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SURGERY

The Endplate and Trabecular Bone in Lumbar Degenerative Disc Disease: A Narrative Review

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Abstract

To review the current knowledge surrounding degenerative disc disease focusing on the changes taking place in the end plate and trabecular bone. A narrative review of the current literature. An age-related reduction in blood supply to the disc contributes to tissue degradation. Degeneration, separate from this process, represents a disruption of the normal homeostasis. A process of vascular and sensory nerve in-growth in the annulus and localised areas of the end plate is associated with markers of inflammation and may represent a pain source. Treatment with local anti-inflammatories has, at best, mixed results. Bone mechanical indentation testing has been used to classify changes in ageing and degeneration demonstrating a location-dependant reduction in strength specific to each process. Modic changes include a process of inflammation, alteration of the mechanical and chemical environment and changes in bone turnover. The underlying cause for their development has multiple explanations including mechanical overload and microfracture, infection and inflammation in response to herniation of disc material through the end plate. We do know, however, that they seem to be at least partially reversible and not all are symptomatic. This reversibility potentially indicates an avenue of exploration for therapy. Restoring the complex balance of disc homeostasis may hold some promise and will rely on greater understanding of the pathological and material changes occurring at the disc-bone interface and their correlation with clinical imaging. Current treatment may be optimised with an understanding of the mechanical environment of the disc in patient subgroups.

Keywords Back pain · Disc degeneration · Modic changes · Histology

Introduction

Low back pain is an established and significant health problem [1] with not only health but also with economic impacts. Wynne-Jones used pooled estimates to find 32% of the working age population suffering with low back pain will not have returned to work after 1 month [2]. In Europe the economic cost of back pain due to time lost from work is estimated to be €12 billion, affecting up to 47% of working age men [3]. Cheung et al. found that 40% of those under 30 displayed MRI evidence of lumbar disc degeneration which increased to 90% by 55 years of age [4]; they also found a strong correlation between disc degeneration and low back pain.

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The adult intervertebral disc is avascular, relying on the adjacent vertebral endplate for nutritional support [5, 6]. Macroscopically the disc consists of an outer annulus and a central nucleus. The annulus connects to the end plate which consists of cartilaginous and bony portions.

Degeneration of the intervertebral disc and its adjacent end plates is complex and multifactorial with genetic and environmental influences [7, 8]. We know from previous work that the disc undergoes an ageing process, and distinguishing this from degeneration can be difficult [9]. Dehydration of the disc can be a normal part of this ageing process [10]. Dehydration has been shown to significantly alter the stress transfer to the end plate causing fracture and remodelling altering the nutrient transfer further contributing to degeneration [11]. In the degenerative disc, it has been shown that the density of neurones increases and that areas of the disc that usually have no innervation can become newly populated with neurones [12, 13]; this has been associated specifically with damaged areas of the disc by Lama et al. [14]. This neoinnervation implicates the disc as a contributing source of pain.

Mechanical Degeneration of the Endplate

Degeneration of the disc is likely to represent a disruption of its normal homeostasis. This may be precipitated by excessive load which has been shown to inhibit the normal synthesis of extracellular proteins [15]. It has been well established that vertebral trabecular bone adjacent to the endplate undergoes a process of microfracture and healing in degeneration [16]. Investigating this mechanical overload hypothesis, mechanical testing has been undertaken on the micro- and nanoscales. Oliver and Pharr published their technique for calculating the elastic modulus of a material using the unloading section of the indentation curve, and this is now widely used [17]. Hou et al. performed indentation on cadaveric vertebral specimens. They found that the inferior lumbar endplate withstood a higher load to failure that the peripheral regions had a higher load to failure and a non-uniform decrease in load to failure in those with degenerate discs (the peripheral regions were less affected than the already weaker central regions further exaggerating the relative difference between the central and the peripheral regions). They also measured bone mineral density with DEXA and found that with a decrease in bone density came a uniform decrease in load to failure, implying that the osteopenia associated with ageing is mechanically separate from the process of degeneration [18].

Liu et al. analysed cadaveric samples with degeneration on MRI using 3 mm spherical tip indentation [19]. They concluded that stiffness and strength both decreased with signs of disc degeneration. On a smaller scale, nanoindentation has the advantage of applying significantly lower loads therefore measuring closer to true material properties (rather than a combination of material and structural). Dall'Ara [20] working on dry and embedded cadaveric vertebral tissue investigated the anisotropy of the bone as a material as well as the elastic properties (including of the osteophytes). They found osteophytes to have a lower elastic modulus (10.9 GPa) and there were demonstrable differences depending on the direction of the applied force (anisotropy) with axial being highest (14.6 GPa), something to be taken into consideration when comparing methodologies. We can conclude from the literature that mechanical changes clearly occur in the context of both ageing and degeneration, and characterization of these changes may hold clues about the underlying process of degeneration and also provide some clinical benefit in implant design and implantation.

Degeneration and End plate Histology

A sensible starting point is to investigate ageing separately from degeneration; Boos et al. established that ageing affects the blood supply to the end plate detrimentally. By investigating the changes found in cadaveric samples from age ranges foetal to 88 years, they conclude that their work 'provided clear histologic evidence for the detrimental effect of a diminished blood supply on the end plate, resulting in the tissue breakdown beginning in the nucleus pulposus and starting in the second life decade' [10].

Analysis of calcification of the endplate and its association with disc degeneration in the cervical spine showed that a decrease in pore number correlated with an increase in disc degeneration [21]. This was, however, pores < 300 μm and most strongly for those between 10 and 50 μm. Suggesting this correlation is not as straight forward as it initially appears. An explanation could be that simple diffusion occurs most effectively across the small (10–50 μm) thin-walled capillaries, and while the larger diameter channels may have a greater flow, their thicker walls will inhibit the process of diffusion that has been established as the main method of nutritional transport [22]. Contrary to this, Zehra et al. found porosity of the endplate to be more closely linked to mechanical loading than degeneration concluding 'disc degeneration is more closely linked to reduced disc stresses' [23]. It is of course not established that all pores contain vessels that contribute to diffusion. Malandrino found that porosity and diffusion of metabolites into the disc were not dependant on each other [24]; however, the movement of the water was related to the porosity (and therefore disc hydration). Histological and permeability analysis of the degenerate cartilaginous end plate has been undertaken by DeLucca et al. They found that with degeneration, the cartilaginous end plate permeability decreases. This not only would decrease the transport of nutrients into the disc but also would inhibit the transport of lactic acid out of the disc [25]. Some work suggests the contrary; however, Rodriguez et al. found, when looking at degenerate discs, that 'vertebral endplate porosity increased between 50 and 130%' [26]. They also commented that perfusion increased with this suggesting the issue was not one of poor perfusion but more likely a cellular process.

When considering therapeutic intervention, especially disc preserving methods, an understanding of the perfusion to the disc (and how to assess this) will be vital in the successful implementation of such procedures.

Neurone Involvement in Degeneration

We know that in the normal spine, the outer 1/3 of the annulus and the vertebral body contain nerve fibres [12]. A study of 69 normal spine samples using H&E staining noted that 'Neurovascular bundles and intraosseous nerves were routinely identified within human vertebral bone' [27]. Is the presence of nerve fibres evidence that they are the source of pain? Freemont et al. used diseased human disc specimens using PGP 9.5 to stain for nerve fibres and substance P as a marker of nociception. They found that in their group of control samples, the nerve fibres seemed to be exclusively limited to the outer 1/3 of the annulus as expected; however, in the diseased

group, the nerve fibres were seen to extend into the middle and inner thirds in 46%. Both groups of nerves expressed substance P suggesting that they could be involved in nociception [28].

A histological study of 15 patients with degenerative disc disease staining for substance P, calcitonin gene-related peptide (CGRP), neuropeptide Y (NPY) and PGP 9.5 (representing autonomic (PGP 9.5 and NPY) and sensory nerve fibres (PGP 9.5, substance P and CGRP)) showed that vascular channels around the end plate were accompanied by nerves of autonomic origin which they conclude and suggests that perfusion to the area and hence nutrition of the disc are under autonomic control. They found 'very localised' areas of increased nerve fibres staining for sensory neuropeptide CGRP (but not PGP 9.5) [29]. It is worth noting, however, that there was no overall difference in nerve density of the end plate, and the diseased groups had a mean age of 36 compared to 61 for the control samples – could these changes simply represent an ageing phenomenon? Work by Lama et al. would suggest that this very localised increase might represent the areas of local damage. Their work showed that nerve growth was limited only to areas of disrupted tissue [14].

Ohtori et al. performed histological analysis on spine samples with abnormal MRI (mainly focusing on Modic pathology). When staining for PGP 9.5, they found a significant difference between diseased and non-diseased groups. This correlated with a significant increase in TNF staining suggesting an inflammatory aetiology [30]. Niv et al. [31] commented on the success of vertebroplasty regardless of technique or cement volume indicating more than a pure mechanical improvement. They commented that the immediate effects are likely due to the toxicity of the cement to the nerve tissue which would support the hypothesis that the nerves within the vertebral body can be responsible for pain.

Modic Changes and Degeneration

The changes seen on MRI in degeneration include disc dehydration, loss of disc height and end plate signal changes (Modic changes) [32]. Later other parts of the functional spinal unit become affected including facet joint and ligamentum flavum. Both Modic and end plate changes are found in non-symptomatic individuals.

Modic described 3 patterns of visible changes in the end plate on MRI [32]. It has been shown that Modic changes can transition from one type to another and that there is an increased incidence of radiological degenerative disc disease in those discs surrounded by Modic type changes in the adjacent vertebral bodies [33, 34]. Hutton also documented that Modic changes do not necessarily transition in one direction, finding that some patients transitioned from type 2 back to type 1 suggesting the process might be at least partially reversible [35]. We know that type 2 Modic changes are the most prevalent in the symptomatic population, more common in degenerate disc disease and in the presence of spondylolisthesis [36, 37]. The overall evidence about the clinical significance of Modic changes remains unclear [38]. One MRI study aver a 3 year period and found Modic changes did not correlate with the onset of low back pain [39].

There are several mechanisms proposed as the driver for Modic changes including mechanical changes as a consequence of disc degeneration resulting in abnormal load and shear stresses [40].

Another proposed mechanism is an autoimmune response to disc material originating from the nucleus pulposus that enters the vertebral body through microfractures in the end plate which are known to occur in degenerative disc disease [41]. Histological and CT analysis of bone from transpedicular biopsy in patients exhibiting Modic changes found that Modic type one was associated with changes that one would expect in high bone turnover situations. Modic type 2 changes showed reduced bone turnover/remodelling and Modic type 3 showed changes consistent with a sclerotic/stable phase [42, 43].

Ohtori [30] used immunohistology to stain for TNF and PGP 9.5 and found both to be increased in those with type 1 or 2 Modic changes suggesting inflammation and nerve ingrowth could be contributing factor to pain. Antonacci worked on bone sustaining osteoporotic fractures (not degeneration) finding that in areas of fracture, there is new bone formation as one would expect but also neovascularisation alongside an increase in localised nerve density when staining for PGP 9.5 [44]. We could draw from this (taking into account the work from Ohtori) that it is the inflammation associated with the fracture that stimulates this increase. The presence of inflammation is further supported by work from Rannou [45] who took serum high-sensitivity CRP measurements in those with different Modic type changes, finding levels were significantly higher in those with Modic type 1. Dudli et al. [46] demonstrated in their rat model that the bone marrow (with some inflammatory upregulation from Il-1) mounts a response when exposed to nucleus pulposus cells potentially contributing to Modic changes. This is in keeping with work from the same group [47] in humans displaying Modic changes in which 'pro-inflammatory cross-talk between the bone marrow and adjacent discs' was found when comparing marrow and disc aspirated from levels displaying Modic changes or no changes in the same patients. Extrapolating this into clinical work, the results of a randomised controlled trial comparing and anti-TNF medication to placebo for back pain did not show any significant benefit [48] suggesting that the process is either not reversible or the true mechanism is not yet understood. It has been shown that intra-discal corticosteroids do improve pain again supporting the inflammation hypothesis [49].

Modic Changes and Infection

Stirling et al. proposed that these Modic changes could represent a form of chronic vertebral osteomyelitis associated with *Propionibacterium acnes* [50]. His paper found that 53% of included patients with herniated lumbar discs were found to have anaerobic organisms isolated.

Albert took nuclear disc material from 61 patients undergoing lumbar discectomy. Patients were grouped according to their microbiological cultures (aerobic, anaerobic or no growth). Forty six percent of these patients had microbiological growth. In those with anaerobic growth, 80% developed new Modic changes, 0% of those with aerobic growth and 44% of those with no growth [51]. *Propionibacterium acnes* was the most cultured organism. It is worth noting that this study had very strict inclusion criteria.

Modic Changes and Mechanics

Analysis of extruded disc material at the time of discectomy in 51 patients found the presence of and percentage of end plate involvement of Modic changes both correlated with the presence of cartilaginous end plate in the extruded material [52]. This would infer that the pathology responsible for Modic changes weakens the anchorage of the cartilaginous end plate increasing the likelihood of it detaching. Investigating the mechanical and structural properties further, Liu et al [19] used cadaveric samples and micro-indentation to conclude that stiffness and strength of the end plate reduce with degenerative changes; when Modic changes were present, this was more pronounced.

A review [53] exploring Modic changes comments on the similarities with bone marrow lesions in knee osteoarthritis citing similar risk factors, pain profiles and evolution. The work concludes that structural damage allows the creation of a pro-inflammatory environment which causes nociception and an inflammatory signalling cascade in the bone marrow affecting both marrow composition osteoclast function. It highlights disc/endplate damage, composition of the bone marrow, occult infection, treatment effectiveness and further exploration of the link in osteoarthritis as areas in which further research is required.

The pathological process of Modic changes has yet to be fully understood; histological analysis has, however, shown a correlation with markers of inflammation and nerve ingrowth associated with type 1 changes. Histology has also shown features indicating that there is an alteration in the mechanical environment in which Modic changes exist – it is not clear if this is a cause or effect style relationship. Inflammation is involved, stimulating nerve and local vascular ingrowth. Further work is required for a full understanding and may prove useful when formulating a clinical solution to this significant health problem.

Conclusion

Degeneration represents a disruption of the homeostasis of the normal function of a healthy disc in susceptible individuals. It has been shown to be separate from the ageing process. Restoring this complex balance may hold some promise but identifying the correct patients in who a favourable environment can be achieved will rely on greater understanding of the pathological changes and their correlation with imaging modalities. The endplate is closely entwined with the homeostasis and mechanical environment of the disc, an unbalancing of one clearly affect the other. Matching pathology with symptoms is not straightforward. Markers of inflammation have been shown to be increased but treatment with anti-inflammatories has produced mixed results. Non-uniform micromechanical strength reductions indicate that the homeostasis of the vertebral bone is affected which may hold some clues to the underlying pathology. Modic changes have multiple proposed underlying mechanisms including inflammation, infection, alteration of the mechanical and chemical environment and changes in bone turnover. We do know they seem to be partially reversible, perhaps an avenue of promise for therapy?

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