# Management of Degenerative Disk Disease and Chronic Low Back Pain

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**KEYWORDS**

• Disk • Degeneration • Chronic • Low back • Pain • Conservative • Surgery • Genetic

Low back pain (LBP) affects every population and is one of the world's foremost debilitating conditions.[1] Such pain may lead to diminished function and quality of life, psychological distress, and loss of wages.[2] LBP is one of the most common conditions motivating individuals to seek medical care and often results in prolonged therapeutic interventions.[2,3] Therefore, LBP is a global burden associated with severe socioeconomic and health care consequences.[4–6]

LBP can be divided into several groups based on cause: 80% to 90% mechanical (eg, degenerative disk or joint disease, vertebral fracture, deformity); 5% to 15% neurogenic (eg, herniated disk, spinal stenosis), 1% to 2% nonmechanical conditions (eg, neoplastic disease, infection, inflammatory), 1% to 2% referred visceral pain (eg, gastrointestinal disease, renal disease, abdominal aortic aneurysm), and 2% to 4% other (eg, fibromyalgia, somatoform disorder, malingering).[7] Typically, patients with LBP complain of local pain aggravated by mechanical loading, usually at worst when being upright, and they have no or minimal symptoms at rest. It is generally agreed that intervertebral disks are a major tissue source in chronic LBP.[8,9] Typically, chronic LBP has been defined as pain occurring for 3 months or more, frequently recurring, or lasting beyond the normal healing period for a low back injury.[10,11] If, in case of prolonged LBP, magnetic resonance imaging (MRI) is obtained and a common finding is disk degeneration at the 2 or 3 lowest lumbar levels (**Figs. 1–3**).[12,13]

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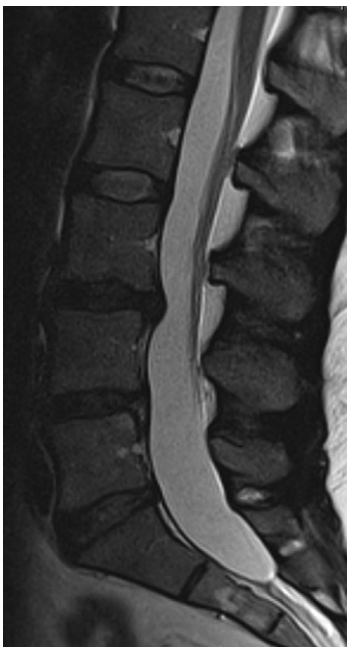

**Fig. 1.** A 33-year-old woman with chronic LBP for 1 year and left-sided sciatica for 4 months. T2-weighted sagittal MRI images showed disk degeneration from L3 to S1. An L4/5 discectomy was performed, and on last follow-up the patient was asymptomatic.

According to international clinical guidelines, treatment of acute LBP (ie, <3 months) is straightforward in the absence of red flags (**Table 1**) or sciatica symptoms. Often, pain medication is provided and the patient is advised to stay active.[14] However, in the context of chronic LBP, there are several treatment options, but no clear answer exists as to how the physician should plan the treatment process. This article reviews treatment options for the management of chronic LBP and assesses the evidence on their effectiveness, with particular emphasis on degenerative disk disease.

## THE ROLE OF DISK DEGENERATION IN CHRONIC LBP

MRI is not recommended early in the disease course unless red flags or signs of nerve root entrapment are present. The reason is that MRI in acute LBP increases medical costs without giving additional information influencing clinical decision making.[15–17] Furthermore, MRI in the current form is not useful in diagnosing discogenic pain when compared with discography.[9] However, discography per se has been found to enhance progression of disk degeneration,[18] and therefore recently published guidelines were not in favor for discography.[19] According to Ohtori and colleagues,[20] injection of a small amount of

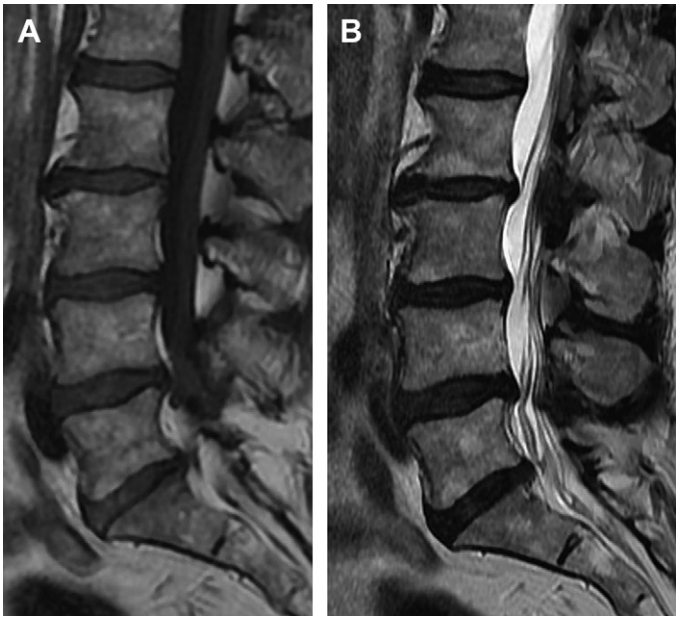


**Fig. 2.** A 52-year-old woman with chronic LBP for 10 years. She experienced left-sided sciatica for 1 year with no relief with conservative treatment, including physiotherapy and nerve root blockade. (*A*) T1- and (*B*) T2-weighted MRI sagittal images showed disk degeneration from L1 to S1 with mixed type I/II Modic lesion at L5/S1. She eventually underwent an L4/5 discectomy and decompression.

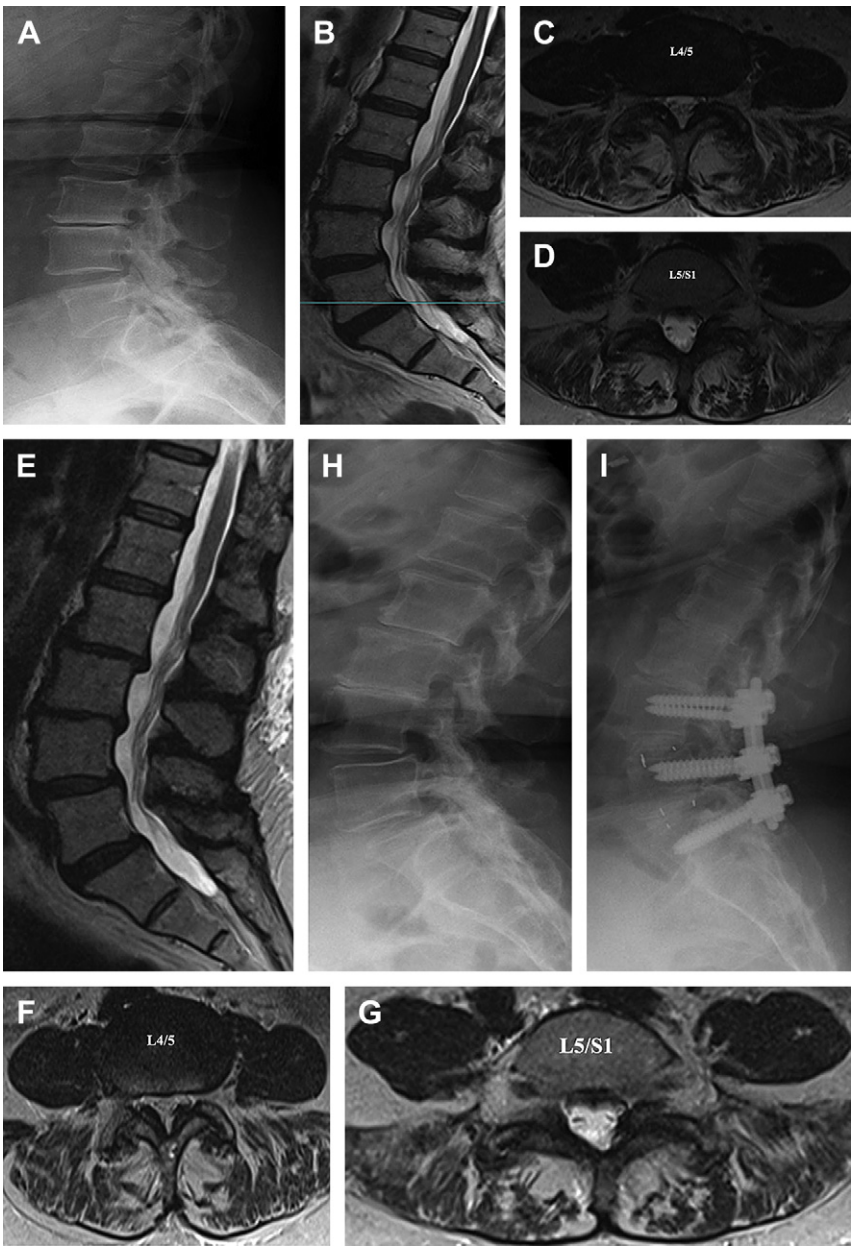


**Fig. 3.** A 71-year-old woman with (*A*) multilevel disk degeneration from L2 to S1 and a (*B*) grade 1 degenerative spondylolisthesis at L4/5 and L5/S1 (standing radiograph), resulting in (*C*, *D*) both central and neuroforaminal stenosis. Conservative measures were instituted with good initial results. However, 3.5 years later she presented with recurrent leg, greater than back, symptoms. A second round of conservative treatment yielded only temporary relief. Updated imaging revealed progression of the (*E–G*) degeneration changes at all levels, particularly at L3/4 with (*H*) progression of the degenerative slip (standing radiograph). Surgical intervention was performed for decompression, realignment, and stabilization. Because her main complaint was leg pain, only the stenotic levels from L4 to S1 were addressed. (*I*) A transforaminal lumbar interbody fusion with instrumentation from L4 to S1 was performed with interbody cages and local autograft to restore neuroforaminal height and alignment.

bupivacaine into the painful disk may be a better test for discogenic LBP than discography.[20] However, this procedure is also invasive and may accelerate disk degeneration. Therefore, in most cases of chronic LBP the true tissue origin has remained unknown. In most randomized trials focused on patients with chronic LBP, the tissue source of pain has not been speculated.

**Table 1**
**LBP red flags that contraindicate nonsurgical treatment**

| Condition | History | Physical Examination |
|---|---|---|
| Fracture | Major trauma<br>Minor trauma (older patient) | Kyphosis |
| Tumor | Age <15 or >50 y<br>Known cancer<br>Unexplained weight loss<br>Night pain | — |
| Infection | Recent fever or chills<br>Recent bacterial infection (urinary tract infection)<br>Intravenous drug use<br>Immune suppression<br>Unrelenting pain | Fever |
| Cauda equina syndrome | Saddle numbness<br>Urinary retention, incontinence<br>Severe (progressive) lower extremity neurologic deficit | Weak anal sphincter<br>Perianal sensory loss<br>Flaccid motor weakness<br>Hyporeflexia |

*Data from* Shen FH, Samartzis D, Andersson GB. Nonsurgical management of acute and chronic low back pain. J Am Acad Orthop Surg 2006;14:478.

According to a systematic review by Hancock and colleagues,[21] MRI findings, such as endplate changes and presence of disk degeneration, were found to increase the likelihood of the discogenic origin from discography. Several recent studies support the concept that disk degeneration is associated with low back symptoms.[22–26] All these studies indicate that a higher degree of lumbar disk degeneration is related to a higher likelihood of symptoms, and moreover the presence of moderate disk degeneration or degenerative changes at multiple levels increases the likelihood of pain.[23,26] According to Samartzis and colleagues,[24] the global severity of disk degeneration increases the likelihood of LBP, with a potential dose-response exposure of degenerative changes implicated in the association.

The role of disk degeneration in the development of chronic LBP has received considerable attention; nonetheless, few large-scale studies have addressed the relationship. According to studies by Kjaer and colleagues,[13] Visuri and colleagues,[27] and Paajanen and colleagues,[28,29] disk degeneration on MRI is significantly associated with chronic LBP, whereas Savage and colleagues[30] contend otherwise. More recently, a systematic review by Chou and colleagues[31] assessing degenerative spine findings on MRI in relation to chronic LBP, noted a significant association between the presence of disk degeneration and back pain. However, because of clinical heterogeneity between studies, the investigators hesitated in making any robust conclusions of a direct association or causal pathway between disk changes and LBP. Nonetheless, a recent study by DePalma and colleagues[32] using numerous diagnostic injections concluded that intervertebral disk degeneration is the most common tissue source of chronic LBP. The likelihood of the intervertebral disk implicated in chronic LBP was highest in young and middle-aged individuals, whereas the probability of pain related to facet or sacroiliac joints was highest in older individuals. In addition, new imaging modalities, such as T1-ρ, T2-relaxation mapping, and chemical exchange saturation transfer, are being developed that are more sensitive to disk changes and could further elaborate more quantitatively on the disk degeneration phenotype as well as possess the potential to image pain (see article by Majumdar and colleagues elsewhere in this issue).[33–38]

In this article, presumed discogenic origin of chronic LBP is referred to as degenerative disk disease. The pathophysiologic mechanism leading to the development of pain in the disk is described elsewhere in this focus issue (see articles by Chan and colleagues, Grunhagen and colleagues, Inoue and Espinoza Orias, and Bae and Masuda). In general, mechanical and chemical mediators brought on by the degenerative process irritate sensory nerve endings (nociceptive fibers) located in the annulus fibrosus, which contribute to pain (**Fig. 4**). As the degenerative process progresses, this situation may further affect the kinematics and load transmission throughout the motion segment, thereby stimulating nociceptive fibers in the facet joints as well.

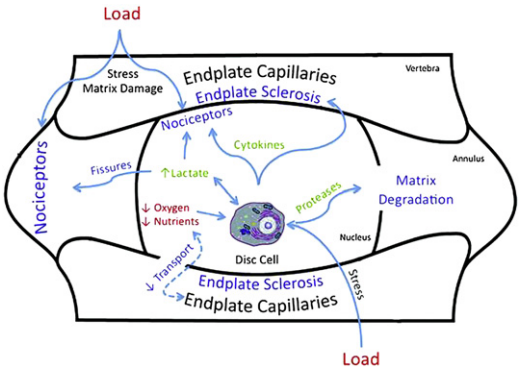


**Fig. 4.** Numerous risk factors, such as age, abnormal physical loading, and genetics, may lead to the development of intervertebral disk degeneration. Disk cells are adversely influenced by mechanical load (pressure), hypoxia, and nutrient/metabolite deprivation (*red*). In response, they can secrete lactate, cytokines, and proteases (*green*). The damaged matrix may cause endplate sclerosis, sensitize nociceptors, and exacerbate the adverse effects of load and diminished nutrient/metabolite transport (*blue*). Sensitized nociceptors can, in turn, be stimulated by tissue stress and mediators to cause pain. (*Modified from* Masuda K, Lotz JC. New challenges for intervertebral disk treatment using regenerative medicine. Tissue Eng Part B Rev 2010;16:148; with permission.)

## THE ROLE OF CENTRAL SENSITIZATION IN CHRONIC LBP

Nociceptive stimuli from peripheral tissue, such as in the intervertebral disk, are transmitted mainly via the spinothalamic tract to the cerebral cortex. In case of persistent injury, C fibers fire repetitively to the dorsal horn, which may lead to central sensitization.[39] Central sensitization is characterized by altered pain sensibility both peripherally and centrally.[40] Even although intervertebral disks are the original pain generators in degenerative disk disease, central sensitization may obscure a peripheral nociceptive tissue source in chronic LBP. The central areas activated by pain include almost constantly secondary somatosensory cortex, insular regions and anterior cingulate cortex, and with slightly less consistency contralateral thalamus and primary somatosensory cortex.[41] There is reasonable evidence that chronic LBP is associated with abnormal brain anatomy and function, especially in the dorsolateral prefrontal cortex, thalamus, brainstem, primary somatosensory cortex, and posterior parietal cortex.[42,43] According to a study by Ruscheweyh and colleagues[44] that assessed structural MRI of the brain and pain status in 205 German subjects, regional brain matter reduction (mainly in cingulate, prefrontal, and motor/premotor regions) was present in chronic LBP sufferers with symptoms greater than 12 months. However, a recent Canadian study by Seminowicz and colleagues[45] indicated that brain abnormalities in chronic pain may be reversible.[45] These investigators reported that successful treatment of patients with chronic LBP either with spine surgery (n = 8) or with a facet joint injection (n = 6) resulted in restoration of both structure and function of the left dorsolateral prefrontal cortex, which correlated with reduction of both pain and disability.

## TREATMENT OF CHRONIC LBP

Existing clinical guidelines list several treatment options for chronic LBP, which include pain medication, exercises, behavioral therapy, multidisciplinary rehabilitation, and surgery (**Box 1**).[14,46]

**Box 1**
**Factors associated with the development and persistence of LBP**

Previous episode of back pain[a,c]
Poor job satisfaction or low pay[a,c]
Inadequate coping skills[c]
Fear-avoidance behavior[a,c,d]
Manual labor or physically stressful job[a,c]
Obesity[a,c]
Somatization[a,c]
Smoking[a,c]
Low baseline activity levels[a,c]
Ongoing litigation[c]
Older age[a,c]
Low educational level[c]
Higher pain intensity or disability[c]
Neurologic symptoms[c]
Anxiety[a,c]
Depressed mood[c]
Emotional distress[a,c]
Pain genes[b]

Association does not imply causality. Evidence is mixed for some factors, including smoking, obesity, and low educational level.

[a] Associated with development of LBP in some studies.
[b] Associated with pain severity after surgery. Limited studies exist.
[c] Associated with persistence of LBP in some studies.
[d] The avoidance of physical activities that stems from patients' fears that their pain will worsen.

*Modified from* Cohen SP, Argoff CE, Carragee EJ. Management of low back pain. BMJ 2008;337:103; with permission.

Patient information is not reviewed in detail here. Yet, patient advice is an integral part of care at all stages. Such advice should preferably be given early in the disease course, because 2.5-hour sessions of individual oral education were found to be more effective than no intervention in return to work in subacute LBP, whereas in chronic LBP education was less effective on back-related function than more intensive interventions.[47] Advice includes information on the benign nature of nonspecific LBP and encourages the patient to be physically active and continue with normal activities as possible.[46]

Some new promising biologic treatment alternatives have been introduced recently. They include stem cell regeneration, gene therapy, tissue engineering, and molecular therapy. All these treatments are reviewed elsewhere in this issue (see articles by Sakai, Woods and colleagues, Leung and colleagues, and Bae and Masuda). This article pays special attention to the following treatment domains: pain medication, exercise therapy, behavioral therapy, multidisciplinary rehabilitation, injection therapy, and surgery.

### *Initial Clinical Assessment*

In the initial assessment, primary health care services, which include occupational health care in those countries where it is available, are of importance. A thorough clinical examination is paramount because it serves both the needs of diagnostics, and is also a part of evidence-based pain treatment.[48] It is generally recommended that every patient with LBP should be examined carefully, with follow-up visits in case of prolonged or recurrent pain (**Table 2**).[49] Degree of baseline disability (rather than pain intensity) is an important prognostic factor for recovery of LBP.[50] Functional impairment can be best evaluated with thorough clinical examination. In addition, patient-reported disability indices, such as the Oswestry Disability Index[51] and the Roland-Morris Questionnaire,[52] are helpful and widely used in the clinical assessment. A further tool in the initial assessment of patients with LBP is pain drawing, which is a simple and inexpensive diagnostic measure to characterize an abnormal psychological profile.[53]

### *Pain Medication*

The clinical guidelines recommend paracetamol as the first medication choice and nonsteroidal antiinflammatory drugs (NSAIDs) or weak opioids, or both, if paracetamol alone does not provide sufficient pain relief.[14,46] NSAIDs are effective for short-term symptom relief in patients with chronic LBP without sciatica, but the effect sizes are small and the various types of NSAID are equally effective.[54,55] In addition, the clinician should evaluate the risk of side-effects in each individual case and take into account the patient's preference as well. In case of persistent pain, strong opioids can be used for short-term management. Overall, the benefits of opioids for long-term management of chronic LBP remain questionable.[56] In addition, early use of opioids for LBP patients increases risk of work disability and leads to overall poor outcomes.[57,58] Tricyclic antidepressants may be

**Table 2**
**Nonsurgical treatment alternatives for LBP**

| Nonsurgical Treatment Alternatives | |
|---|---|
| **Treatment** | **Subclassification** |
| Education | – |
| Medication | Analgesics<br>Nonnarcotic<br>Narcotic<br>Topical<br>NSAIDs<br>Muscle relaxants<br>Corticosteroids<br>Antidepressants |
| Cognitive behavioral therapy | Operant<br>Cognitive<br>Respondent |
| Multidisciplinary rehabilitation | – |
| Immobilization and supports | – |
| Exercise therapy | – |
| Massage therapy/physical therapy | – |
| Acupuncture/dry needling | – |
| Manipulation | – |
| Traction | – |
| Injections | Epidural<br>Facet<br>Trigger point<br>Sacroiliac<br>Intradiscal<br>Prolotherapy |
| Orthoses | Braces<br>Corsets<br>Unloading corset |
| Transcutaneous electrical nerve stimulation | – |
| Acupuncture | – |

*Data from* Shen FH, Samartzis D, Andersson GB. Nonsurgical management of acute and chronic low back pain. J Am Acad Orthop Surg 2006;14:480.

offered if other drugs are insufficient in pain relief[46]; however, there is no evidence on their efficacy in chronic LBP.[54,59]

### *Exercise Therapy*

Exercise therapy is the key element in the treatment of chronic LBP. Exercise therapy is effective at decreasing pain and improving function.[60] However, exercise therapy was noted to have only a modest effect size[61] and most statistically significant trial results on the efficacy of exercise in chronic LBP were not of clinical importance.[62,63]

Selecting the type of exercise therapy for optimum effectiveness for chronic LBP is of importance. According to a meta-regression analysis by Hayden and colleagues,[64] exercise therapy should consist of individually designed programs, include stretching or strengthening, and should be delivered with supervision. In addition, high-dose exercise programs fared better than low-dose exercise programs. In general, no specific exercise type was superior to other types.[60] However, patient populations in the trials have been heterogeneous, whereas treatment interventions based on validated classification systems may result in larger effect sizes for the given treatments.[65] Moreover, exercise therapy may not be tolerated by all patients with degenerative disk disease (at least at advanced degenerative disease). Patients with type I and mixed types I/II Modic changes do not respond well to exercise therapy.[66,67]

The role of exercise therapy is supported by a review on the effectiveness of exercises for prevention of recurrences of LBP.[68] The review found moderate-quality evidence that posttreatment exercise programs can prevent recurrences of LBP. Additional exercise programs after formal treatment of LBP has been completed are beneficial. However, evidence on treatment interventions, defined as treatment of a current episode of LBP with the aim to prevent new episodes of pain, was conflicting.[68]

### *Behavioral Therapy*

The main behavioral treatment approaches in chronic LBP are operant, cognitive, or respondent therapies (see **Table 3**).[69–71] There is moderate evidence that operant therapy is more effective than waiting list, and that behavioral therapy in general is more effective than usual care in short-term pain relief in chronic LBP.[72] The strength of evidence on the efficacy of behavioral therapy was found to be mostly of low quality.[63,72]

Two high-quality trials, published after the systematic reviews, suggest that cognitive therapy is an essential part in the treatment of chronic LBP.

**Table 3**
**Various behavioral approaches for the treatment of LBP**

**Behavioral Treatment Approaches**

| Type | Definition |
|---|---|
| Operant | Removes positive reinforcement of pain behaviors and promotes healthy behaviors |
| Cognitive | Identifies and modifies harmful cognitions, such as maladaptive thoughts, feelings, and beliefs about LBP, using cognitive restructuring techniques (eg, imagery and attention diversion) |
| Respondent | Modifies the physiologic responses to pain through reduction of muscular tension using different relaxation techniques |

In a Danish pragmatic trial,[73] a cognitive, educational intervention for chronic LBP resulted in at least as good outcomes as exercise therapy despite fewer treatment sessions. Moreover, they used a classification system in which the delivery of specific exercise therapy was based on assessment findings. According to a British multicenter study by Lamb and colleagues,[74] cognitive behavioral therapy was found to significantly improve back-specific function compared with the usual care in subacute or chronic LBP. Furthermore, the effect was sustained over the 1-year follow-up period. In the intervention group, participants attended a program that targeted behaviors and beliefs about physical activity and avoidance of activity and consisted of individual assessment (up to 1.5 hours in duration) and 6 sessions of group therapy (1.5 hours per session).

### *Multidisciplinary Rehabilitation*

Multidisciplinary rehabilitation has been defined to include multidisciplinary biopsychosocial rehabilitation coupled with a minimum of 1 physical dimension (ie, psychological or social or occupational).[75] There is strong evidence that intensive multidisciplinary biopsychosocial rehabilitation with functional restoration improves function, and there is moderate evidence that multidisciplinary rehabilitation with functional restoration reduces LBP when compared with less intensive treatments.[75] More recently, moderate evidence of multidisciplinary rehabilitation compared with other kinds of active treatment on pain intensity

in the short-term was found[63]; however, no effect on pain intensity in the long-term was observed.[63]

The optimal content of multidisciplinary rehabilitation remains to be defined. Behavioral therapy is widely considered to be an essential part of multidisciplinary rehabilitation, but the addition of behavioral therapy to inpatient rehabilitation did not seem to increase the effect of inpatient rehabilitation alone.[72] Similarly, the addition of cognitive behavioral therapy did not increase the efficacy of physical conditioning.[76] Multidisciplinary rehabilitation can be performed as outpatient rehabilitation as well. Based on a study by Lambeek and colleagues[77] addressing a Dutch population, multidisciplinary outpatient work-related intervention was effective in return to work.

Based on systematic reviews by Guzman and colleagues[75] and Ravenek and colleagues,[78] there is contradictory evidence regarding vocational outcomes after multidisciplinary rehabilitation. In addition to multidisciplinary rehabilitation, physical conditioning programs, sometimes referred to as work conditioning, work hardening, or functional restoration/exercise programs, have a small effect on sickness absence at long-term follow-up in workers with chronic LBP.[76] Return to work should be a feasible and realistic outcome of multidisciplinary rehabilitation according to Buijs and colleagues,[79] who used a multidisciplinary outpatient care program, including workplace intervention and graded activity aiming at function restoration (instead of pain elimination) and return to work. Their program was well accepted by patients. Patient expectations were low at the start but the program was successful in changing patients' goal setting from pain-oriented toward function restoration and return to work. In support of the positive effect of multidisciplinary rehabilitation on vocational outcomes, a high-quality Dutch trial by Lambeek and colleagues[77] addressing patients who were on sick leave because of chronic LBP reported significantly less median duration of days until sustainable return to work in the so-called integrated care group (88 days) compared with to the usual care group (208 days). The integrated care intervention included a workplace intervention based on participatory ergonomics and a graded activity program based on cognitive behavioral principles, whereas the multidisciplinary team consisted only of a clinical occupational physician, a medical specialist, an occupational therapist, and a physiotherapist.

### *Injection Therapy*

There is insufficient evidence to support epidural and facet joint injections, or local trigger point injections, in subacute and chronic LBP.[80] A recent practice guideline by Chou and colleagues[81] recommended against facet joint steroid injections, prolotherapy, and intradiscal steroid injections in nonradicular LBP, and strongly recommends against provocative discography. Epidural or transforaminal steroid injection is recommended in patients with persistent radiculopathy caused by a herniated lumbar disk because there is evidence for moderate short-term benefits. Furthermore, the benefits of botulinum and epidural steroid injection, intradiscal electrothermal therapy, therapeutic medial branch block, radiofrequency denervation, intrathecal therapy with opioids or other medications, and sacroiliac joint steroid injection are questionable in nonradicular LBP.[81]

It could be argued that intradiscal injections with other more potent antiinflammatory drugs than steroids could be beneficial in nonradicular LBP. Tumor necrosis factor $\alpha$ (TNF-$\alpha$) antagonists are eagerly evaluated in the treatment of sciatica.[82] However, the current evidence does not support their use in degenerative disk disease.[83] Fibrin injection in the experimentally damaged disks resulted in reduced TNF-$\alpha$ synthesis.[84] No in vivo human studies have been performed. In addition, various growth factors and stem cell therapies that entail direct injection into the disk for repair/regeneration have been studied, largely in animal models and in disks with mild to moderate degeneration (see articles elsewhere in this issue by Sakai, Woods and colleagues, Leung and colleagues, and Bae and Masuda).[85–93] Although their effectiveness for pain management in symptomatic degenerated disks has not been fully addressed, such disk therapies could serve as a viable option in the future and warrant further investigation.

Peng and colleagues[94] reported their findings based on their randomized controlled trial (RCT) assessing the efficacy of methylene blue intradiscal injection (n = 36) compared with a placebo group (n = 36) in 72 patients with chronic discogenic LBP lasting longer than 6 months. These investigators noted at 24-month postinjection follow-up that intradiscal injection of methylene blue significantly reduced mean pain and Oswestry Disability Index scores by 41 and 35, respectively, among patients with chronic discogenic pain compared with 1% and 2%, respectively, in the placebo group. The investigators concluded that methylene blue acts to denervate the nociceptive fibers found in annular fissures. However, the study has not been replicated. Thus, the benefit of methylene blue injection remains speculative. Alternatively, although Peng and

colleagues[94] reported their procedure to be safe, an animal study performed by O'Neill and colleagues[95] noted that methylene blue if leaked out of the disk and into the epidural space may prove extremely neurotoxic, resulting in paralysis in their animal models. O'Neill and colleagues[95] have advocated that until the exact mechanism of toxicity and dose response of the relation are determined, the use of methylene blue to address symptomatic degenerative disk disease should be avoided or at least used in the setting of an intact annulus fibrosus that may diminish the risk of leakage of the injected agent.

### *Surgery*

Surgery is an option for patients with degenerative disk disease nonresponsive to conservative treatment (see **Figs. 1–3**). Although controversial, in the carefully selected patient, lumbar spinal fusion may be regarded as the gold standard of surgical treatment of degenerative disk disease. Spinal fusions are a relatively common spine procedure that continues to grow in popularity. According to Rajaee and colleagues,[96] the rate of spinal fusion has increased 2.4-fold from 1998 to 2008 in the United States.

Because pain relief has been achieved in other arthritic joints of the body through the elimination of painful motion, it has been assumed that analogous relief can be achieved through a successful spinal fusion. In a multicenter randomized trial, Fritzell and colleagues[97] compared 3 common surgical techniques (posterior only, anterior only, and combined anterior posterior approaches) used to achieve a lumbar fusion. In this study, all fusion techniques were found to reduce pain and improve function, but there was no difference among the techniques used to achieve fusion. The investigators concluded that immobilization of the motion segment appeared to be the important component, whereas the surgical technique used appeared to be less important.[97] Similarly, the use of instrumentation also remains unclear. Meta-analysis[98] and randomized, prospective studies[99] have suggested that although fusion rates are increased with pedicle screw fixation, an improvement in clinical outcomes may not be noted. Conversely, several have advocated that specific appropriateness criteria may improve surgical outcomes in patients with LBP.[100] Nonetheless, according to a systematic review by Chou and colleagues,[101] fusion is no more effective than intensive conservative rehabilitation for degenerative disk disease. Furthermore, fusion was associated with small to moderate benefits compared with standard (nonintensive) conservative therapy. Moreover, based on the Medical Research Council Spine Stabilization RCT assessing patients with chronic LBP at a minimum of 1-year duration who were randomized to undergo lumbar fusion or an intensive rehabilitation program based on cognitive behavioral principles, no difference in disability and functional outcome was noted in both treatment groups.[102]

The efficacy of total disk replacement (TDR) has been scrutinized throughout the years (see article by Mayer and Siepe elsewhere in this issue). Based on a systematic review by van den Eerenbeemt and colleagues,[103] it was concluded that studies assessing the efficacy of TDR lacked proper control groups and were generally of low quality. The results indicate that TDR is at best only of similar efficacy to lumbar fusion. In clinical practice, TDR is used mostly for single-level disk disease and not for multilevel disease. Nevertheless, the investigators concluded that the existing evidence, specifically regarding long-term effectiveness or safety, is considered insufficient to justify the widespread use of TDR for single-level degenerative disease. Furthermore, the correlation between radiographic evidence of motion preservation and clinical improvement in pain intensity has not been completely supported.[104] In a recent prospective study addressing TDR by Blondel and colleagues,[105] superior clinical outcomes based on Oswestry Disability Index and pain scales were observed in individuals with Modic type I endplate changes on MRI compared with Modic type II or no Modic changes. The findings from this study have stressed the importance of proper patient selection in individuals undergoing TDR to maximize surgical outcomes.

In general, rehabilitation is needed after disk surgery. Exercise programs starting 4 to 6 weeks after surgery seem to lead to a faster decrease in pain and disability than no treatment. Moreover, high-intensity exercise programs seem to lead to a faster decrease in pain and disability than low-intensity programs.[106] No systematic reviews are available to assess the efficacy of rehabilitation regime after lumbar fusion surgery, but 1 recent RCT by Abbott and colleagues[107] found a beneficial effect for rehabilitation after lumbar fusion surgery. However, the investigators concluded that in addition to neuromuscular exercises, rehabilitation should also address maladaptive pain coping.

Newer surgical techniques focusing on the use of dynamic stabilization have been described for the management of degenerative disk disease. Several systems currently exist and can be subdivided into 4 groups: (1) dynamic interspinous spacers, (2) static interspinous spacers, (3) pedicle screw/rod-based posterior dynamic stabilizing

system, and (4) total facet replacement systems. Theoretically, they all attempt to address the degenerative segment through either direct distraction forces to unload the disk, or to shield the disk and facet joints from motion, or reduce facet contact and pressure. High-quality RCTs and systematic reviews on the role and outcomes of these systems on the management of degenerative disk disease are absent.

## PROGNOSTIC FACTORS

According to a systematic review, maladaptive pain coping behavior, in addition to baseline disability, is an important prognostic factor for poor recovery of LBP.[50] Throughout the past decade, genetic analysis has been used to screen and identify risk factors for various spine-related conditions (eg, disk degeneration),[108–112] and to prognosticate the development of disease progression (eg, scoliosis).[113–115]

### *Maladaptive Pain Coping*

Recent studies uniformly suggest that abnormal fear-avoidance behavior predicts prolonged LBP.[50,116,117] Similarly, low expectations on return to work and abnormal fear-avoidance behavior predicted slow recovery after disk surgery.[118] A nonorganic pain drawing is defined as one with poorly defined pain patterns, pain with expansion to other parts of the body, and pain with a bizarre or nonanatomic appearance. In a recent study by Andersen and colleagues,[119] a nonorganic pain drawing was a significant risk factor for inferior outcome after spinal fusion surgery.

### *Genetic Factors*

Strong evidence, primarily based on twin studies, has suggested that LBP may have a genetic predisposition.[120–123] Some investigators, such as Karppinen and colleagues,[124] have noted that prognostic genotypes (eg, interleukin 6 haplotype

**Table 4**
**Pain genes**

| Gene | Protein | Mutation | Phenotype | Reference |
|---|---|---|---|---|
| ABCB1 | ATP-binding cassette, B1 | SNP | Altered morphine sensitivity | Campa et al[129] |
| COMT[a] | Catechol-*O*-methyltransferase | Multiple SNPs | Increased/decreased pain sensitivity | Dai et al[125]; Diatchenko et al[130] |
| CYP2D6 | Cytochrome P450 2D6 | Multiple SNPs | Altered analgesic efficacy | Stamer and Stuber[131] |
| FAAH | Fatty acid amide hydrolase | Multiple SNPs | Increased pain sensitivity | Kim et al[132] |
| GCH1[a] | GTP cyclohydrolase | Multiple SNPs | Partial analgesia | Kim et al[126]; Tegeder et al[133] |
| IL-6[a] | Interleukin 6 GGGA haplotype | SNP | Increased pain sensitivity | Karppinen et al[124] |
| MC1R | Melanocortin 1 receptor | SNP | Partial analgesia, increased analgesic responsiveness | Mogil et al[134] |
| OPRM1 | Opioid receptor $\mu$1 | Multiple SNPs | Decreased pain sensitivity, decreased opioid analgesia | Fillingim et al[135] |
| OPRD1 | Opioid receptor $\delta$1 | Multiple SNPs | Increased/decreased pain sensitivity | Kim et al[136] |
| SCN9A[a] | $\alpha$-subunit, voltage-gated $Na_v1.7$ | Multiple SNPs | Increased/decreased pain sensitivity | Reimann et al[127]; Yang et al[137] |
| TRPA1 | Transient receptor potential A1 | Multiple SNPs | Increased pain sensitivity | Kim et al[132] |
| TRPV1 | Transient receptor potential V1 | SNP | Decreased pain sensitivity | Kim et al[132] |

*Abbreviation:* SNP, single nucleotide polymorphism.
[a] Reported investigation in spine patients.
*Modified from* Foulkes T, Wood JN. Pain genes. PLoS Genet 2008;4:e1000086; with permission.

GGGA) may predict the duration of pain and may have an interaction effect with certain modifiable risk factors of pain in adults (eg, physical work load). In the setting of spine surgery outcomes, the implications of pain genes, and their role in sensitivity and processing of pain, may predict surgical outcomes in patients undergoing spine fusion for degenerative disk disease. According to Dai and colleagues,[125] who prospectively assessed 69 patients undergoing instrumented spine fusion for chronic discogenic LBP and their 1-year postoperative clinical outcomes, polymorphisms in the catechol-*O*-methyltransferase (COMT) gene were found to improve postoperative 1-year Oswestry Disability Index and pain scores. Based on the same group of patients, Kim and colleagues[126] also showed that polymorphic variations of the guanosine triphosphate cyclohydrolase 1 (GCH1) gene, specifically the T allele at rs998259 of GCH1, was found to improve postoperative clinical outcomes. Another interesting pain gene is *SCN9A*, which encodes the $\alpha$-subunit of the voltage-gated sodium channel $Na_v1.7$. A common polymorphism in the gene was associated with increased likelihood of pain among patients and lowered pain threshold among healthy females.[127] Additional known pain genes are noted in **Table 4**. Others have contended that the presence of chronic LBP may act to potentiate genetic susceptibility to the pain experience through epigenetic modification.[128]

Although additional, larger studies are warranted to assess the detailed role and mechanism of pain genes in individuals suffering from degenerative disk disease and chronic LBP in addition to the need to replicate previous findings in different populations, this field of pain genetics provides a new direction in understanding the pain experience and perception and may be useful for identifying individuals susceptible to LBP or who would benefit most from spine surgery. Furthermore, identification of pain genes may lead to gene therapy to treat LBP conditions. Although promising, the role of pain genes in such settings needs to account for the complex biopsychosocial factors, pain history, and gender differences that may also play a role in the patient's pain profile and that may dictate management and prognostic outcomes.

## SUMMARY

Conservative decisions in the treatment of degenerative disk disease are based on interventions made for patients with chronic LBP. There is convincing evidence that patient education, exercise therapy, and cognitive behavioral therapy are the cornerstones for the treatment of chronic LBP. However, the effect sizes of these treatments are modest. Furthermore, these therapies work best in a multidisciplinary rehabilitation context. Pain medication is needed for most patients with degenerative disk disease, and surgery may be needed for a minority only.

In the future, more research should focus on strategies of early recognition and treatment of high-risk patients. These high-risk patients should perhaps be offered treatment(s) based on their clinical profile (ie, current and past symptoms and clinical finding) or genetic predisposition to pain. For example, a patient with an abnormal psychosocial profile may benefit most from cognitive therapy, whereas exercise therapy may be of lesser importance. Similarly, an individual susceptible to pain sensitivity because of genetic factors may not benefit from surgical intervention and alternative means should be pursued. For those with problems in workability more intensive multidisciplinary outpatient approaches may be needed. Recent evidence suggests that these interventions should include workplace intervention in combination with progressive exercise therapy based on cognitive principles. In addition, biologic therapies for disk repair and regeneration may show promise for the treatment of discogenic LBP.

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