The Lumbar Degenerative Disc: Confusion, Mechanics, Management

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INTRODUCTION

The lumbar disc represents a complex biological ecosystem dependent on a homeostatic environment. Consistent with a natural ecosystem, demise and degeneration occurs as a consequence of one or a combination of environmental disruptions. With this understanding, we must move away from the general term “degenerative disc disease” (DDD) and move toward the determination of etiology-specific conditions and the development of etiology-specific preventative or therapeutic strategies. Our vision must be the optimization of treatment outcomes for specific conditions of the lumbar disc and the implementation of degeneration prevention strategies through genetic or tissue engineering or other biologic modalities.

Confusion

A major source of confusion in the universe of spine care is the reality that the scientific literature contains multiple, widely different and expensive therapeutic algorithms, which have been established as successful in the treatment of the ambiguous, all-inclusive lumbar DDD. Current options range from non-invasive, purportedly less expensive structured physical therapy and the popular, widely used chiropractic manipulation to the invasive, purportedly more expensive discectomy and fusion, and, most recently, disc replacement therapy.

Hayden et al. performed a meta-analysis of 61 randomized, controlled trials (RCT) evaluating the effectiveness of exercise therapy in nonspecific adult acute, subacute, and chronic low back pain (LBP) patients in whom the majority were diagnosed with lumbar DDD. In their review, it was determined that exercise therapy resulted in a statistically significant improvement in functional outcome with decreased pain over other non-interventional treatment options in patients with chronic LBP. A number of RCTs have shown that structured, individually designed programs, including stretching or muscle strengthening, and delivered with supervision, improved overall pain and functional scores in patients with chronic LBP. Furthermore, Hayden et al. indicated that a structured, graded activity program improves absenteeism outcomes in patients with subacute LBP, significant in the fact that worker absenteeism led to $8.8 billion in work-related low back claims in 1995.

Chiropractic manipulation has become the most common “alternative” therapy for management of LBP. An estimated 15% of the United States population seeks chiropractic care annually, with the overwhelming majority of visits for neck and LBP. The availability of practitioners, the perceived low cost of care, and association of symptomatic relief with chiropractic care have contributed to its popularity, even though the mechanisms of pain relief are poorly understood. Meade et al. conducted a RCT comparing chiropractic and hospital outpatient exercise therapy programs in the treatment of LBP. Results from their trial demonstrated long-term benefit of chiropractic care compared with outpatient therapy in patients with chronic or severe pain. Aure et al. reported a multicenter RCT with a 1-year follow-up period demonstrating significantly greater improvement with manual therapy than exercise therapy in patients with chronic LBP in all outcome measures, including pain, functional disability, general health, spinal range of motion, and return to work. Notwithstanding, Andersson et al. found that the only significant difference among chiropractic manipulation, physical therapy, and standard medical care in the treatment of chronic LBP was a favorable reduction in analgesic consumption in the group receiving spinal manipulation. Moreover, a recent meta-analysis revealed statistically significant clinical benefits of spinal manipulative therapy only when compared with either sham manipulation or a group of therapies judged to be ineffective or even harmful.

Intradiscal electrothermal therapy (IDET) was developed in 1997 as a potential alternative therapy for selected patients with symptomatic degenerative disc disease who had failed to improve with activity modification and aggressive nonoperative care. Proponents tout IDET as the optimal non-surgical treatment for LBP secondary to internal disc disruption (IDD), in which pain is thought to be caused by mechanical and chemical mediation of nociceptors within the outer third of the annulus fibrosus (AF). By definition, no
nerve root irritation, radicular pain, or neurological deficit is involved clinically. Hallmark radiographic changes of DDD, such as disc space narrowing, osteophyte formation, endplate sclerosis, and gas formation within the disc space, are not present; furthermore, there is no associated herniation, prolapse of disc material, or segmental instability noted. It is thought that discogenic LBP in this group of patients is caused by radial fissures extending from the nucleus pulposus (NP) to the outermost surface of the AF. These tears are visualized on magnetic resonance imaging (MRI) scans as a high intensity zone (HIZ), considered to be a highly specific finding for IDD. The HIZ is present as a high intensity signal on T2-weighted imaging in the substance of the posterior AF, clearly distinguished from the NP, and surrounded on all sides by the low intensity signal of the AF. These radial tears are thought to involve branches of the recurrent sinuebral nerve (of Luschka), which enters the spinal canal and innervates the superficial annulus of the levels immediately below and above via small A-delta and C pain fibers, providing anatomic rationale for the poor localization of a painful disc.

Clinical success rates of IDET vary significantly from study to study, due in part to the paucity of well-controlled studies with adequate follow-up periods. Nevertheless, appreciable measures of success have been reported. Saal and Saal reported on a prospective outcome study with a minimum 2-year follow-up period in patients with discogenic LBP greater than 3 months in duration. This study has been widely regarded for its design in selecting patients who had failed to improve after a 6-month comprehensive care program, consisting of education, physical therapy, activity modification, anti-inflammatory medication, and epidural steroid injections. Statistically significant improvements in Visual Analog Scale (VAS) and Short Form-36 (SF-36) measurements were reported with a 71% overall success rate. Pauza et al. reported 6-month results of a randomized, prospective double-blind study of 55 patients with statistically significant improvement in the IDET group compared with the placebo as measured by VAS and Oswestry Disability Index (ODI). However, whereas approximately 40% of the patients achieved more than 50% relief of their pain, roughly 50% experienced no appreciable benefit. The authors concluded that IDET seemed to provide worthwhile relief in a small number of strictly defined patients. Complications from IDET may be largely underreported. Although there are nonspecific descriptions of catheter breakage and retention in the literature, there are few reports of infection, bleeding, or procedure-related complications. One case of cauda equina syndrome following treatment has been reported, which was felt to be caused by inadvertent catheter placement into the spinal canal.

The biological effects of IDET continue to be debated, as the theoretical mechanisms of action have not been clearly validated. In fact, review of the current literature provides no clear consensus regarding the effects of IDET on neuronal deafferentation, collagen modulation, or spinal stability. Many proponents feel that thermal ablation of the pain-sensitive nerve fibers in the outer annulus is responsible for decrease in discogenic LBP following IDET. However, a recent animal study demonstrated that IDET did not denervate posterior annular lesions on histological and immunohistochemical evaluation, giving rise to the possibility that reported benefits of IDET seem to be related to factors other than denervation. Others theorize that collagen architectural modulation occurs following IDET, providing increased stiffness and annular stability, though no alteration of annular morphology was observed when IDET-treated regions were compared with non-heated regions of the same disc in a cadaveric study. This same study also showed no difference in stability before or after IDET. In another recent study, HIZ remained visible on lumbar MRI scans of patients 6 months after IDET, challenging the notion the procedure is capable of sealing annular tears by stimulating changes in Type I collagen.

Resnick et al., in their extensive analysis of the literature pertaining to degenerative lumbar disc disease, found Class III evidence to support the use of epidural steroid injection (ESI) therapy in selected patients. Specifically, lumbar ESI were recommended as a treatment option to provide temporary, symptomatic relief in selected patients with chronic low-back pain. The authors noted difficulties in interpreting earlier reports, which did not consistently use fluoroscopic imaging and contrast administration to confirm needle placement before 2000. In addition, a number of earlier studies included mixed patient populations, consisting of those with pain primarily radicular in origin, as well as those with primary LBP. Thus, the ability to discern the effects of lumbar ESI has been confounded by the inclusion of patients with primary radicular complaints in a number of earlier studies. Butterman reported greater improvement in pain and outcome scales in the first 6 months after ESI in patients with symptomatic lumbar DDD with inflammatory endplate changes (Modic Type I) than in those without adjacent endplate changes on MRI scans.

Since the early 1990s, a number of studies have shown lumbar fusion achieves superior results to either nonoperative therapy or decompressive surgery alone in the treatment of refractory LBP owing to degenerative lumbar disorders. However, the greatest debate concerning the use of lumbar fusion exists for the diagnosis of discogenic LBP or IDD. Available information indicates that morphological abnormalities, such as bone spurs, Modic endplate changes, and intervertebral disc bulges seen on MRI scans in conjunction with concordant pain on discography may be predictive of patients who might benefit from a stabilization procedure.

In the only randomized, prospective trial to date on the
surgical treatment of patients with discogenic LBP, Fritzell et al.\textsuperscript{21} evaluated a series of 294 patients undergoing either conservative management or one of three lumbar fusion procedures. Two-year follow-up data demonstrated significantly better outcomes in fusion patients over conservatively treated patients in clinical and functional assessment scales, including ODI and VAS. Although not blinded, the Swedish Lumbar Spine Study Group provided Class I evidence for the beneficial outcome derived from lumbar fusion in patients with discogenic LBP.\textsuperscript{21} As such, it has led to the increasing opinion that lumbar arthrodesis can provide clear benefit in reducing pain and improving overall function in patients with a painful lumbar motion segment who fail conservative therapy.

Whereas instrumentation seems to increase fusion rates and likely prevents progression of spondylolisthesis, the existing literature is equivocal on whether or not associated improvement in clinical outcome exists. Fritzell et al.\textsuperscript{21} demonstrated that posterolateral fusion (PLF) with or without pedicle screw fixation, and circumferential fusion consisting of interbody and PLF with instrumentation both markedly reduce pain and improve function in patients with chronic, discogenic LBP without a statistically significant difference between the techniques. Conversely, Zdeblick\textsuperscript{22} prospectively randomized a series of 124 patients requiring surgery for various degenerative lumbar conditions to undergo either instrumented or noninstrumented PLF. A statistically significant difference was demonstrated in radiographic fusion rates between the two groups. In addition, the proportion of patients rated as having good or excellent clinical results, based on pain relief and reduced work absenteeism, was highest in the rigid transpedicular fixation group. These findings provided Class I evidence that rigid pedicle screw/rod fixation leads to markedly higher fusion rates with better clinical outcomes than noninstrumented posterolateral fusion.

From a biomechanical, anatomic, and physiological standpoint, the theoretical advantages of interbody fusion versus PLF seem obvious. Interbody support restores disc space height, facilitates correction of alignment and balance, acts to prevent progression of spondylolisthesis, and provides load sharing to prolong the life of instrumentation. Whereas many studies have shown that lumbar interbody fusion achieves a higher fusion rate than posterolateral fusion, results to the contrary have also been reported. The question of whether or not interbody fusion significantly improves outcome remains to be determined in this patient population with chronic, discogenic LBP. Furthermore, complications, such as pseudarthrosis, problems owing to graft site harvest, and accelerated adjacent level deterioration remain factors limiting successful outcomes as well. In fact, symptomatic adjacent level deterioration requiring reoperation is estimated to occur in as many as 20 to 25% of patients in the decade after a successful lumbar fusion.\textsuperscript{23}

Although considered to be the “gold standard” of surgical treatment of lumbar DDD, the results of discectomy and fusion remain suboptimal in a large number of cases. Aforementioned complications, including pseudarthrosis, iliac crest donor site pain, neural injury from pedicle screw malposition, and adjacent level deterioration have led to the development of total disc replacement (TDR) with an artificial device. The concept of a prosthetic disc has gained popularity owing to the perceived benefits of motion preservation, reduction in adjacent level deterioration, and avoidance of donor site morbidity. Currently, the only artificial disc approved by the Food and Drug Administration (FDA) for use in the lumbar spine is the Charite™ device (DePuy Spine, Raynham, MA). Although the ProDisc-II™ (Synthes, Paoli, PA) has completed its FDA Investigational Device Exemption (IDE) clinical trial and evaluation of 2-year follow-up data, it has not yet received FDA approval at this time. The Maverick™ (Medtronic Sofamor Danek, Memphis, TN) and Flexicore™ (Stryker, Kalamazoo, MI) artificial discs are currently undergoing multicenter trials.

Blumenthal et al.\textsuperscript{24} reported 2-year follow-up data on the prospective, randomized, multicenter FDA IDE trial of the Charite™ artificial disc versus lumbar fusion. The authors validated clinical outcomes with this device as equivalent to those with anterior lumbar interbody fusion with a BAK device (Zimmer Spine, Minneapolis, MN). However, the artificial disc group demonstrated statistically significant superiority in two areas, a 1-day shorter hospitalization and a lower reoperation rate (5.4 versus 9.1%). Furthermore, the authors reported significantly higher patient satisfaction rates in the TDR group than that seen in the fusion group (73.7 versus 53.1%).

Successful outcomes with long-term follow-up data have been reported in the European experience with lumbar disc arthroplasty. Lemaire et al.\textsuperscript{25} reported 105 cases with the Charite™ artificial disc with mean follow-up duration of 51 months. Excellent results were reported in 79% of the cases, with 87% of the patients returning to work. Marnay\textsuperscript{25} reported on his series of 93 ProDisc™ devices implanted in 64 patients with an average follow-up period of 8.6 years. A 93% patient satisfaction rate was reported with no device-related safety issues identified during review.

Even with this recent breakthrough technology in the treatment of symptomatic lumbar DDD, it is not clear at what point in the degenerative cascade that TDR should be instituted with a reasonable risk-to-benefit expectation. The mechanics of the degenerative cascade in the lumbar spine are complex and interrelated with three basic stages of pathophysiology along the path (Figure 3.1).\textsuperscript{27} The lumbar motion segment proceeds through dysfunction, instability, and immobility/stabilization with arthrosis of the pathological level. Patients most likely to benefit from TDR may be those who are likely ideal candidates for IDET, chiropractic care, or
structured physical therapy with less risk involved. Those with symptomatic, severe end-stage disease with disc space collapse are likely too far advanced for nonoperative therapy or disc prosthesis. In these cases, lumbar fusion may be the superior alternative.

Our current state of confusion derives from the fact that there is a wide range of successful treatment options for the ambiguously defined symptomatic lumbar DDD, with each of these treatment strategies supported by credible clinical trials which may or may not be successful in any given situation. In this environment, the reality is that technological innovation may actually add to the confusion, rather than helping to resolve it.

Contributing to confusion surrounding symptomatic lumbar DDD is ambiguous diagnostic terminology and technology which attempts to differentiate subsets of DDD based on imaging characteristics. In Figure 3.2, the arrows point to a HIZ representing an annular tear. In addition, one can also appreciate the degree of degeneration in the L4–L5 disc in the upper left image, as well as the relative dark disc and mild disc bulge noted at the L5–S1 level in the upper right image. These findings may or may not be classified under the heading of DDD or conversely, all of the above findings might be described in the spectrum of DDD by a given clinician.

With regards to the lumbar intervertebral disc as a complex ecosystem, the intent of treatment should be aimed at repair and prevention of further degeneration. Key to this strategy is identification of the component problem with a strategy aimed at prevention or correction of the problem. Interventions in cases in which symptoms have become chronic in nature are likely to have little chance of reversing the degenerative process.
The intervertebral discs comprise the largest avascular tissue in the body and exist in a largely anaerobic environment. The AF consists primarily of Type I collagen, and the NP consists of a well-hydrated extracellular matrix (ECM) of proteoglycans and collagens (mainly Type II, with Types VI, IX, X, XI to a lesser degree). Type IX collagen is thought to provide mechanical support in the NP by acting as a bridging molecule. The strength of the lumbar disc is related to the fluid and proteoglycan content of the disc. Proteoglycans are hydrophilic, negatively charged molecules which serve to internally pressurize the disc by drawing water via osmosis into the NP; aggregan is the primary proteoglycan of the NP. Collagens provide the tensile strength of the disc, whereas proteoglycans provide stiffness, compression resistance, and viscoelasticity. Figure 3.3 depicts a “healthy” disc with Type II collagen fibrils attached to proteoglycans, contributing to the hydration of the nucleus and its capacity to sustain substantial loads and shear forces. With aging, Type II collagen, proteoglycan, and therefore water content in the disc decrease as the process of disc degeneration ensues (Figure 3.4). In addition, the amount of hydration within the disc is inversely proportional to applied stress, suggesting that applied mechanical loads and shear forces also contribute to a loss of hydration and proteoglycan content in the disc.28

The disc itself has a low metabolic rate and receives most of its nutrition via passive diffusion from a network of capillary beds in the subchondral endplate region of the vertebral body. This process is dependent upon nonvascular pores or channels in the endplate region through which major nutrients, including oxygen and glucose, diffuse across into the discs. There seems to be a small component of convection delivery and bulk flow attributed to the motion of the lumbar spine as well. The endplate capillary beds and diffusion channels are critical to the maintenance of the homeostatic environment in which adequate nutrient inflow is balanced with egress of cellular metabolites or waste products. After the third to fourth decades of life, or with injury, metabolic derangement, or nicotine use, there is a decrease in the endplate capillary bed blood supply to the intervertebral disc, which disrupts the homeostasis and allows for an increasingly anaerobic, acidic environment with accumulation of lactate and other waste by-products. As a result, cellular dysfunction ensues with decreased proteoglycan production, increased catabolism, and loss of structural integrity of the ECM, all of which contribute to dehydration of the disc and initiation of the degenerative cascade. A vicious cycle is created as early disc degeneration may stress the disc leading to an acidic environment, which results in shutdown of normal cellular metabolism. The loss of cellular function in this setting leads to a decrease in the production of matrix proteins, causing further disc degeneration.

The disc is further susceptible to injury as repetitive mechanical loads and trauma become more unevenly distributed across the disc space and endplate with further loss of hydration of the NP. Radial tears or fissures in the AF develop as a result of the mechanical stress in the disc, as well as the loss of the well-organized lamellar architecture of the AF. This sets off an inflammatory process within the disc, leading to angiogenesis and release of cytokines, interleukins, prostaglandins, and other mediators, which are cytotoxic and purported pain generators in the disc. The increased vascularity facilitates macrophage and polymorphonuclear recruitment in the environment surrounding a radial fissure. With further degeneration leading to cartilaginous endplate thickening and calcification, diffusion of nutrients and metabolic waste products comes to a near halt. This impaired nutrient exchange leads to further dehydration and degradation of the ECM with severe, advanced disc degeneration, disc space collapse, and arthroses of the vertebral bodies across the disc space manifested as bony hypertrophy and marginal osteophyte formation.

Recent findings have provided a greater understanding of the significance of activity at the cellular level in acceleration of the degenerative process of the lumbar disc. Specifically, interleukin-1 (IL-1) seems to play a role in destruction...
of the ECM by decreasing proteoglycan synthesis by disc cells and inducing prostaglandin E2. Other related cytokines, including IL-6, have also been identified in degenerated disc specimens.\textsuperscript{28} In addition to cytokines and other inflammatory mediators involved in the degenerative cascade, degradative enzyme activity is also increased in degenerated disc specimens. Catabolic enzymes active in the disc include cathepsins, lysozymes, aggrecanases, tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and several matrix metalloproteinases (MMPs). Furthermore, toxic cellular byproducts, such as nitric oxide and oxygen free radicals, are also elevated in degenerated disc specimens and have been demonstrated to damage cellular membranes and act as an intracellular second messenger inducing degenerative pathways.

Apoptosis may also play a major role in the reduction of the number of cells in the aging and degenerating human disc. Gruber et al.\textsuperscript{29} were among the first to investigate the role of apoptosis in disc degeneration. They found a higher incidence of apoptosis in AF cells in surgical specimens of aging and degenerated disc versus normal controls. The authors also noted that surviving AF cells were not synthet-
inic.
ral-mediated gene transfer of TIMP-1 to degenerated disc cell cultures and demonstrated increased proteoglycan synthesis, which exceeded that measured in cells undergoing transfection with BMP-2 at lower viral concentrations. The results further indicated an optimal dose for gene delivery of TIMP-1, beyond which the increase in proteoglycan synthesis diminished, whereas adenoviral-mediated BMP-2 transfer exhibited a clear dose-response relationship between increasing viral load and increased proteoglycan production.

Other adenoviral-mediated gene therapy in lumbar DDD involve intracellular regulators which promote anabolic activity. Transfection with Sox-9, a chondrocyte marker which upregulates transcription of Type II collagen messenger ribonucleic acid (mRNA), led to increased Type II collagen production in in vitro experiments and prevented histological evidence of degenerative changes in the NP in a rabbit puncture model. The LIM mineralization protein-1 (LMP-1) was first described as an essential regulator of osteoblastic differentiation and bone formation by Boden et al. Yoon et al. demonstrated significant increases in BMP-2, 7 and corresponding aggrecan levels after transfection of intervertebral disc cells with LMP-1 in vitro and in vivo. The authors established that LMP-1 mediates control of proteoglycan production through its action on BMP in the NP.

Overall, attempts to apply gene therapy systematically have been met with frustration, leading to efforts directed at local delivery of gene therapy. A number of different vectors have been used to deliver genetic material into cells of the disc. Viral vectors include adenovirus, adeno-associated virus or Parvovirus, and retrovirus. By and large, the adenovirus has been used most frequently in gene therapy application in DDD. Its advantages include the fact that it does not require cell division for transduction, which is highly efficient with this virus, and it also has a large genetic carrying capacity. The adeno-associated virus also has the capacity to infect non-dividing cells, but has a small carrying capacity. It is also difficult to produce, as limited titers of the virus can be generated. However, its risk of insertion mutagenesis and development of a malignancy is minimal, in comparison with the adenovirus. The retrovirus does not have the ability to infect nondividing cells and has a limited carrying capacity, which do not make this a favorable vector in gene therapy applications of the degenerated disc. Nonviral vectors are relatively easy to produce, chemically more stable than viral vectors, do not elicit an immune response in general, and are not limited by the size of genetic material to be introduced. However, they have low efficiency of transfection and short duration of protein expression. Plasmids, cationic liposomes, and DNA-ligand complexes are examples of nonviral vectors. The gene gun is a particle-mediated transfer technique by which microscopic metallic debris is coated with DNA and injected into the cell under an accelerating force. Its efficiency is lower than that of viral methods, and though it is thought to be safer than viral-mediated delivery, there is concern of tissue toxicity arising from contact with the metallic debris.

Strategies for gene transfer involve either in vivo or ex vivo approaches. In vivo therapy involved the direct injection of vector-gene construct into the body. A concern is that direct exposure to either the virus or DNA poses potential risks. In addition, this technique of transfection is less controlled with less reliable transgene expression. Most in vivo techniques utilize the adenovirus because of its ability to transduce nondividing cells. The ex vivo strategy involves harvest of cells from the host which are then transfected with the therapeutic gene in tissue culture. Cells with proper transgene expression are then implanted into host target tissue. Although more complex, this technique does not directly expose the patient to any naked viral or DNA components. In addition, conversion of cells in vitro is more controlled, presumably allowing for more efficient transfection with the therapeutic gene. Another advantage of the ex vivo technique is ability to couple converted cells with certain biomaterials, such as a scaffold or carrier. However, this method is more complex, time-consuming, and may potentially be less cost-effective than the in vivo strategy.

The ultimate goal of management of lumbar DDD is to maintain the balance between synthesis and degradation of the ECM and subsequent disc hydration in spite of all of the degenerative factors involved, with the belief that maintenance or restoration of disc health will be accompanied by symptom reduction and prolonged function of the lumbar motion segment. The real tools for management of lumbar DDD lie ahead in the future. Diagnostic and therapeutic strategies will be aimed at the underlying mechanisms involved in degeneration. The understanding of specific processes responsible in each patient will require bioanatomic imaging correlated with specific mechanisms of degeneration, such as the loss of diffusion capacity, apoptosis, or an increase in catabolic activity. Safe and effective gene or cell-mediated therapies must be established in valid animal models of disc degeneration and reproduced in human in vivo studies as well. We must appreciate the inadequacies of our current diagnostic and treatment modalities and strive for better understanding of the pathological, degenerative processes involved in each patient. Our Quo Vadis must embrace the concept of the intervertebral disc as a complex biological system, and we must foster and participate in the research of the causes, prevention, and treatment at the cellular level.

REFERENCES


