■ INSTRUCTIONAL REVIEW: SPINE

The pathogenesis of degeneration of the intervertebral disc and emerging therapies in the management of back pain

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This article reviews the current knowledge of the intervertebral disc (IVD) and its association with low back pain (LBP). The normal IVD is a largely avascular and aneural structure with a high water content, its nutrients mainly diffusing through the end plates. IVD degeneration occurs when its cells die or become dysfunctional, notably in an acidic environment. In the process of degeneration, the IVD becomes dehydrated and vascularised, and there is an ingrowth of nerves. Although not universally the case, the altered physiology of the IVD is believed to precede or be associated with many clinical symptoms or conditions including low back and/or lower limb pain, paraesthesia, spinal stenosis and disc herniation.

New treatment options have been developed in recent years. These include biological therapies and novel surgical techniques (such as total disc replacement), although many of these are still in their experimental phase. Central to developing further methods of treatment is the need for effective ways in which to assess patients and measure their outcomes. However, significant difficulties remain and it is therefore an appropriate time to be further investigating the scientific basis of and treatment of LBP.

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Low back pain (LBP) is a common cause of sick leave in the United Kingdom.[1] It has a significant impact on health care resources and contributes to both disability and loss of work. However, the subject receives limited research funding.

The causes of back pain are mostly unknown. Degeneration of the intervertebral disc (IVD) is believed to precede or to be associated with many clinical conditions, including low back and/or lower limb pain, paraesthesia, spinal stenosis and disc herniation.[2] Factors suggested as its primary cause include mechanical loading of the spine, age, biochemical influences and smoking.[3,4] Genetics and ethnicity have also been shown to have a role in degeneration of the IVD,[3,5] and recently it has been suggested that herpes simplex virus type-1 (HSV-1) together with cytomegalovirus can be isolated from the intervertebral discs of patients with back pain undergoing surgery.[6]

Evidence of spinal degeneration is present in between 90% and 100% of people aged > 63 years[7] and is seen in autopsy studies even in the absence of any known history of LBP.[8] This demonstrates the relatively poor association between the radiological evidence of disc degeneration and the clinical presence of pain.

This article reviews the basic structure of the IVD and the processes that lead to disc degeneration, and provides an overview of new and emerging treatments. One of the purposes of this article is to encourage research workers to study both the pathogenesis and treatment of low back pain.

The normal intervertebral disc

The IVD is a largely avascular, aneural structure with only sparse nerves and blood vessels in its outer part. It consists of an outer collagenous annulus fibrosus (AF) surrounding a central more gelatinous nucleus pulposus (NP). Both regions contain small numbers of IVD cells. At the interface between the disc and the vertebral bodies is the end plate, which is made up of the cortical bone of the vertebral body and a region of hyaline cartilage (Fig. 1).[9]

The IVD enables movement such as twisting and bending as the body adopts different postures.[10] It can withstand applied pressures varying from 0.1 MPa when prone to 2.3 MPa when lifting with a flexed back.[11] However, there is no evidence that it acts as a shock absorber.[12,13]

Cadaver studies have suggested that compression damages the endplates, but not the AF.[14] Prolapse of disc tissue secondary to damage to the annulus is instigated by twisting and/or bending.[15] Many factors may be involved in back pain, including the zygapophyseal (or facet) joints and spinal ligaments, spinal

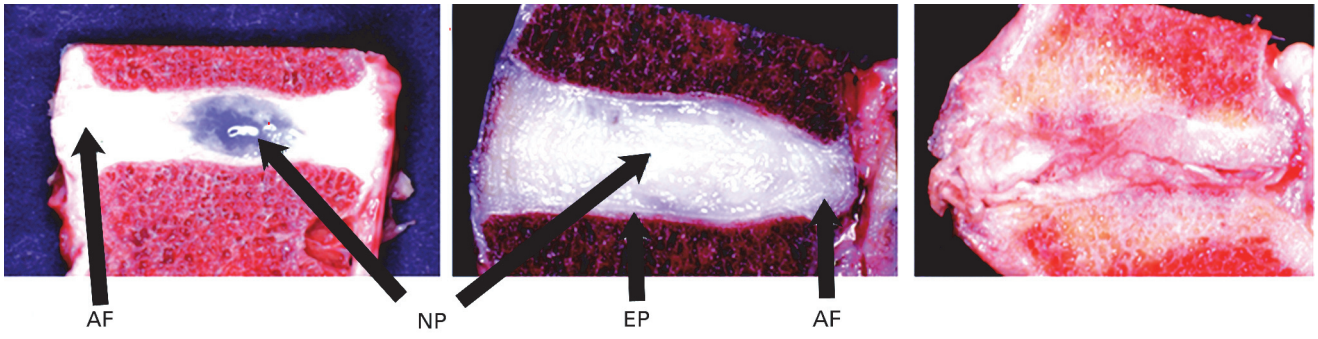

Fig. 1a Fig. 1b Fig. 1c

Photographs of excised discs, a) from a young patient, showing an obvious gelatinous nucleus pulposus (NP), b) from an adult, showing how the NP has become less distinct from the annulus fibrosus (AF), with the bony and cartilaginous endplates (EP) interfacing the disc and the vertebral body, and c) after degeneration, showing a loss of disc matrix with indistinct regions and possible changes in the vertebral bone (modified with permission from **Boos et al.** Classification of age-related changes in lumbar intervertebral discs: 2002 Volvo Award in basic science. *Spine (Phila Pa 1976)* 2002;27:2631–2644).[9]

mechanics, pressure from within the abdomen, the muscles of the back and abdomen, the thoracolumbar fascia and even the joints of the lower limb.[16]

Nutrition to the disc is dependent on the transfer of solutes from the vessels at the edges of the disc (in the periphery of the AF and the vertebral end plate). The end vessels in the cartilaginous end plate are shown to be in continuity with the systemic circulation via the lumbar arteries.[17] Molecules move into and out of the IVD by diffusion that, according to Fick's law[18], depends on the concentration gradient and the nature of the solute molecules involved.

Blood flow to the end plates of sheep is 4 ml/100 gm/min, similar to that seen in cortical bone of sheep[19]: neurohumeral agents such as acetyl choline affect the flow.[20] This vasculature influences both the supply of nutrients to the cells of the IVD as well as the clearance of their metabolites. While IVD cells are able to remain viable with very low levels of oxygen, the synthesis of molecules such as proteoglycans is low. The level of glucose is a more crucial factor with low levels leading to premature cell death, particularly in an acidic environment.[21]

Activity of IVD cells is influenced by many environmental factors including mechanical load. A short application of hydrostatic pressure such as 2 MPa for 20 seconds, leads to a two- to threefold increase in proteoglycan production *in vitro*. *In vivo*, the cells experience constantly changing complex signals from their physical environment (Fig. 2).[22]

Function of the IVD is entirely dependent upon the physicochemical properties of the AF, NP and cartilage end plate. Proteoglycans (mainly aggrecan) in the NP are hydrophilic because of their constituent glycosaminoglycans (GAGs) and generate a pressure by swelling from the attraction of water into the IVD from surrounding tissues – which results in the vertebral bodies being pushed apart. This pressure is resisted by tension in the collagen fibres of the AF. The balance between expansion of the NP and tension in the AF leads the IVD to resist compression. Consequently the whole composite disc can be weight-bearing, while allowing flexion and torsion in an otherwise rigid structure.

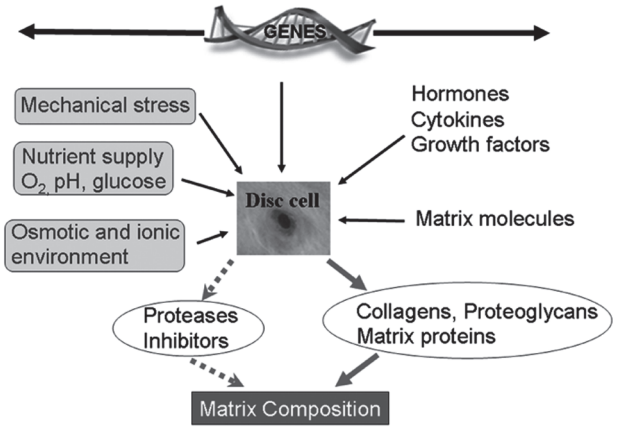

Fig. 2

Diagram showing how disc cell activity is influenced by environmental factors, many of which (in the shaded boxes) are powerful regulators but are often ignored (modified with permission from **Urban JP, Roberts S.** Cells of the intervertebral disc: making the best of a bad environment. *Biochemist* 2003;25:15–17 ©2003 The Biochemistry Society).[22]

Since the disc has a very limited blood supply, IVD cells, particularly those in the centre of the avascular NP, operate in an environment that would be unviable to most other cells. They appear to have adapted to this hypoxic, acidic environment. Accordingly, caution should be practised when studying their condition using a standard cell culture. This is an important factor, which influences the investigation of cell function and the understanding of the pathological processes that occur within the IVD.

Pathology of disc degeneration

In addition to laying down disc matrix with the correct composition and organisation, disc cells can also cause its

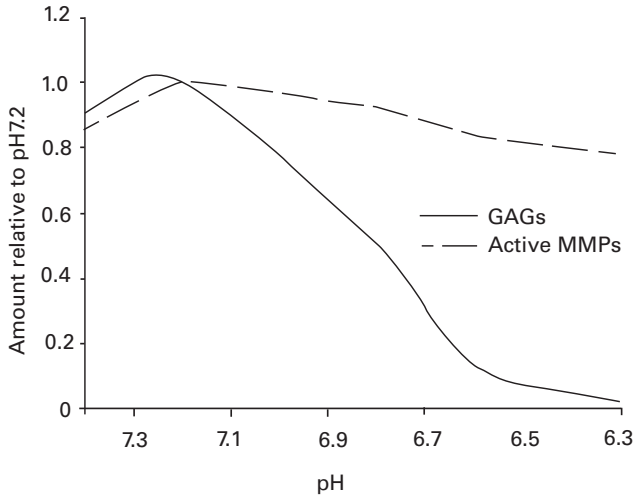

Fig. 3

Graph showing how a lowered pH level reduces the glycosaminoglycan (GAG) synthesis by disc cells much more than that of matrix metalloproteinase (MMP) production so favouring degradation of the matrix (modified with permission from **Razaq MS.** *The effect of extracellular pH on cartilage tissue metabolism and turnover.* Oxford: University of Oxford, 2002).[27]

degeneration. The IVD cells can synthesise many enzymes that are capable of degrading disc components.[23,24] For example, collagenases attack the triple helix of collagen, elastases degrade elastin and several different enzymes, including aggrecanases (ADAMTS 4 and 5), cysteine proteinases, stromelysins and other members of the matrix metalloproteinase (MMP) family, are all capable of degrading proteoglycans and causing loss of GAGs.[25] IVD cells promote further degradation by synthesising cytokines, such as interleukin (IL)-1, or tumour necrosis factor-α (TNFα), which act as intermediate signalling molecules, increasing production of MMPs and other proteases.[26] The cells maintain the production of MMPs better in an acid environment (such as reported in degenerate IVDs), while GAG synthesis is drastically reduced, thereby leading to a vicious spiral of degeneration (Fig. 3).[27]

Many studies have examined different noxious stimuli including increased load, osmotic pressure and reduced glucose, and have shown they can lead to altered cell function, not only directly but also via stress-induced premature senescence.[28] These senescent cells not only stop dividing and replicating, but can also produce increased levels of cytokines and matrix-degrading enzymes.

The function of IVD cells, and their response to cytokines and growth factors, varies with the degree of degeneration. For example, cells from degenerate IVD express more MMP13 and aggrecanase in response to IL-1 than those from non-degenerate discs.[29] They also have a different response to loads (mechanotransduction) with a possible alternative mechanotransduction pathway being involved in cells from degenerative discs, replacing the RGD pathway seen in normal disc cells.[30] Additionally there are complex interactions between different environmental factors that affect the activity of the IVD. For example, the vascularisation of degenerate IVDs increases causing greater availability of growth factors, such as platelet derived- (PDGF) or insulin-like growth factors (IGF-1). These are known to increase the proliferation of disc cells (via the extracellular signal regulated kinase (ERKs) and phosphatidylinositol 3-kinase (pl-3-K/Akt) pathways, generally regarded as pivotal signalling pathways in regulating cell proliferation).[31] However, this proliferative response of the cells varies with osmolality, being greatest at low osmolalities that are present in degenerate IVDs.[32] Growth factors can also influence disc cells in other ways rescuing them from senescence or apoptosis.[33]

Once the disc becomes degenerate, it can cause LBP in different ways. One effect of disc degeneration is a loss of disc height[34,35] with subsequent altered stress on the facet joints and other spinal tissues, such as ligaments and muscles that can potentially lead to LBP. Loss of disc height can contribute further to compression of the exiting nerve root, resulting in pain in the buttock and lower limb, particularly if the nerve is sensitised in response to molecules like TNFα, which is produced in the degenerate IVD. Olmarker and Rydevik[36] demonstrated that long-term compression of the exiting nerve root has been found to lead to changes within the spinothalamic tract.[37] In addition, neurohumeral markers, such as substance P, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and platelet endothelial cell adhesion molecule (PECAM), which are not found in normal IVD, have been seen in discs excised from patients with LBP.[38-40] Other structures, including the ligamentum flavum, also undergo changes in patients with LBP.[41] In addition the growth of nociceptive nerves into the usually aneural IVD is a well-recognised feature of painful degenerative IVD.[42,43]

New and emerging therapies

Total disc replacement. Total disc replacement (TDR) is intended to be an alternative to spinal fusion with the advantage of restoring flexibility to the intervertebral joint. Most current designs of TDR are ball-and-socket joints involving the articulation of ultra-high molecular-weight polyethylene-on-metal or metal-on-metal. Metal-on-metal prostheses are made of cobalt-chrome alloys with highly polished surfaces. The technology is based on that of total hip replacement, with the aim of achieving a low-friction joint. However, a simple ball-and-socket joint fixes the axes about which the prosthesis can twist and bend. By contrast, a natural disc has a flexion/extension axis that is able to shift. Since most artificial joints cannot shift their axes, there is a danger of loosening. More recently, TDR prostheses have been manufactured from flexible polymeric materials to mimic more closely the natural disc. Laboratory studies have shown that the flexibility of a polymeric prosthesis can be comparable to that of a normal human disc[44] with one version predicted to have a fatigue life of about 50 years.[45] It should be noted, however, that such studies cannot reproduce *in vivo* conditions, and the fixation of a

flexible device to a vertebral body is a potential source of problems. Current TDR prostheses can restore flexion/extension but the clinical outcome does not yet appear to be better than fusion. Consequently, TDR should still be considered an experimental procedure.[46]

Biological treatments. Biological treatments offer an attractive alternative to major surgery. It is envisaged that they could have the potential of effecting a permanent repair, either by stimulating existing cells for example through injecting growth factors, like growth differentiation factor-5 (GDF-5), into the disc or as part of tissue engineering with implantation of a cell population such as disc cells or stem cells integrated into scaffolds. These physical materials, which may form a mesh or network, can direct cell behaviour and act as physical cues for cell alignment and subsequent matrix deposition.[47,48] Alternatively they may incorporate a bioactive substance that might attract a particular cell population to the locality or influence endogenous cell functions. Implanted cells, particularly mesenchymal stem cells (MSCs), can also restore the function of endogenous cells or alternatively differentiate into normally functioning IVD cells.[49]

Cell therapy for disc repair. Cell therapy has been used for the repair of articular cartilage for almost two decades[50] but has only recently been applied to the IVD. Accessing autologous disc cells is difficult. Not only is it difficult to obtain sufficient numbers, but they are difficult to harvest and there is always the possibility that they might be senescent or unhealthy. Cells from herniated disc tissue have been shown to have limited regenerative potential in comparison to those from non-herniated regions.[51] Other non-autologous sources of cells, such as notochordal cells, have been investigated. These have been studied because disc degeneration occurs less frequently in animals, where they survive, such as in non-chondrodystrophoid dogs, and they promote proteoglycan production by NP cells if grown as co-cultures.[52]

Stem cells. Stem cells are attractive as a source of autologous or allogeneic cells as large numbers can be harvested from embryos, placenta and umbilical cord, and adult tissues such as bone marrow and fat. In addition, stem cell 'niches', hosting endogenous stem cells, have been identified in most tissues and potentially multi-potent progenitor cells capable of forming cartilage, bone, fat, neuronal and endothelial markers have been reported to occur in samples of non-degenerative human AF.[53] MSCs can adopt a gene expression profile resembling that of native disc cells *in vitro*, by using transforming growth factor-β (TGFβ) to mediate differentiation[54] or by co-culturing with NP cells.[55] MSCs have been shown to proliferate and differentiate when injected into degenerative rabbit discs either alone or in a collagen gel.[56] In addition, MSCs can activate or trigger a response from endogenous cells and a mechanism has been identified whereby they stimulate the native stem cell niche and encourage those cells to effect repair. Using this approach could negate the need to introduce additional cells and so avoid many of the challenges of cell therapy in the disc, such as choosing the best cell or scaffold to use, avoiding cell transformation or infection during culture-expansion of the population, in addition to the cost associated with cell therapies.

Tissue engineering. Tissue engineering of the disc can be targeted at repairing or regenerating different regions. Many studies aim to repair the NP, this being the main region that degenerates. Recreating the AF may be more important in some groups of patients who have tears or herniations, or for repair after insertion of inert nuclear implants or prostheses. The use of topography or aligned scaffolds, whether of polycaprolactone, silk or some other material, has gone a long way to control the alignment of the introduced cells and the orientation of subsequently deposited matrix.[48,57] Progress has also been made in forming a complete intervertebral disc with integration of all three of its components (nucleus pulposus, annulus fibrosus and cartilage endplate).[48,58] A tissue-engineered construct would compete with allogeneic disc transplants, such as have been undertaken by Ruan et al[59] who implanted cadaveric cervical discs into patients with cervical IVD degeneration with encouraging clinical results and minimal loss of disc height at five-year follow-up.

Despite all the challenges and unknowns associated with cell therapy, it has been used in several centres. A clinical trial for treating herniated IVD after culture expansion of the resident cells reported a reduction in the level of the patient's pain without loss of disc height.[60] Autologous MSCs, either within a collagen sponge implanted percutaneously or injected directly into the discs have also been used to treat patients.[61,62]

However, there remain important issues to be addressed around cell-based therapies for patients with discogenic LBP due to degeneration of the IVD. Central to this is whether a normally functioning end plate is needed for treatment to be successful in order for IVD nutrition to be maintained. Additional challenges include: which cell types to use; how and when should the cells be inserted into the disc in relation to progression of degeneration; should cells be inserted alone or attached to scaffolds and could cells be administered as part of an intervertebral 'organ transplant'?

Relevant outcome measures for new therapies

In the current era of evidence-based practice, a clinical trial is required if a new intervention is to gain acceptance. Randomised controlled trials constitute the reference standard but such studies require initial feasibility and pilot studies to ensure the correct design, powering and outcomes: these can be lengthy as well as costly. Clinical outcomes for treating LBP can be assessed against a range of parameters, which include function, disability, quality of life, general health, pain, anxiety and depression. Quantitative measures are ideal and most large trials focus on patient-rated measures or scales, especially those of patient satisfaction and expectation.

The past decade has seen the widespread use of the Short-Form 36 (SF-36),[63] or its associated shorter versions, the SF-12[64] and SF-8.[65] The SF-36 is a global measure of the quality of life, and covers dimensions such as general health perception, pain, physical function, social function, mental health and vitality. When used to assess physical function, pain and social function in spinal conditions, it has been found to be sensitive to change.[66,67] The Oswestry Disability Index (ODI), first published in 1980,[68] has been revised and validated.[69] It is a disease-specific measure of functional disability as its focus is on back pain rather than more global indices such as the SF-36. It has ten dimensions scoring function in a range of tasks from walking to sleeping. Alternative disease-specific instruments include the Roland Morris Disability Questionnaire,[70] the Low-Back Outcomes Score,[71] the Waddell Disability Index[72] and Core Outcome Measures Index (COMI).[73]

As understanding of these various measures improves, there has been a growing awareness that results should be interpreted as clinically significant rather than statistically significant, so that they are relevant to the needs of the patient. This has led to the term 'Minimum Clinically Important Difference' (MCID): the change that would be considered meaningful and worthwhile for a patient such that they would consider repeating the intervention if given the choice again.[74] There has also been a change in emphasis given to the patient's experience with a range of new and different approaches used.[75,76] Hazard et al[77] noted that patient satisfaction was strongly correlated with the ease with which patients were able to achieve their personal recovery goals. Care must be taken, though, as many factors can influence patient satisfaction. The patient's satisfaction with the surgical procedure and its success needs to be considered alongside their satisfaction levels with the service provided by the hospital in particular, including such factors as the standard of cleanliness and the patient's relationship with health care professionals.

Attempts to quantify these clinical tests can be difficult. A useful test is the shuttle-walking test,[78] which was developed for tests of respiratory function. It was first used for patients with back pain as part of the Medical Research Council Spine Stabilisation Trial[79] and was an adaptation of a respiratory function test. It requires the patient to walk up and down a 10-metre course at speeds dictated by an audio tape. The walking speed is incrementally increased until the patient can no longer complete the course in the allotted time.[80] In the past other measures of movement have also been used,[81] and the growing field of wireless sensing offers many new opportunities for quantifying function.[82]

Summary

Our understanding of the clinical presentation of disc disorders, the normal physiology of the IVD and the pathological changes that occur as discs undergo degeneration has no doubt improved in recent years. For example, we know that IVD cells become dysfunctional with possible contributory factors including reduction in the blood supply, inheritance[3,5] or even viral infection.[6] However, there remain many gaps in our knowledge, such as the exact pathways involved that lead to deleterious consequences.

New treatments have been developed, including TDR and improved spinal implants, as well as more biological approaches such as cell therapy, with or without whole organ replacement. While these may have the potential to improve the future management of patients with disorders of the IVD, it remains to be seen whether these methods will deliver improvements in the treatment of back pain. They will certainly need to be thoroughly measured and evaluated.

Despite developments in both the basic science and treatment, it is clear that there remain large areas in which further research into LBP is needed. For example, it could prove fruitful to study the link between pain and degenerate disc disease and to determine exactly how stem cells might prevent or reverse disc degeneration. Advances are most likely to come from a further improved understanding of the biology, pathology and biomechanics of disc degeneration and if this is supported by improved outcome measures it will soon be possible to unravel some of the mysteries that lead to patients suffering from LBP.

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