**CURRENT TREATMENT OPTIONS FOR INTERVERTEBRAL DISC PATHOLOGIES**

**Abstract**

The complex structure of the intervertebral disc within the spine is well suited to its mechanical function. However, it is also prone to degeneration, which is associated with various clinical symptoms and conditions, ranging from disc herniation to back pain to spinal stenosis. Most patients’ conditions are managed conservatively but a small proportion progress to having surgery. This may be decompression (to remove tissue such as the disc, bone or hypertrophic ligaments impinging on nerves) or fusion of the normally mobile intervertebral joint to immobilise it and so reduce pain. These used to involve fairly major surgical procedures but in the last decade there has been much progress to make the surgery more refined and less invasive, eg using endoscopic approaches. Simultaneously the research world has been studying and developing tissue engineering and cellular techniques for attempting to regenerate the intervertebral disc, whether simply the central nucleus pulposus or a complete intricate assembly to replicate the native structure of this and the surrounding annulus fibrosus, cartilage endplate and bone. To date, none of the complex entities have been trialled, whilst cellular approaches are easier to utilise, have progressed to clinical trials and may offer a better solution.

**Keywords**: intervertebral disc degeneration, back pain, surgery, cell therapy

**Introduction**

There is nothing simple about the intervertebral disc. It is a highly organised structure which has many anatomical and biochemical peculiarities. For example, the healthy adult disc is generally considered to be the largest avascular structure in the body with its cells in the central nucleus pulposus being further from blood vessels (and so a source of nutrients) than in any other tissue. Biochemically, the molecules of the main protein present, collagen, have more crosslinking between them than anywhere else in the body.

A major function of the intervertebral disc is, of course, mechanical. Interspersed between, but directly attached to the vertebrae at its outer edges, they not only carry large loads due to the body weight and muscle activity, but they must allow movement in all planes to avoid rigidity in the spine. They are located within a 'functional spinal unit’ (FSU) with its many different components, including ligaments, muscles, facet joints, in addition to the vertebrae and the thin hyaline cartilage endplates between the vertebrae and the discs themselves (Figure 1a). Each of these units has six degrees of freedom and is exposed to huge forces and moments which are a part of the twisting and bending that it is subjected to, being controlled mostly by the enormously complex arrangement of the paravertebral muscles in three different layers. The cervical discs support a delicate stalk carrying a head weighing ~5Kg, whilst the greatest hydrostatic loads arise in the lower lumbar discs. This is due largely to body weight and muscle activity and, together with the natural lordotic curvature of the spine here, likely contributes to the lower two discs being most commonly affected by degenerative changes in the disc; this in turn is associated with low back pain.

The inner nucleus pulposus (NP) and outer annulus fibrosus (AF) derive from different embryological regions (the notochord and sclerotome, respectively) and have different resident cell populations with a very low cell density1. The biochemistry and particularly organisation of the NP and AF also differ greatly. The NP consists of type II collagen and has a higher water and proteoglycan content, being gelatinous in the first decade of Iife in humans, in contrast to the more collagenous (consisting mostly of type I collagen) and highly organised AF with its concentric but interconnected lamellae (Figure 1b).

**Degeneration of the intervertebral disc and clinical sequelae.**

Degeneration of the intervertebral disc is very common, with microscopic changes being seen in the first decade of life2. The poor blood supply of the human disc, with only a few millimetres of the outer disc being supplied after the age of two in humans, is believed to be a major reason for the propensity of the disc to degenerate. In fact, it is remarkable that any disc survives intact for the biblical three score years and ten, let alone many years beyond that, as we all live much longer. The hyaline end plates, superior and inferior to the disc, allow diffusion of vital nutrients from the adjacent vertebral bodies to cells inside the nucleus. A reduction in diffusion due to calcification of these end plates (due either to normal ageing or a cumulative stress phenomenon) is the start of degeneration of the soft nucleus pulpous, with progressive degradation and loss of proteoglycan and loss of water. These changes eventually occur throughout the disc but are most severe in the NP; they then lead to fragmentation, fissure formation, vascularisation, nerve ingrowth and loss of disc height3.

**A**

An annulus fibrosus which is no longer adequately supported because of a dehdrated NP may bulge (prolapse) like a flat car tyre, or even rupture as an extruded or sequestrated herniation. These herniations may irritate or actually compress a branch of the sciatic nerve, resulting in distal radicular symptoms and often unbearable sciatica; if the disc bulges diffusely it may, together with hypertrophied facet joints, contribute to a spinal stenosis syndrome ('jelly legs'). An acute midline rupture of an annulus in the presence of a normal nucleus may produce a large central disc bulge which will compress many branches of the lumbar and sciatic nerve roots on both sides – resulting in a cauda equina syndrome (Figure 2), with lower limb paralysis and loss of control of bladder and bowel. This is a surgical emergency. In addition, the degenerative changes allow more forces to be transmitted to the outer annulus and vertebrae, culminating in changes like non-marginal osteophytes.

As the human population ages, more and more people are reaching the last decades of life surviving and coping with altered biomechanics. Once this process alters at one level, it affects the function at adjacent levels, resulting in a chain reaction- the end result of which is progressive problems, often ending up in a spinal deformity. The rise of adult degenerative scoliosis surgery in the last two decades is proof of that, with the incidence of genetically determined idiopathic adolescent scoliosis not changing, but the incidence of degenerative scoliosis is4.

Whilst both degenerate (black) discs and disc herniations can be clearly identified, for example on magnetic resonance images (MRIs; Figure 2a-c) and no doubt have some bearing on the pain in some individuals, the clinical symptoms of both these conditions do not always appear to correlate well to the MRI changes5. This may in part reflect the complexity of the nerves and their receptors that control signals and function between the different tissues within the functional spine unit (FSU) as well as the coordination between different FSU’s. Referred pain patterns into the limbs can complicate matters further; this, together with the peripheral and central sensitisation phenomenon in the neural circuits proximal to the peripheral stimulus source often makes a surgeon’s job to pinpoint the source of pain difficult. Added to this, there may be overlay of different genetic controls of pain sensation pathways in different individuals6. A recent large genome wide association study (GWAS) of 509,000 individuals, indicates there to be a very complex genetic architecture overlapping the genetic predisposition to back pain with its biopsychosocial risk factors. The authors of this study suggest that there are two strong molecular axes of back pain, one relating to structural or anatomic disc problems and the other relating to pain perception and processing7.

**Current Treatment Options**

**Non-surgical Treatments**

Current treatment options for disc disorders are no different from old treatment options except in the detail. As ever, if the pain is not intrusive, analgesia will likely improve capability and quality of life until the pain passes. If pain persists, then exercise, heat, cold, corsetry, acupuncture, radio frequency/shock waves and varying intensities of massage may make the pain better for a while in some individuals, but, as ever, could make it worse in others. Beyond that we are looking at degrees of invasion such as local infiltration of trigger points with local anaesthetic and steroid, or beyond that again to surgery, if distress, weakness, disability and the passage of time justify it. There is little more to be said about non-surgical current treatment options for disc problems. They are harmless in the main, endless in variety of application and success.

**Surgical Treatments**

There is a broad range of surgical treatments available for certain spinal pathologies. When the natural history of a condition is unlikely to be in the patient’s favour, or non-operative treatment is not effective, then surgical treatment may be offered to the patient. A surgeon’s job is to evaluate by means of clinical history, examination and investigations, situations where surgery is likely to be beneficial. In cases where the main origin of pain is still in the periphery, and localisable to a level, surgical treatments are likely to be successful, but if the pain pattern has peripheral and central sensitisation features, then surgery is unlikely to change that.

There are four main types of surgical procedures:

1. Decompression for neurological problems
2. Fusion to abolish motion at a functional spinal unit
3. Motion preservation/modifying surgery in the form of disc replacement/dynamic fixation devices
4. Deformity surgery to realign biomechanics between a large number of functional spinal units.

**Decompression** is performed for compressive disc or disc-osteophyte lesions in the lumbar and cervical spine presenting as radiculopathy, with symptoms of pain and weakness or numbness. The simplest decompression is a discectomy, that is removal of that part of the disc seen to be pressing on a nerve plus any loose fragments in the intervertebral space. Surgical technique in the lower lumbar spine has progressed from removal (laminectomy) of the posterior arch (lamina) of the vertebra at the relevant level, to small incisions and interlaminar working using a microscope, to percutaneous endoscopic surgery with the surgeon gazing at a TV screen rather than the patient. Recent advances in surgical techniques for this type of surgery have been the development of Fully Endoscopic Spine Surgery (FESS) which allows interlaminar and transforaminal approaches to deal with disc protrusions and osteophytes8. The interlaminar technique is being used to perform lumbar decompressions as well as cervical discectomies and foraminotomies. This miniaturisation in treating disc herniations by endoscopy will likely transform this field of spinal surgery just as laparoscopy and minimally invasive surgery has done in the GI and abdominal field of medicine.

Results of decompression surgery are generally good, with 85-90% patients experiencing rapid relief from the symptoms of ‘sciatica’ or ‘brachalgia’. Patients who have surgery are often worse at baseline than conservatively managed patients, but obtain a quicker recovery back to normal, although the long term results may be no different9. Decompression is also done for compressive spinal cord lesions presenting as myelopathy in the cervical and thoracic spine. The results of this type of surgery are generally good, with 85-90% patients benefiting from it. In cord lesions, recovery is often partial or does not happen, but in most cases further deterioration can be halted.

Decompression is also undertaken for spinal stenosis, an age-related condition which usually presents late in life, resulting from the intervertebral disc degenerating at one or multiple levels and, or hypertrophy of the facet joints and ligamentum flavum, resulting in circumferential squeeze on the cauda equina. Patients may complain of progressive pain and weakness in the lower limbs with every additional metre of distance walked. The only treatment, if treatment is sought, is surgical decompression, probably bilaterally and at multiple levels, much as described for disc prolapse but also perhaps including trimming of those facet joint components which add to the nerve root compression.

**Fusion** is often done to alleviate pain from a limited number (one or two) of FSUs, using the old principle of abolishing pain by abolishing motion. Nature is trying to do that anyway, as most discs towards the end stage of the degeneration process will end up with adjacent vertebral osteophytes that will stiffen motion, and exchange stiffness for less pain. If the patient’s symptoms are disproportionate, then surgery may be helpful. The techniques to achieve fusion have changed over time, although the basic concept has remained the same.

The various approaches to fuse a spinal level used to traditionally be either postero-lateral or anterior interbody fusion using autologous iliac crest bone grafts. Instrumentation in the form of pedicle screws (Figure 3) shortened hospital stays for patients, and obviated the need for post-operative bracing. The use of bone graft substitutes and expanders along with better instruments have improved the union rate of these fusions to 90-95%. Minimally invasive techniques to achieve fusion have also been developed with lateral interbody fusions and minimally invasive trans-foraminal fusions. These have helped patients recover and return to their chosen activities faster10. Because there is always some risk that the transplanted bone will not fuse to the spine, clinicians have been looking for something that will enhance the fusion process to produce a higher success rate. Such a product was considered found in 2002 when early clinical results suggested that BMP-2 (bone morphogenic protein) did improve fusion rates anywhere in the spine when added to bone graft11. Later studies reported a raft of serious complications: implant displacement, subsidence, infection, low sperm count, radiculitis, ectopic bone formation and osteolysis12; these concerns have inevitably lead to a reduction in the use of BMPs more recently.

**Motion preservation/motion modifying surgery** of intervertebral joints has always been an attractive option, with the great success achieved by hip and knee replacements serving as an obvious inspiration and example. The American FDA- approved prospective randomised trials comparing single level fusion with disc replacement in the lumbar spine have been published with 5 year results13, but fears of what happens to these devices in the longer term as they wear out dampens surgical and patient enthusiasm for this technique. Longer results of these devices have not been very successful14. Wear and failure patterns of hip and knee replacements are well known, and similar wear patterns are likely in the spine as well. Whilst revisions of knee and hip arthroplasties are possible, the difficulty in replacing ‘worn out’ disc replacements is a significant surgical and neurological challenge.

Other motion modifying implants have been introduced, and many have failed to catch the fancy of most surgeons. These include devices attached posteriorly in the lumbar spine to restrict flexion and extension at the end range whilst allowing motion in the mid-range, or devices that constrain the motion across the complete range. In addition, in some patients who may also have osteoarthritic changes in the facet joint, it is difficult to see how a disc replacement alone will serve any long term purpose. Whilst cervical disc implants are generally more satisfactory than in the lumbar region, there have been reports of a large number of disc replacement devices in the cervical spine ending up with heterotopic ossification and fusion naturally15.

**Adult deformity surgery** has grown a lot in this century, with the ever increasing demands to remain active by a rapidly ageing population forcing surgeons to address this problem. Concepts of whole spine sagittal balance, co-relation with pelvic tilt and relative contributions of various parts of the spine to this overall balance have been put forward**16,17**. These concepts are being used to surgically treat this complex but demanding group of patients, but complication rates in some studies have reached 50%**18**. Surgical techniques have advanced, initially borrowing the open techniques from the expertise of adolescent idiopathic scoliosis surgeons, and building on them. Vertebral osteotomies are used commonly to achieve large corrections, but equally the use and benefit of minimally invasive techniques is likely to grow and help reduce surgical morbidity in this group of patients. Minimally invasive surgery is already being used effectively for dealing with metastatic spine cord compression patients**19**, and this experience of fixing multiple FSU’s is likely to spill over into adult deformity along with use of better instruments and minimally invasive fusion techniques.

Most of what has been written above refers to the lumbar spine. It applies equally to the cervical spine except that cervical discectomy is likely to be combined with anterior interbody fusion to prevent kyphosis deformity. Surgery of the cervical spine presents an element of greater risk than in the lumbar spine because of the proximity of the spinal cord. Disc problems in the thoracic spine are uncommon perhaps because of splintage via the ribs to the sternum.

**Biological and Cellular Therapies**

The dull fact is that the current conservative and surgical treatment options for disc problems are no different from what they were decades ago, except in the details of technique and in the increase in cost. However, there are exciting treatment options in prospect by cell biologists and biochemists rather than surgeons and which could represent a great advance at last. This edition of the journal reports some of these advances, and there are others. For example, nucleus pulposus cells may be converted to osteogenesis, so that discs may eventually be turned into bone - providing a cellular and biological fusion, rather than a surgical one20. Autologous mesenchymal stromal cells have been embedded in tricalcium phosphate and used as a bone graft substitute for spinal fusion in an ongoing trial21. This work holds out the prospect of avoiding the need to harvest bone graft from the pelvis and the associated complications22.

Cells removed from different connective tissues have been injected into intervertebral discs of patients in isolated studies for more than 20 years now, whether these be freshly isolated from, for example, bone marrow, or whether they be culture-expanded to result in a more homogenous population of cells. The populations of autologous and allogeneic cells have ranged from uncharacterised cells isolated from herniated discs23,23 to chondrocytes, fibroblasts, and several sources of mesenchymal stromal cells (MSCs), but most commonly from adipose tissue or bone marrow24,24. Interestingly, MSCs sourced from adipose tissue respond differently to hypoxic conditions, such as would typically be found within the disc, by producing greater levels of angiogenic and neurotrophic factors (Ang2, VEGF A, NGF and NT-3) than bone marrow derived MSCs25,25.

Whilst most cells in clinical trials have been sourced from adult tissues, there have also been many investigations into notochordal, embryonic and foetal cells, as well as induced pluripotent stem cells (iPS)26,27. Another approach is to trigger the population of endogenous progenitor cells within the disc, identified by various markers such as ‘stem cell’ markers, Notch1, Delta4, Jagged1, C-KIT, KI67, and Stro-128,28; certain glycosaminoglycan epitopes29,30 or Tie+ and GD2+31. The frequency of some of these populations, eg the Tie+ and GD2+ cells decreases with an individual’s age31, which may be a limitation in future clinical strategies.

Scaffolds and support matrices have also been used; fairly simple chemicals such as collagen and atellocollagen gels and sponges32 or hyaluronan (HA) have commonly been used with and without cells whilst there have also been many sophisticated tissue engineering solutions created in vitro. Hamilton et al33, for example, have created composite structures of NP, CE and bone, or complete disc-like structures, using a variety of materials such as silk, polycapralactone (PCL) and calcium triphosphate (reviewed in 34). Taking these to a clinical product would require further development and challenges but they do allow excellent test and model systems for studying biological processes.

Repair of the AF alone, such as would likely be beneficial to reduce reherniation, brings different challenges. These are mainly due to the high tensile and shear stresses arising in the outer lamellae which have to retain the high hydrostatic pressure of the inner AF and NP. Whilst some limited natural repair can occur35, it is generally felt that a suitable biomaterial would render a tissue engineered solution more successful. Various collagen preparations have been examined but generally are mechanically inept. Synthetic materials, such as PCL, polylactide and polyglycide monomers and polymers offer more strength or even polyurethane and polyamide, sometimes in conjunction with natural polymers such as HA or fibrin (reviewed in 36,37).

There has been considerable scepticism about the challenges cells being injected or implanted to regenerate intervertebral disc tissue would face in comparison to, for example, articular cartilage in the knee38,39. Some of these relate to the lack of an adequate nutrient supply to the centre of the disc (the region furthest from the source of nutrients but also most prone to degeneration), but there is also concern about applying cells to the disc via an injection and so creating a puncture hole, since this is known to precipitate degeneration in animal studies40 and humans who had discography as a diagnostic procedure41. The much larger hydrostatic pressure in the centre of the disc is another factor thought to perhaps have a negative effect on implanted cells42.

Despite these concerns, there are actually some encouraging results coming through from some trials which have been undertaken recently. For example, a Phase 3 trial with a subpopulation of allogeneic Stro3+ mesenchymal progenitor cells (MPCs) sourced from human bone marrow and culture-expanded is underway in the US and Australia following a successful completion of Phase 1 and 2 trials. This success may be due to a different mode of action (MoA) of the implanted cells than often assumed with MSCs. Whilst it is commonly accepted that MSCs can produce immunomodulatory and anti-inflammatory factors, there is also evidence from *in vitro* and *in vivo* ovine studies that the MSCs implanted into the disc have the effect of reducing catabolic enzymes such as the aggrecanases (ADAMTS4/5) and the MMPs 2,3,9 and 13, so inhibiting their degradation of proteoglycans and aggrecan43 . Hence if the main MoA is not to differentiate into disc cells with anabolic effects, but rather to reduce catabolism, then if the degradation can be halted, the implanted cells may not even need to remain alive for long, so nutrient flow may be irrelevant.

The Phase 3 trial of MPCs (MPC-06-ID; [NCT02412735](https://clinicaltrials.gov/show/NCT02412735)) has recruited 404 patients and is coming to completion with 24 month follow up in 202044. Patients were randomised to one of 3 arms (saline, hyaluronan (HA) or HA plus 6 million MPCs) and injected once with the appropriate treatment or placebo into the intervertebral disc. Outcome measures are pain via a visual analogue score (VAS) and a reduction in Oswestry Disability Index (ODI) functional score at 12 and 24 months. If this replicates the encouraging results of the Phase 2 trial of 100 patients with 4 arms (saline, HA, HA + 6 million MPCs and HA + 18 million MPCs), it could provide a huge boost to the use of MSCs, not only in the disc but in orthopaedics generally.

Certainly from a safety perspective, there appears to be little of concern for using MSC therapy in orthopaedic conditions. Centeno et al45 demonstrated that in >3000 procedures performed on 2400 patients (59 being in the spine), the incidence of neoplasm up to 9 years post-treatment was actually lower than in the general population.

**Conclusion**

The future could be an exciting time for clinicians in the spine field. The demand for regenerative approaches to intervertebral disc and vertebral bone is likely to increase significantly with changing demographics leading to more age-related disc degeneration and better cancer treatments meaning that patients survive the primary carcinoma longer, so more will go on to develop metastases in the spine. Looking even further into the future, treatment options for disc problems could well be largely by injection and the end of surgical interventions as we know them.

**FIGURE LEGENDS**

**Figure 1a.** The intervertebral disc is key to positioning all the other tissues, including the spinal cord (SC) and nerve roots (NR) within a functional spinal unit. Its different regions, the annulus fibrosus (AF), nucleus pulposus (NP) and cartilage endplate (CE) are populated with cells of different phenotypes, which synthesise the matrix in a random pattern in the NP and with a highly structured organisation in the AF.

**Figure 1b.** The lamellae of the AF are clearly integrated into the adjacent ones via both collagen fibres as seen with a form of polarising light in (A) and schematically (B). There is also an elastin network between and across lamellae (not shown). Image from Schollum et al46.

**Figure 2.** (A) Degeneration of the intervertebral disc can be identified by loss of signal on MRI (synonymous with loss of water) often described as a ‘black disc’ , seen at L4-5 and L5-S1 (arrows). This may be accompanied by ‘Modic’ changes in the adjacent vertebrae (\*). (B) Herniated disc at L5-S1 (arrow). A cauda equina caused by bilateral herniation of the L4-5 disc (arrow), seen in both an A-P view (C) and axial plane (D).

**Figure 3**. (A.) Post-operative X-ray image of L4-S1 percutaneous pedicle screw fixation providing L4-5 & L5-S1 anterior lumbar interbody fusion.

(B.) Pre-operative lateral erect radiograph of L3-4 degenerative listhesis with severe disc height collapse and foraminal stenosis (indicated with arrow)

(C.) Post-operative erect radiograph of the patient in (B.) with lateral trans-psoas inter body fusion (\*) & percutaneous pedicle screw fixation resulting in increased disc height and foraminal dimensions (indicated by arrow).

**Conflict of Interest**

The Authors declare that there is no conflict of interest

.

**References**

 1. Roberts S, Evans H, Trivedi J, Menage J. Histology and pathology of the human intervertebral disc. *J Bone Jt Surg [Am].* 2006;88:10-14.

 2. 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 (Phila Pa 1976 ).* 2002;27:2631-2644.

 3. Urban JPG, Roberts S. Degeneration of the intervertebral disc. *Arth Res Ther.* 2003;5:120-130.

 4. Schwab F, Dubey A, Gamez L, El Fegoun AB, Hwang K, Pagala M, Farcy JP. Adult scoliosis: prevalence, SF-36, and nutritional parameters in an elderly volunteer population. *Spine (Phila Pa 1976 ).* 2005;30:1082-1085.

 5. Brinjikji W, Diehn FE, Jarvik JG, Carr CM, Kallmes DF, Murad MH, Luetmer PH. MRI Findings of Disc Degeneration are More Prevalent in Adults with Low Back Pain than in Asymptomatic Controls: A Systematic Review and Meta-Analysis. *AJNR Am J Neuroradiol.* 2015;36:2394-2399.

 6. Williams FM, Scollen S, Cao D, Memari Y, Hyde CL, Zhang B, Sidders B, Ziemek D, Shi Y, Harris J, Harrow I, Dougherty B, Malarstig A, McEwen R, Stephens JC, Patel K, Menni C, Shin SY, Hodgkiss D, Surdulescu G, He W, Jin X, McMahon SB, Soranzo N, John S, Wang J, Spector TD. Genes contributing to pain sensitivity in the normal population: an exome sequencing study.  *PLoS Genet.* 2012;8:e1003095-

 7. Freiden MB, Tsepilov YA, Palmer M, Karssen LC, CHARGE Musculoskeletal working group, Suri P, Aulchenko YS, Williams FMK. Insight into the genetic achitecture of back pain and its risk factors from a study of 509,000 individuals. *bioRvix.* 2018;

 8. Ruetten S, Komp M, Merk H, Godolias G. Full-endoscopic interlaminar and transforaminal lumbar discectomy versus conventional microsurgical technique: a prospective, randomized, controlled study. *Spine (Phila Pa 1976 ).* 2008;33:931-939.

 9. Atlas SJ, Keller RB, Wu YA, Deyo RA, Singer DE. Long-term outcomes of surgical and nonsurgical management of lumbar spinal stenosis: 8 to 10 year results from the Maine lumbar spine study. *Spine (Phila Pa 1976 ).* 2005;30:936-943.

 10. Lee CS, Hwang CJ, Lee DH, Kim YT, Lee HS. Fusion rates of instrumented lumbar spinal arthrodesis according to surgical approach: a systematic review of randomized trials. *Clin Orthop Surg.* 2011;3:39-47.

 11. Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. *Spine (Phila Pa 1976 ).* 2002;27:2662-2673.

 12. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. *Spine J.* 2011;11:471-491.

 13. Zigler JE, Delamarter RB. Five-year results of the prospective, randomized, multicenter, Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential arthrodesis for the treatment of single-level degenerative disc disease. *J Neurosurg Spine.* 2012;17:493-501.

 14. Ross R, Mirza AH, Norris HE, Khatri M. Survival and clinical outcome of SB Charite III disc replacement for back pain. *J Bone Joint Surg Br.* 2007;89:785-789.

 15. Kong L, Ma Q, Meng F, Cao J, Yu K, Shen Y. The prevalence of heterotopic ossification among patients after cervical artificial disc replacement. *Medicine (Baltimore).* 2017;96:e7163-

 16. Roussouly P, Nnadi C. Sagittal plane deformity: an overview of interpretation and management. *Eur Spine J.* 2010;19:1824-1836.

 17. International Spine Study Group, Schwab FJ, Lafage V, Shaffrey CI, Smith JS, Moal B, Klineberg E, Ames CP, Hostin R, Fu K-MG, Kebaish KM, Burton DC, Akbarnia BA, Gupta MC, Deviren V, Mundis GM, Jr., Boachie-Adjei O, Hart RA, Bess RS. The Schwab-SRS Adult Spinal Deformity Classification: Assessment and Clinical Correlations Based on a Prospective Operative and Nonoperative Cohort. *Spine J.* 2012;12:S18-

 18. Worley N, Marascalchi B, Jalai CM, Yang S, Diebo B, Vira S, Boniello A, Lafage V, Passias PG. Predictors of inpatient morbidity and mortality in adult spinal deformity surgery. *Eur Spine J.* 2016;25:819-827.

 19. Hamad A, Vachtsevanos L, Cattell A, Ockendon M, Balain B. Minimally invasive spinal surgery for the management of symptomatic spinal metastasis. *Br J Neurosurg.* 2017;31:526-530.

 20. Brown SJ, Turner SA, Balain BS, Davidson NT, Roberts S. Is Osteogenic Differentiation of Human Nucleus Pulposus Cells a Possibility for Biological Spinal Fusion? *Cartilage.* 2018;1947603518754628-

 21. Blanco JF, Villaron EM, Pescador D, da Casa C, Gomez V, Redondo AM, Lopez-Villar O, Lopez-Parra M, Muntion S, Sanchez-Guijo F. Autologous mesenchymal stromal cells embedded in tricalcium phosphate for posterolateral spinal fusion: results of a prospective phase I/II clinical trial with long-term follow-up. *Stem Cell Res Ther.* 2019;10:63-

 22. Summers B, Eisenstein SM. Donor site pain from the ilium. A complication of lumbar spine fusion. *J Bone Joint Surg Br.* 1989;71B:677-680.

 23. Meisel HJ, Siodla V, Ganey T, Minkus Y, Hutton WC, Alasevic O. Clinical experience in cell-based therapeutics: Disc chondrocyte transplantation - A treatment for degenerated or damaged intervertebral disc. *Biomolecular Engineering.* 2006;24:5-21.

 24. Sakai D, Schol J. Cell therapy for intervertebral disc repair: Clinical perspective. *J Orthop Translat.* 2017;9:8-18.

 25. Binch ALA, Richardson SM, Hoyland JA, Barry FP. Combinatorial conditioning of adipose derived-mesenchymal stem cells enhances their neurovascular potential: Implications for intervertebral disc degeneration. *JOR Spine.* 2019;2:e1072-

 26. Purmessur D, Cornejo MC, Cho SK, Hecht AC, Iatridis JC. Notochordal cell-derived therapeutic strategies for discogenic back pain. *Global Spine J.* 2013;3:201-218.

 27. Quintin A, Schizas C, Scaletta C, Jaccoud S, gerber S, Osterheld MC, Juillerat L, Applegate LA, Pioletti DP. Isolation and in vitro chondrogenic potential of human foetal spine cells. *J Cell Mol Med.* 2009;13:2559-2569.

 28. Henriksson H, Thornemo M, Karlsson C, Hagg O, Junevik K, Lindahl A, Brisby H. Identification of cell proliferation zones, progenitor cells and a potential stem cell niche in the intervertebral disc region: a study in four species. *Spine (Phila Pa 1976 ).* 2009;34:2278-2287.

 29. van Ooij A, Oner FC, Verbout AJ. Complications of artificial disc replacement: a report of 27 patients with the SB Charite disc. *J Spinal Disord Tech.* 2003;16:369-383.

 30. Turner S, Balain B, Caterson B, Morgan C, Roberts S. Viability, growth kinetics and stem cell markers of single and clustered cells in human intervertebral discs: implications for regenerative therapies.  *Eur Spine J.* 2014;23:2462-2472.

 31. Sakai D, Nakamura Y, Nakai T, Mishima T, Kato S, Grad S, Alini M, Risbud MV, Chan D, Cheah KS, Yamamura K, Masuda K, Okano H, Ando K, Mochida J. Exhaustion of nucleus pulposus progenitor cells with ageing and degeneration of the intervertebral disc. *Nat Commun.* 2012;3:1264-

 32. Yoshikawa T, Ueda Y, Miyazaki K, Koizumi M, Takakura Y. Disc Regeneration Therapy Using Marrow Mesenchymal Cell Transplantation: A report of Two Case Studies. *Spine.* 2010;35:E475-E480.

 33. Hamilton DJ, Seguin CA, Wang J, Pilliar RM, Kandel RA. Formation of a nucleus pulposus-cartilage endplate construct in vitro. *Biomat.* 2006;27:397-405.

 34. Nerukar NL, Elliot DM, Mauck RL. Mechanical design criteria for intervertebral disc tissue engineering. *J Biomech.* 2010;1017-1030.

 35. Melrose J, Roberts S, Smith S, Menage J, Ghosh P. Increased nerve and blood vessel ingrowth associated with proteoglycan depletion in an ovine anular lesion model of experimental disc degeneration. *Spine.* 2002;27:1278-1285.

 36. Guterl CC, See EY, Blanquer SB, Pandit A, Ferguson SJ, Benneker LM, Grijpma DW, Sakai D, Eglin D, Alini M, Iatridis JC, Grad S. Challenges and strategies in the repair of ruptured annulus fibrosus. *Eur Cell Mater.* 2013;25:1-21.

 37. Melrose J. Strategies in regenerative medicine for intervertebral disc repair using mesenchymal stem cells and bioscaffolds. *Regen Med.* 2016;11:705-724.

 38. Kandel R, Roberts S, Urban JPG. Tissue engineering of the intervertebral disc. *European Spine Journal.* 2008;17:480-491.

 39. Johnson WE, Roberts S. 'Rumours of my death may have been greatly exaggerated': a brief review of cell death in human intervertebral disc disease and implications for cell transplantation therapy. *Biochem Soc Trans.* 2007;35:680-682.

 40. Alini M, Eisenstein SM, Ito K, Little C, Kettler AA, Masuda K, Melrose J, Ralphs J, Stokes I, Wilke HJ. Are animal models useful for studying human disc disorders/degeneration? *Eur Spine J.* 2008;17:2-19.

 41. Carragee EJ, Don AS, Hurwitz EL, Cuellar JM, Carrino JA, Herzog R. 2009 ISSLS Prize Winner: Does discography cause accelerated progression of degeneration changes in the lumbar disc: a ten-year matched cohort study. *Spine (Phila Pa 1976 ).* 2009;34:2338-2345.

 42. Malandrino A, Noailly J, Lacroix D. The effect of sustained compression on oxygen metabolic transport in the intervertebral disc decreases with degenerative changes. *PLoS Comput Biol.* 2011;7:e1002112-

 43. Shu CC, Dart A, Bell R, Dart C, Clarke E, Smith MM, Little CB, Melrose J. Efficacy of administered mesenchymal stem cells in the initiation and co-ordination of repair processes by resident disc cells in an ovine (Ovis aries) large destabilizing lesion model of experimental disc degeneration. *JOR Spine.* 2018;1:e1037-

 44. Mesoblast Ltd. Chronic low back pain due to disc degeneration. *https://www mesoblast com/product-candidates/spine-orthopedic-disorders/chronic-discogenic-low-back-pain.* Accessed 17th January 2020

 45. Centeno CJ, Al Sayegh H, Freeman MD, Smith J, Murrell WD, Bubnov R. A multi-center analysis of adverse events among two thousand, three hundred and seventy two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions. *Int Orthop.* 2016;40:1755-1765.

 46. Schollum ML, Robertson PA, Broom ND. ISSLS Prize Winner: Microstructure and Mechanical Disruption of the Lumbar Disc Annulus. Part I: A Microscopic Investigation of the Translamellar Bridging Network. *Spine.* 2008;33:2702-2710.