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REVIEW

Pathophysiology, diagnosis, and treatment of discogenic low back pain

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Abstract

Discogenic low back pain is a serious medical and social problem, and accounts for 26%-42% of the patients with chronic low back pain. Recent studies found that the pathologic features of discs obtained from the patients with discogenic low back pain were the formation of the zones of vascularized granulation tissue, with extensive innervation in fissures extending from the outer part of the annulus into the nucleus pulposus. Studies suggested that the degeneration of the painful disc might originate from the injury and subsequent repair of annulus fibrosus. Growth factors such as basic fibroblast growth factor, transforming growth factor β1, and connective tissue growth factor, macrophages and mast cells might play a key role in the repair of the injured annulus fibrosus and subsequent disc degeneration. Although there exist controversies about the role of discography as a diagnostic test, provocation discography still is the only available means by which to identify a painful disc. A recent study has classified discogenic low back pain into two types that were annular disruption-induced low back pain and internal endplate disruption-induced low back pain, which have been fully supported by clinical and theoretical bases. Current treatment options for discogenic back pain range from medicinal anti-inflammation strategy to invasive procedures including spine fusion and recently spinal arthroplasty. However, these treatments are limited to relieving symptoms, with no attempt to restore the disc's structure. Recently, there has been a growing interest in developing strategies that aim to repair or regenerate the degenerated disc biologically.

Key words: Intervertebral disc; Degeneration; Diagnosis; Treatment; Discogenic low back pain; Classification; Internal disc disruption; Internal annular disruption; Internal endplate disruption

Core tip: Discogenic low back pain is the most common type of chronic low back pain. Why lumbar disc degeneration leads to pain is one of the most important topics in medical field. Studies have revealed that pathologic features of painful discs were the formation of the zones of vascularized granulation tissue, with extensive innervation in annular fissures. Provocation discography now still is the only available means by which to identify a painful disc. There are a multitude of treatments used in clinical practice to treat chronic low back pain, with little consensus amongst clinicians as to which is the best approach.

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INTRODUCTION

Chronic low back pain is a serious medical and social problem, and one of the common causes responsible for disability. It is estimated that, in all populations, an individual has an 80% probability of having low back

pain at some period during their life time, and about 18% of the population experiences low back pain at any given moment[1,2]. According to US National Center for Health Statistics reports, 14% of new patients that went to a hospital for treatment were patients with low back pain, which represents 13 million people. About 3% of all patients discharged from hospitals have symptomatic low back pain. The expense of treating low back pain is higher than $100 billion each year[3].

The prerequisite for successfully treating low back pain is to make an accurate pathological diagnosis. Despite the inherent challenge in elucidating the specific etiology of chronic low back pain, diagnostic procedures can reveal its source in 90% of patients. DePalma *et al*[4] found that the prevalence of zygapophysial joints, sacroiliac joints, and lumbar discs was 31%, 18%, and 42%, respectively. They confirmed the disc as the most common etiology of chronic low back pain in adults. Crock[5] first proposed the concept of internal disc disruption (IDD), which indicated the discogenic pain syndrome caused by disc degeneration and non-nerve root referred pain. IDD causing discogenic low back pain accounts for 26%-42% of chronic low back pain patients[4,6,7]. IDD had been assigned as a separate clinical entity to differentiate it from other types of disc degenerative low back pain, such as lumbar disc herniation, degenerative disc disease (DDD) and lumbar segment instability[8]. Lumbar X-ray images of IDD patients show no characteristic changes in degenerative disc diseases such as intervertebral space narrowing, osteophyte formation, endplate sclerosis, and gas formation within disc space[8].

This paper reviews the pathophysiology, diagnosis, and treatment of discogenic low back pain according to the existing literature.

PATHOPHYSIOLOGY

The intervertebral disc is the main joint between two consecutive vertebrae in the vertebral column. Each disc consists of three different structures: an inner gelatinous nucleus pulposus, an outer annulus fibrosus that surrounds the nucleus pulposus, and two cartilage endplates that cover the upper and lower surfaces of vertebral bodies. The cells that form the annulus fibrosus, particularly in the outer region, are fibroblast-like and arranged parallel to the collagen fibers, whereas those in the inner annulus fibrosus are chondrocyte-like. The nucleus pulposus contains collagen fibers that are randomly distributed and elastin fibers that are radially organized embedded in a highly hydrated aggrecan-containing gel. Chondrocyte-like cells synthesize type Ⅱ collagen, proteoglycans, and non-collagenous proteins that form the matrix of the nucleus pulposus and the cartilage endplate. Fibroblast-like cells synthesize type I and type Ⅱ collagen for the annulus fibrosus[9]. Proteoglycans consist of a core protein from which radiate chains of glycosaminoglycans containing keratin sulphate and chondroitin sulphate. Multiple proteoglycans are joined to a hyaluronic acid chain to form aggrecan. Aggrecans are held together by type Ⅱ collagen, which is cross-linked by type Ⅸ collagen. Aggrecan is the most common proteoglycan in the disc, and comprises approximately 70% of the nucleus pulposus and 25% of the annulus fibrosus. Aggrecan provides a high level charge density, which creates a high osmotic pressure for retaining water within the nucleus pulposus[10]. A young healthy disc behaves like a water bed, with the high water content of the nucleus and inner annulus enabling the tissue to act like a fluid. Only the outermost annulus acts as a tensile "skin" to restrain the nucleus.

Disc cells synthesize their matrix and break down existing matrix by producing and activating degradative enzymes, including matrix metalloproteinases (MMPs) and "a disintegrin and metalloproteinase" (ADAMS). Degradation of the matrix allows it to be refreshed by newly-synthesized components. Several growth factors, such as bone morphogenetic protein-2 (BMP-2), BMP-7 (also known as osteogenic protein-1; OP-1), growth differentiation factor-5 (GDF-5), transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), and others have been found to stimulate matrix production, while interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) inhibit the synthesis of matrix by enhancing its catabolism[9,10].

Disc degeneration will occur if the matrix is not normal. At a molecular level, degeneration will be expressed by the production of abnormal components of the matrix or by an increase in the mediators of matrix degradation, such as IL-1 and TNF-α, and of MMPs and a reduction in the levels of tissue inhibitors of metalloproteinases (TIMPs). Several factors have been considered to cause disc degeneration. Genetic predisposition, mechanical load, and nutritional factors are widely regarded as important contributors to the degenerative process[11]. However; detailed characterization of this complex interplay remains elusive. With the disc degeneration, there is a net loss of proteoglycans and water from the nucleus, leading to poor hydrodynamic transfer of axial stresses to the outer anulus fibrosus. The disc degeneration may result from an imbalance between the anabolic and catabolic processes or the loss of steady state metabolism that is maintained in the normal disc. Alterations in both anabolic and catabolic processes are thought to play key roles in the onset and progression of disc degeneration.

Disc degeneration usually appears in magnetic resonance imaging (MRI) T2-weighted images as a decline in signal intensity, *i.e.*, the so-called "black" disc. MRI may identify a degenerative disc and an annular tear, but it will not help differentiate between a disc which is pathologically painful and one which is physiologically aging[12]. Disc degeneration is a very complicated biological process. Previous views on disc degeneration and the mechanism underlying it were mainly based on histological and biochemical studies using human disc herniation specimens from surgery and animal models of aging and degenerative discs[13,14]. However, the main histological

changes and the exact molecular mechanisms underlying the painful pathological disc remain unknown.

With the development and popularization of lumbar fusion, a greater number of painful pathological disc specimens can be obtained, which are beneficial for studies regarding the pathogenesis of painful disc degeneration. Based on our previous histological studies[15-17], we found that the composition and structure of painful disc differed from those of non-painful degenerative disc. Specifically, normal fibroblasts in the annulus fibrosus were replaced by cartilage-like cells. The annulus fibrosus lamellar structure was disordered and fractured. The normal highly hydrated gelatin-like nucleus pulposus, whose matrices showed obvious fibrosis, and cartilage-like cells, were completely replaced with fibroblasts, was substituted by fibrous tissues. The histological changes in the nucleus pulposus were divided into 3 major types: obvious fibrosis, vascular invasion, and inflammatory granulation tissue formation. In addition, we found that the characteristic change in painful pathological discs was the formation of inflammatory vascular granulation tissues with extensive innervation along the tears in the posterior annulus fibrosus, along with mass expression of some growth factors such as basic fibroblast growth factor (bFGF), TGF-β1, and connective tissue growth factor (CTGF). Vascular granulation tissue was not formed in asymptomatic degenerative discs, and only a few growth factors were expressed. Asymptomatic degenerative discs with tears are not painful, because these discs have not been innervated[15].

Blood vessels only exist in the longitudinal ligaments and the outermost layers of the annulus fibrosus in a normal disc. The ingrowth of vascularized granulation tissue along the tear deep into the inner annulus and nucleus pulposus in the painful disc probably begins soon after the injury when repair of the tear starts from the margin of the annulus fibrosus[15]. Owing to the absence of blood vessels in the inner annulus fibrosus and nucleus pulposus, it is unlikely that vascularized granulation tissue which is induced by the tear should originate from there. Different animal models of outer annular injury have proved that the healing of the annulus might initiate a progressive degeneration of the disc[18-24]. In addition, the whole process of healing of annulus fibrosus injury, including inflammatory reaction, formation of granulation tissue, and tissue reconstruction had been observed, implying that the disc has actually been torn and there has been a process of healing in progress[16].

According to recent researches on injury and repair, growth factors have been considered to be essential to regulate and control the whole process of repair of an injury. Some growth factors, such as bFGF, TGF-β, and CTGF, may be important as promoters in tissue repair. Growth factors that control cellular proliferation and differentiation *in vitro* have been identified. These factors mediate cellular interactions *in vivo*, which not only contribute to development and growth, regeneration, and wound healing, but also may incite abnormal changes[16]. Growth factors through their each receptor signal transduction pathway, promote cellular proliferation and collagen synthesis of matrix cells such as fibroblast and vascular endothelial cells, which exert a strong effect on adjustment and control of wound and repair[16]. Previous studies have indicated that bFGF as an important mitogen accelerator may directly act on the mitotic cycle of tissue repair cells (for example fibroblast), resulting in shortening of G1 phase, prolongation of G2 and M phases, thus mitotic cycle is shortened, and cell division and proliferation accelerates. TGF-β, as a multi-functional growth factor, not only can attract inflammatory cells and tissue repair cells to aggregate in the wound region, but also directly act on fibroblasts to stimulate synthesis of type I procollagen, formation of granulation tissue, and tissue reconstruction in the later stage of repair[25-27]. Nagano *et al*[28] in an animal model of disc degeneration found that bFGF was a proliferation stimulating factor promoting proliferation of chondrocytes to replace normal annular cells in degenerated discs in an autocrine or paracrine manner. Tolonen *et al*[29] studied expression of bFGF and TGF-β in painful degenerative discs, and found that growth factors strongly express in both the annulus fibrosus and the nucleus pulposus. Their study suggests that these growth factors promote cellular remodeling, and create a cascade in the process of disc degenerateion.

Disc tissues are different from other tissues because they comprise the largest avascular tissue. In other tissues, injury healing proceeds from the inside to the outside. On the contrary, healing in disc tissues proceeds from the outside to inside[16]. When the annulus fibrosus is lacerated or injured, vascular tissues can only gradually develop from the outer to the inner annulus fibrosus. Endothelial cells migrating into discs form the principal parts of a new capillary vessel. With the help of various growth factors, endothelial cells migrating into the avascular disc tissues differentiate, proliferate, and gradually form complicated capillary networks. Our studies[15-17] suggested that as annulus fibrosus injuries stimulated local vascular inflammatory reactions, cells including macrophages and mast cells in inflammatory regions produce a large number of growth factors such as bFGF, TGF-β1, and CTGF. The cells in normal disc are separated from the circulatory system. These increased growth factors acted on the intervertebral disc cells, and promoted disc cell dedifferentiation and proliferation, as well as large-scale extracellular matrix synthesis via signal transduction. This may be the main cause of painful disc fibrosis and degeneration. The strong expression of proliferating cell nuclear antigen (PCNA) in painful discs seemed to be an evidence of this hypothesis. PCNA, a nucleoprotein of nonhistone, is an essential auxiliary protein of DNA polymerase-δ[16]. It can markedly increase activity of DNA polymerase-δ, and its expression level is believed to be an important measure of cell proliferation activity[30].

The normal disc is believed to be an organ that is poorly innervated supplied only by sensory and sym-

pathetic perivascular nerve fibers. In the early 1980s, Bogduk[31] clarified the innervation of the outer layers of the annulus. The posterior part of the human disc was supplied not only from the sinuvertebral nerve but also received direct branches in its posterolateral aspect from the ramus communicans or the ventral ramus. Branches from the grey ramus communicans also supplied the lateral aspect of the disc. Anterior discal nerves were observed to arise solely from the sympathetic plexus surrounding the anterior longitudinal ligament. The sensory fibers that innervated the disc are mainly nociceptive and, to a lesser extent, proprioceptive. The sympathetic fibers are considered vasomotor efferents, and also sympathetic afferents conveying pain impulses[32]. The close association of the postganglionic efferent and sympathetic afferent fibers reflected a similar pattern to that seen in certain enteric organs, leading them to suggest that low back pain is a kind of visceral pain[33-35]. In human degenerated disc, as well as in animal models of disc degeneration, the number of nerve fibers in the disc increases[15,36,37]. Furthermore, the nociceptive nerve fibers grow into what are usually aneural inner parts of the annulus and even into the nucleus. In addition to the sensory nerve fibers, there is growing evidence that sympathetic afferents are also increased in degenerated disc and that they play a significant role in low back pain[38-40]. In human normal disc, protein gene product 9.5-positive nerve fibers, either associated with blood vessels or distant from them, innervate the outer layers of the annulus. These nerve fibers are also positive for acetylcholinesterasem NFP, SP, CGRP, VIP, neuropeptide Y, C-flanking peptide and synaptophysin. The nerves entering the rat disc have an identical expression pattern[32]. Mechanical stimuli which are normally innocuous to disc nociceptors can, in certain circumstances, generate an amplified response which has been termed 'peripheral sensitization'. This may explain why some degenerative discs are painful and others not. There is growing evidence that these pain receptors in painful disc are peripherally sensitized by the activity of sympathetic efferents which may initiate a pain impulse in response to ischaemia, pressure changes or inflammatory irritation[32].

It is accepted that the lumbar disc, which are the main source of discogenic back pain in humans, are innervated segmentally. However, the ventral portions of the rat lower lumbar discs are innervated by upper (L1-L2) dorsal root ganglion neurons and the nerve fibers innervating the posterolateral portion of the disc come from the upper and lower dorsal root ganglion (L3-L6)[38,39]. Nerve fibers reach the lumbar disc through the sinuvertebral nerves or from branches of the paravertebral sympathetic trunks[40]. Clinical studies have indicated those local anaesthetic blocks of L2 nerve root can relief discogenic low back pain[41].

DIAGNOSIS

The diagnostic criteria for IDD established by the International Association for the Study of Pain (IASP) are emergence of a concordant pain response during discography, internal annular disruption shown by CT after discography (CTD) and at least one adjacent disc without concordant pain[42]. The term IDD was first coined by Crock[5] on the basis of a large group of patients whose disabling back and leg pain became worse after operation for suspected disc prolapse. He reported this condition, characterizing it by disruption of the internal architecture of the disc, discogenic back pain in the absence of peripheral disc shape abnormality, and the absence of nerve root compression. At present, IDD has been described as a distinct clinical entity to be distinguished from other painful processes such as degenerative disc disease and segmental instability[8]. In our a previous study, according to discography, we classified discogenic low back pain into two types that were annular disruption-induced low back pain (IAD) and internal endplate disruption-induced low back pain (IED), which have been fully supported by clinical and theoretical bases[43]. The term IAD should be more reasonable than the term IDD clinically and pathologically. Clinically, these two types of low back pain should be confirmed by lumbar discography. The diagnostic processes, radial tear and pain responses are identical. During the process of contrast medium injection, the contrast medium was either flowing to the outside of disc through a radial annular tear, or flowing to the vertebral body through the radial endplate tear. The concordant pain responses would be induced in either way.

According to the "Modified Dallas Discogram Description" method[44,45], the degrees of annular disruption could be classified into four grades. The definitions are Grade 0: the contrast medium is confined within the normal nucleus pulposus; Grade 1: the contrast medium flows into the inner third of the annulus through annular fissure; Grade 2: the contrast medium flows into the middle third of the annulus; Grade 3: the contrast medium flows into the outer third of the annulus, and extends circumferentially less than 30° arc at the disk center; Grade 4: the contrast medium flows into the outer third of the annulus, and extends circumferentially more than 30° arc at the disk center; and Grade 5: the contrast medium leakage into the outer space. Grades 0, 1 and 2 are normal, while Grades 3 and above are indicative of annular disruption. We combined the discogram and CT scan after discography to evaluate the degree of endplate disruption in IED patients. The disruptive degrees were classified into four grades (Figure 1): Grade 0 (no disruption), Grade 1 (contrast medium flows into the cartilage endplate through tear), Grade 2 (contrast medium flows into the bony endplate), Grade 3 (contrast medium flows into the cancellous bone of vertebra under endplate, showing local dispersion) and Grade 4 (contrast medium disperses extensively in the cancellous bone)[43]. In this group of patients with IED, all intervertebral discs that showed concordant pain responses had endplate disruptions more severe than Grade 3, which was consistent with the distributions of blood vessels and nerves in the

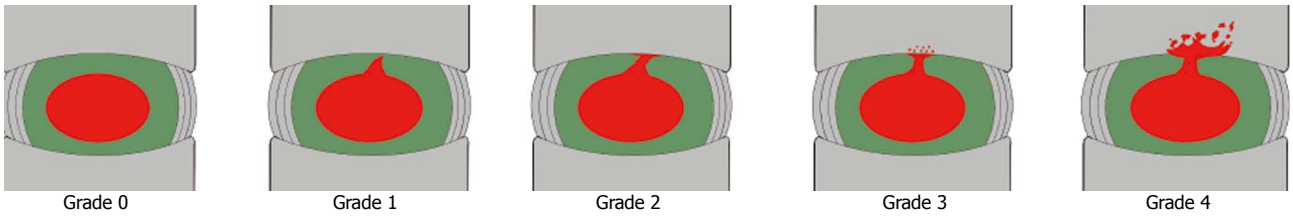

Figure 1 Endplate disruption grading method schematic diagram.

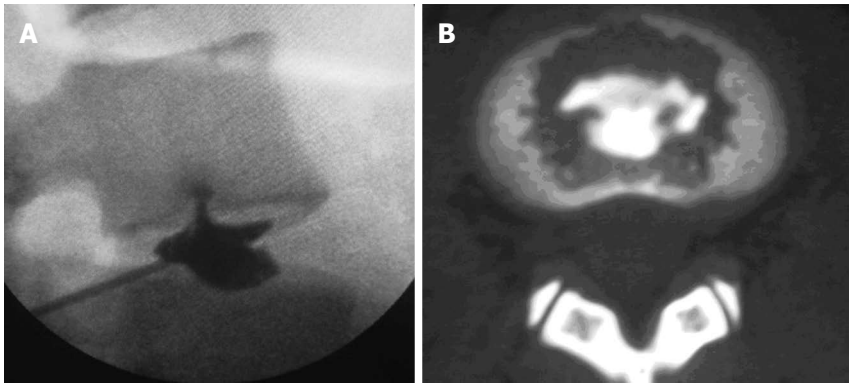

Figure 2 Discography and computed tomography. A: Discography showing a radial disruption on the lower endplate of L4 vertebra and that the contrast medium flows into the cancellous bone of the lower endplate of L4 vertebra through the fissure; B: Computed tomography scan showing the contrast medium dispersed in the lower endplate of L4 vertebra, with Grade 4 endplate disruption.

endplate (Figure 2)[43].

Theoretically, any innervated vertebra and its peripheral structures might be the source of low back pain. An intervertebral disc has such a structure that, except for the peripheral parts around annulus fibrosus, the endplate also has nerve supplies. Normally, one vertebral endplate has two nerve supplies: one enters the endplate along with perivertebral blood vessels, while the other that belongs to the sinuvertebral nerve branch that enters the endplate through the intervertebral foramen. The nerve density within the endplate is similar to that of the annulus, indicating that the endplate is also an important source of discogenic low back pain[46]. Recently, we published a clinical study article[47], 21 patients with chronic back pain originating from the endplate injuries were selected to explore the methods of diagnosis and surgical treatment. Pain level of disc was determined through discography in each patient. All 21 patients with a diagnosis of back pain originating from endplate injuries according to discography were treated with anterior or posterior fusion surgery. After operation, through a mean follow-up of three years and five months, we found that in all the 21 patients, 20 (20/21) reported a disappearance or marked alleviation of low back pain and experienced a definite improvement in physical function. The study suggests that discography and fusion surgery may be very effective methods for the diagnosis and treatment, respectively, of chronic back pain originating from the endplate injuries. In fact, endplate damage-induced low back pain occurs quite often clinically. In clinical research, we found that endplate damage-induced low back pain accounted for 16.7% of chronic discogenic low back pain. Epidemiological investigation showed that the incidence of endplate damage among populations without low back pain was 30%[48].

Theoretically, the pathogenesis of endplate disruption-induced discogenic low back pain is presumed to be consistent with that of annular disruption. A large number of animal experiments have indicated that damage to the outer layer of the annulus could induce a progressive degeneration of the entire disc[19-23]. Similarly, animal models have indicated that needle punctures from the vertebral side all the way through the endplate into the disc could induce a progressive degeneration of the entire disc[49]. It was found that the apoptosis of nucleus pulposus cells increased and the proteoglycan content decreased after endplate injury in the endplate damage animal model[50]. The ingrowth of nerves and blood vessels is a characteristic of tear discs, and is also directly correlated with discogenic low back pain. Freemont *et al*[51] found that blood capillaries grew in companion with nerve endings into the painful discs through endplates.

Basic and clinical studies have overwhelmingly illustrated the nerve supply of the disc and pathomorphologic correlates[6-9,15,18,36,37,52-58]. Based on controlled evaluations, the lumbar intervertebral discs have been shown to be sources of chronic low back pain without disc herniation in 26% to 42%[4,6,7]. Because of the variety of anatomic and pathophysiologic causes of chronic low back pain, it is a difficult diagnosis for clinicians to make. Clinicians primarily use advanced imaging techniques, such as MRI to diagnosis low back pain. Studies show that MRI findings such as disc degeneration do not correlate with the presence or severity of low back symptoms. Lumbar

provocation discography is a procedure that is used to characterize the pathoanatomy and architecture of the disc and to determine if the disc is a source of chronic low back pain. Recently, the American Pain Society developed and published multiple guidelines[59,60] in managing low back pain which did not recommend discography as a diagnostic test because of poor evidence for its sensitivity, specificity, and predictive value. However, subsequently, these guidelines were severely criticized[52]. There were deficiencies and inappropriate evaluation in almost all areas; inappropriate studies were included and appropriate studies were excluded. The basic deficiency of these guidelines by Chou and Huffman[59] was their failure to recognize the discography must not be performed in asymptomatic volunteers or patients with mild low back pain. They also utilized outdated guidelines from AHCPR and European COST guidelines[52]. In the interim, questioning the validity of discography warrants questioning the role of the disc as a discrete pain generator, or more specifically, challenges the concept of symptomatic internal disc disruption. If one considers discography to be a useless test, then one may have to abandon the concept of the disc as a discrete pain generator and abandon the pursuit of intradiscal therapies, whether surgical or non-surgical[52]. Recent systematic reviews have concluded that there is strong evidence that lumbar discography can identify the subset of patients with chronic discogenic pain[61,62].

TREATMENT

Treatment for discogenic low back pain has traditionally been limited to either conservative management or surgical fusion. However, to accurately assess the effect of any therapy for treating discogenic low back pain, the natural history of such pain should be known beforehand. Recently, our a clinical study indicated that the natural history of discogenic low back pain was continuous and chronic[63]. This result indicates that most patients are expected to experience low back pain after a longer time interval, and their pain severity is expected to remain nearly the same. The elucidation of natural history of discogenic low back pain has important clinical significances for decision-making of treatments.

There are a multitude of treatments used in clinical practice to treat chronic low back pain, with little consensus amongst clinicians as to which is the best approach. Pharmacologic treatment usually includes analgesics, nonsteroidal anti-inflammatory drugs, and muscle relaxants, but the evidence for their efficacy is not compelling. In randomized trials, the differences in pain after a patient has taken nonsteroidal anti-inflammatory agents as compared with placebo have generally been in the minimally detectable range[64]. A meta-analysis revealed that opioids seem to have a small effect in improving function and relieving pain for the patients with chronic low back pain[65]. Long-term treatment with narcotics is generally discouraged, given the associated risks of tolerance and side effects. Physical therapy, exercise, manipulation, and back school seem to have some effects, but it is unknown if effects are sustained for the long term[64]. Exercise therapy by the McKenzie method is a popular treatment for low back pain among physical therapists. Clinical studies have indicated that the McKenzie method is slightly more effective than manipulation or is equal to strengthening training for patients with chronic low back pain[66,67].

If conservative treatment fails, then epidural injections are commonly performed for chronic discogenic pain. Epidural injections are administered by accessing the lumbar epidural space by multiple routes including interlaminar, caudal, and transforaminal[68-79]. Epidural procedures continue to be debated regarding their effectiveness, indications, and medical necessity. Recent systematic reviews indicated that effectiveness of epidural injections for treatment of discogenic low back pain was fair[80]. The underlying mechanism of action of epidurally administered steroid and local anesthetic injection is still not well understood. It is believed that the achieved neural blockade alters or interrupts nociceptive input, the reflex mechanism of the afferent fibers, self-sustaining activity of the neurons, and the pattern of central neuronal activities[80]. Further, corticosteroids have been shown to reduce inflammation by inhibiting either the synthesis or release of a number of pro-inflammatory mediators and by causing a reversible local anesthetic effect[81-85].

As alternative treatments, percutaneous treatments directed at altering the internal mechanics or innervation of the disc by heat (intradiscal electrothermal annuloplasty, IDET, and biacuplasty) have recently been advocated[7,86,87], but data supporting their use are controversial[86]. IDET was first used to treat discogenic low back pain in 1996, using a concection technology with a 5 cm active tip placed at the uncleoannuar junction. Two randomised trials have shown either no effect or benefit in only a small number of highly selected subjects[88-90]. Further, of the 6 observational studies[91-96], 4 studies showed positive results, one study showed negative results, and one study showed undermined results. Recent a systematic review evaluated these studied, and concluded that the evidence is fair for IDET[97]. Biacuplasty is one of the minimally invasive treatment methods. It creates heat across the posterior annulus using a cooled bipolar radiofrequency device[98]. The initial study results are promising[99,100], but the effectiveness needs to be evaluated further to use randomized controlled trials.

During recent decades, surgical fusion of the lumbar spine has been performed in increasing number on patients with chronic low back pain[4]. However, the reported results vary considerably in different studies, and the complication rate after fusion surgery in the lumbar spine is not negligible[101-105]. Consequently, artificial disc replacement has been proposed as a substitute for spinal fusion with the aim of treating back pain while preserving vertebral motion at the operated levels and protecting adjacent levels from undergoing degenerative changes, but so far, only several studies have been reported on the

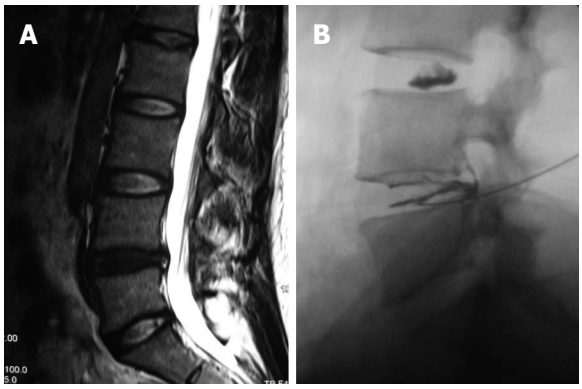

Figure 3 Magnetic resonance imaging and discography. A: A 35-year-old woman had a 5-year history of low back pain. Sagittal T2 weighted magnetic resonance imaging showed L4/5 disc degeneration with a high intensity zone in the posterior annulus fibrosus; B: Discography showed L4/5 disc disruption with exact pain reproduction. After discography, 10 mg methylene blue was injected into the painful disc through discographic needle. Low back pain was almost totally relieved. No recurrence was observed at a 12-mo follow-up interval.

results of lumbar disc prosthesis[106-108]. Recent a systematic review suggested that the spine surgery community should be prudent to adopt this technology on a large scale because harm and complications may occur after some years[109]. The results with longer follow-up need to be observed further.

Based on the recent insights into signal transduction mechanisms that might lead to the induction of pain by degenerative discs, it is conceivable that therapies aiming at disrupting pro-inflammatory signaling pathways and the pathway of nerve conduction might be successful in the foreseeable future. Such therapies might not have the ability to reverse the progressing tissue destruction which occurs with aging but may transform a symptomatic to asymptomatic disc degeneration and thereby greatly improve life quality of the affected patients[10]. Recently, a minimally invasive method, intradiscal methylene blue injection for the treatment of painful disc degeneration, had been reported (Figure 3)[110,111]. This successful outcome subsequently was demonstrated by the animal experiments which indicated that methylene blue indeed had destroyed the nerve endings or nociceptors and alleviated inflammatory response in the degenerated discs[112,113].

Recently, there has been a growing interest in developing strategies that aim to repair or regenerate the degenerated disc biologically. Treatments for degenerated discs have two main objectives: restoration of the disc' s structure and elimination of pain[114]. The benefits of biologically based treatments appear to be limited to restoring disc structure. Whether disc regeneration would result in pain relief remains unclear. That said recent data from animal studies have shown changes in cytokine expression following growth factor injection, indicating a possible mechanism for pain relief. Further, the first human clinical trial for growth factor injection therapy is currently underway and may shed light on the clinical outcome. Mesenchymal stem cells (MSCs) may also help relieve pain by reducing inflammation. A recent study indicates that MSCs can induce the production of anti-inflammatory cytokines[115]. However; additional studies are needed to elucidate the underlying mechanisms of pain relief.

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