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Contribution of the endplates to disc degeneration

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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

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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

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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 $30 \times 10^{-10} \text{ m}^4/\text{N-s}$ [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 $1.2 \times 10^{-10} \text{ m}^4/\text{N-s}$) [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 ($26.8 \pm 9.3 \mu\text{m}^2/\text{s}$) and lactate diffusivity ($45.2 \pm 14.7 \mu\text{m}^2/\text{s}$) 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 ($\text{pH} < 6.3$) 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 entheses 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 *Propionibacterium 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.

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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.