J Biomech 2010;43(7):1330–6. [PubMed: 20167323]
71. Kauppila LI. Atherosclerosis and disc degeneration/low-back pain--a systematic review. Eur J Vasc Endovasc Surg 2009;37(6):661–70. [PubMed: 19328027]
72. Tokuda O, Okada M, Fujita T, Matsunaga N. Correlation between diffusion in lumbar intervertebral disks and lumbar artery status: evaluation with fresh blood imaging technique. J Magn Reson Imaging 2007;25(1):185–91. [PubMed: 17152057]
73. Grunhagen T, Shirazi-Adl A, Fairbank JC, Urban JP. Intervertebral disk nutrition: a review of factors influencing concentrations of nutrients and metabolites. Orthop Clin North Am 2011;42(4):465–77, vii. [PubMed: 21944584]
74. Holm S, Nachemson A. Nutrition of the intervertebral disc: acute effects of cigarette smoking. An experimental animal study. Ups J Med Sci 1988;93(1):91–9. [PubMed: 3376356]
75. Rajasekaran S, Venkatadass K, Naresh Babu J, Ganesh K, Shetty AP. Pharmacological enhancement of disc diffusion and differentiation of healthy, ageing and degenerated discs : Results from in-vivo serial post-contrast MRI studies in 365 human lumbar discs. Eur Spine J 2008;17(5):626–43. [PubMed: 18357472]
76. Turgut M, Uysal A, Uslu S, Tavus N, Yurtseven ME. The effects of calcium channel antagonist nimodipine on end-plate vascularity of the degenerated intervertebral disc in rats. J Clin Neurosci 2003;10(2):219–23. [PubMed: 12637054]
77. 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(3):703–9. [PubMed: 14593190]
78. Whitby LEH, Britton CJC. Disorders of the blood: diagnosis, pathology, treatment and technique New York: Grune & Stratton; 1963.
79. Drescher W, Li H, Qvesel D, Jensen SD, Flo C, Hansen ES et al. Vertebral blood flow and bone mineral density during long-term corticosteroid treatment: An experimental study in immature pigs. Spine 2000;25(23):3021–5. [PubMed: 11145813]
80. Wei F, Zhong R, Pan X, Khaleel M, Hammoud A, Zhou Z et al. Computed Tomography Guided Subendplate Injection of Pingyangmycin for A Novel Rabbit Model of Slowly Progressive Disc Degeneration. Spine J 2015.
81. Wei F, Zhong R, Wang L, Zhou Z, Pan X, Cui S et al. Pingyangmycin-induced in vivo lumbar disc degeneration model of rhesus monkeys. Spine (Phila Pa 1976) 2015;40(4):E199–210. [PubMed: 25679953]
82. Wang Y, Videman T, Battie MC. Lumbar vertebral endplate lesions: prevalence, classification, and association with age. Spine (Phila Pa 1976) 2012;37(17):1432–9. [PubMed: 22333959]
83. Berg-Johansen B, Jain D, Liebenberg EC, Fields AJ, Link TM, O'Neill CW et al. Tidemark Avulsions are a Predominant Form of Endplate Irregularity. Spine (Phila Pa 1976) 2018.

84 ••. Rade M, Maatta JH, Freidin MB, Airaksinen O, Karppinen J, Williams FMK. Vertebral Endplate Defect as Initiating Factor in Intervertebral Disc Degeneration: Strong Association Between Endplate Defect and Disc Degeneration in the General Population. Spine (Phila Pa 1976) 2018;43(6):412–9. This analysis of MR images from the TwinsUK cohort showed that total endplate damage score assigned to each disc was strongly and independently associated with degeneration severity. The probability of having disc degeneration was significantly increased for individuals with the highest damage scores. These findings are important since they suggest that endplate damage has a causative role in disc degeneration. [PubMed: 28749857]

85 ••. Feng Z, Liu Y, Yang G, Battie MC, Wang Y. Lumbar Vertebral Endplate Defects on Magnetic Resonance Images: Classification, Distribution Patterns, and Associations with Modic Changes and Disc Degeneration. Spine (Phila Pa 1976) 2017 This study found that the presence and size of endplate defects was associated with increased severity of disc degeneration, including lower disc signal intensity, shorter disc height, and increased disc bulging. Importantly, endplate defects and MCs had similar distribution patterns, and the presence and size of endplate defects were associated with the presence of MCs (OR = 4.29, $p<0.001$). These findings suggest that endplate defects may play an etiologic role in bone marrow lesions seen on MRI, i.e. Modic changes.

86. Wang Y, Videman T, Battie MC. ISSLS prize winner: Lumbar vertebral endplate lesions: associations with disc degeneration and back pain history. Spine 2012;37(17):1490–6. [PubMed: 22648031]

87. Lotz JC, Fields AJ, Liebenberg EC. The Role of the Vertebral End Plate in Low Back Pain. Global Spine J 2013;3(3):153–64. [PubMed: 24436866]

88. Brinckmann P, Horst M. The influence of vertebral body fracture, intradiscal injection, and partial discectomy on the radial bulge and height of human lumbar discs. Spine 1985;10(2):138–45. [PubMed: 4002037]

89. Ranu HS. Multipoint determination of pressure-volume curves in human intervertebral discs. Ann Rheum Dis 1993;52(2):142–6. [PubMed: 8447694]

90. Dolan P, Luo J, Pollintine P, Landham PR, Stefanakis M, Adams MA. Intervertebral disc decompression following endplate damage: implications for disc degeneration depend on spinal level and age. Spine (Phila Pa 1976) 2013;38(17):1473–81. [PubMed: 23486408]

91. Adams MA, Freeman BJ, Morrison HP, Nelson IW, Dolan P. Mechanical initiation of intervertebral disc degeneration. Spine 2000;25(13):1625–36. [PubMed: 10870137]

92. Hsieh AH, Lotz JC. Prolonged spinal loading induces matrix metalloproteinase-2 activation in intervertebral discs. Spine (Phila Pa 1976) 2003;28(16):1781–8. [PubMed: 12923463]

93. Walsh AJ, Lotz JC. Biological response of the intervertebral disc to dynamic loading. J Biomech 2004;37(3):329–37. [PubMed: 14757452]

94. 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(10):1085–91. [PubMed: 9160466]

95. 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(3):839–46. [PubMed: 8964745]

96. Chan SC, Ferguson SJ, Wuertz K, Gantenbein-Ritter B. Biological response of the intervertebral disc to repetitive short-term cyclic torsion. Spine (Phila Pa 1976) 2011;36(24):2021–30. [PubMed: 21343864]

97. Kasra M, Merryman WD, Loveless KN, Goel VK, Martin JD, Buckwalter JA. Frequency response of pig intervertebral disc cells subjected to dynamic hydrostatic pressure. J Orthop Res 2006;24(10):1967–73. [PubMed: 16900539]

98. Holm S, Baranto A, Kaigle Holm A, Ekstrom L, Sward L, Hansson T et al. Reactive changes in the adolescent porcine spine with disc degeneration due to endplate injury. Vet Comp Orthop Traumatol 2007;20(1):12–7. [PubMed: 17364090]

99. Holm S, Holm AK, Ekstrom L, Karladani A, Hansson T. Experimental disc degeneration due to endplate injury. J Spinal Disord Tech 2004;17(1):64–71. [PubMed: 14734978]

100. Dudli S, Haschtmann D, Ferguson SJ. Fracture of the vertebral endplates, but not equienergetic impact load, promotes disc degeneration in vitro. J Orthop Res 2012;30(5):809–16. [PubMed: 22025207]

101. 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(23):2654–67. [PubMed: 15564914]

102. Bae WC, Statum S, Zhang Z, Yamaguchi T, Wolfson T, Gamst AC et al. Morphology of the cartilaginous endplates in human intervertebral disks with ultrashort echo time MR imaging. Radiology 2013;266(2):564–74. [PubMed: 23192776]

103. Moon SM, Yoder JH, Wright AC, Smith LJ, Vresilovic EJ, Elliott DM. Evaluation of intervertebral disc cartilaginous endplate structure using magnetic resonance imaging. Eur Spine J 2013;22(8):1820–8. [PubMed: 23674162]

104. 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):193–9. [PubMed: 3336678]

105. de Roos A, Kressel H, Spritzer C, Dalinka M. MR imaging of marrow changes adjacent to end plates in degenerative lumbar disk disease. AJR Am J Roentgenol 1987;149(3):531–4. [PubMed: 3497539]

106. Kerttula L, Luoma K, Vehmas T, Gronblad M, Kaapa E. Modic type I change may predict rapid progressive, deforming disc degeneration: a prospective 1-year follow-up study. Eur Spine J 2012;21(6):1135–42. [PubMed: 22249308]

107. Crock HV. Internal disc disruption. A challenge to disc prolapse fifty years on. Spine 1986;11(6): 650–3. [PubMed: 3787337]

108. Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. Eur Spine J 2016;25(11):3723–34. [PubMed: 26914098]

109. Dudli S, Liebenberg E, Magnitsky S, Lu B, Lauricella M, Lotz JC. Modic type 1 change is an autoimmune response that requires a proinflammatory milieu provided by the 'Modic disc'. Spine J 2018;18(5):831–44. [PubMed: 29253635]

110 ••. Dudli S, Sing DC, Hu SS, Berven SH, Burch S, Deviren V et al. ISSLS PRIZE IN BASIC SCIENCE 2017: Intervertebral disc/bone marrow cross-talk with Modic changes. Eur Spine J 2017 This study analyzed relative gene expression profiles of matched marrow and disc samples from levels with and without Modic changes. The results showed fibrogenic and pro-inflammatory crosstalk between MC bone marrow and adjacent discs, which provides insight into the pain generator at MC levels and informs novel therapeutic targets for treatment of MC-associated LBP.

111. Perilli E, Parkinson IH, Truong LH, Chong KC, Fazzalari NL, Osti OL. Modic (endplate) changes in the lumbar spine: bone micro-architecture and remodelling. Eur Spine J 2015;24(9):1926–34. [PubMed: 25063369]

112. Dudli S, Miller S, Demir-Deviren S, Lotz JC. Inflammatory response of disc cells against Propionibacterium acnes depends on the presence of lumbar Modic changes. Eur Spine J 2018;27(5):1013–20. [PubMed: 28884220]

113. Chen Z, Zheng Y, Yuan Y, Jiao Y, Xiao J, Zhou Z et al. Modic Changes and Disc Degeneration Caused by Inoculation of Propionibacterium acnes inside Intervertebral Discs of Rabbits: A Pilot Study. Biomed Res Int 2016;2016:9612437. [PubMed: 26925420]

114. Patel KB, Poplawski MM, Pawha PS, Naidich TP, Tanenbaum LN. Diffusion-weighted MRI "claw sign" improves differentiation of infectious from degenerative modic type 1 signal changes of the spine. AJNR Am J Neuroradiol 2014;35(8):1647–52. [PubMed: 24742801]

115. Mok FP, Samartzis D, Karppinen J, Fong DY, Luk KD, Cheung KM. Modic changes of the lumbar spine: prevalence, risk factors, and association with disc degeneration and low back pain in a largescale population-based cohort. Spine J 2016;16(1):32–41. [PubMed: 26456851]

116. 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(3):849–55. [PubMed: 19244050]

117. Jensen TS, Bendix T, Sorensen JS, Manniche C, Korsholm L, Kjaer P. Characteristics and natural course of vertebral endplate signal (Modic) changes in the Danish general population. BMC Musculoskelet Disord 2009;10:81. [PubMed: 19575784]

118. Jensen TS, Karppinen J, Sorensen JS, Niinimaki J, Leboeuf-Yde C. Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with nonspecific low back pain. Eur Spine J 2008;17(11):1407–22. [PubMed: 18787845]

119. Kaapa E, Luoma K, Pitkaniemi J, Kerttula L, Gronblad M. Correlation of size and type of modic types 1 and 2 lesions with clinical symptoms: a descriptive study in a subgroup of patients with chronic low back pain on the basis of a university hospital patient sample. Spine (Phila Pa 1976) 2012;37(2):134–9. [PubMed: 21415809]

120. Kuisma M, Karppinen J, Niinimaki J, Ojala R, Haapea M, Heliovaara M et al. Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. Spine (Phila Pa 1976) 2007;32(10):1116–22. [PubMed: 17471095]

121. Jarvinen J, Karppinen J, Niinimaki J, Haapea M, Gronblad M, Luoma K et al. Association between changes in lumbar Modic changes and low back symptoms over a two-year period. BMC Musculoskelet Disord 2015;16:98. [PubMed: 25897658]

122. Brown MF, Hukkanen MV, McCarthy ID, Redfern DR, Batten JJ, Crock HV et al. Sensory and sympathetic innervation of the vertebral endplate in patients with degenerative disc disease. J Bone Joint Surg Br 1997;79(1):147–53. [PubMed: 9020464]

123. Ohtori S, Inoue G, Ito T, Koshi T, Ozawa T, Doya H 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(9):1026–31. [PubMed: 16641780]

124. Luoma K, Vehmas T, Kerttula L, Gronblad M, Rinne E. Chronic low back pain in relation to Modic changes, bony endplate lesions, and disc degeneration in a prospective MRI study. Eur Spine J 2016;25(9):2873–81. [PubMed: 27480265]

125. Farshad-Amacker NA, Hughes A, Herzog RJ, Seifert B, Farshad M. The intervertebral disc, the endplates and the vertebral bone marrow as a unit in the process of degeneration. Eur Radiol 2017;27(6):2507–20. [PubMed: 27709276]

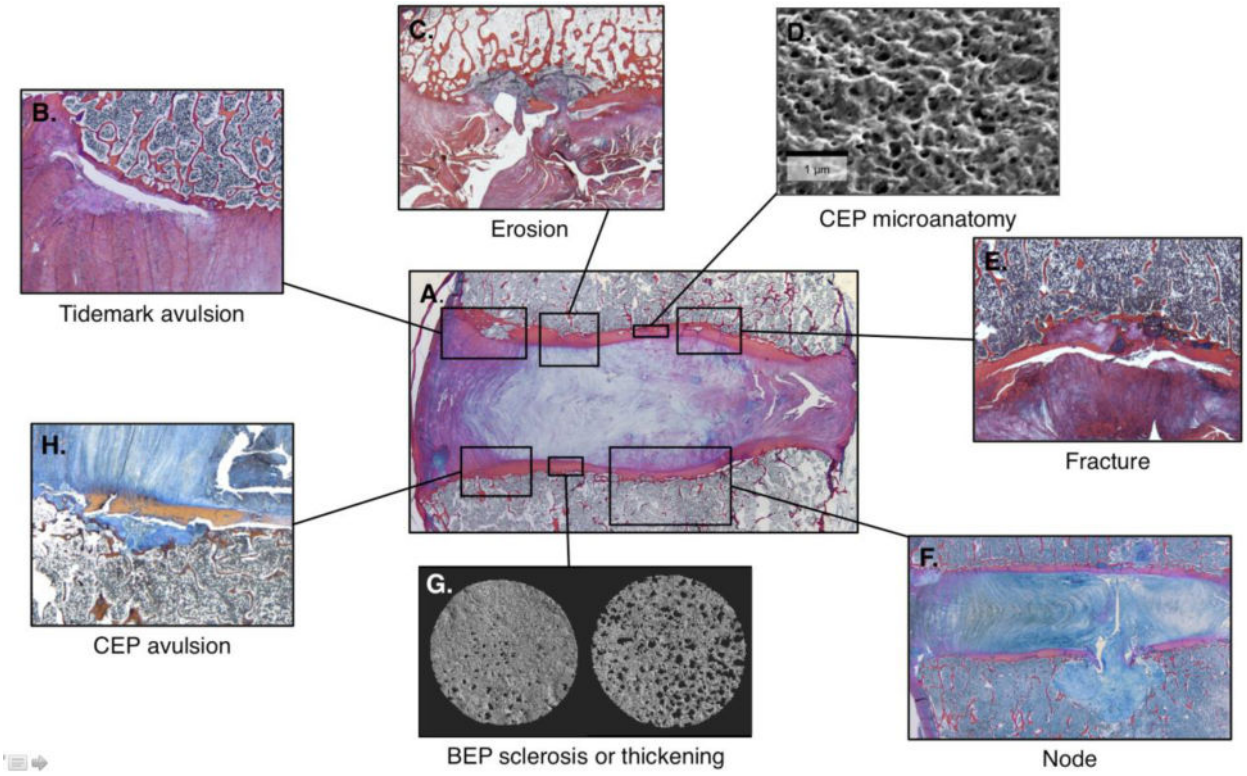

Figure 1.

(A) In a healthy spine, the endplate, including cartilage and bone, forms a continuous interface between the disc and vertebral body. Structural defects and degenerative changes may include: **(B)** tidemark avulsions of the outer annulus at the vertebral rim; **(C)** erosions of the cartilage endplate and/or underlying endplate bone; **(D)** changes to the cartilage matrix, including calcification, dehydration, and loss of matrix protein homeostasis; **(E)** fissuring and fracture of the bony endplate; **(F)** herniation of the nucleus pulposus into the underlying trabecular bone and subsequent depressurization of the disc with inward bulging of the annulus; **(G)** sclerosis or thickening of the bony endplate (note: samples are 8.25 mm diameter); **(H)** avulsion of the cartilage endplate at the inner annulus-endplate junction with fibrovascular bone marrow lesion.