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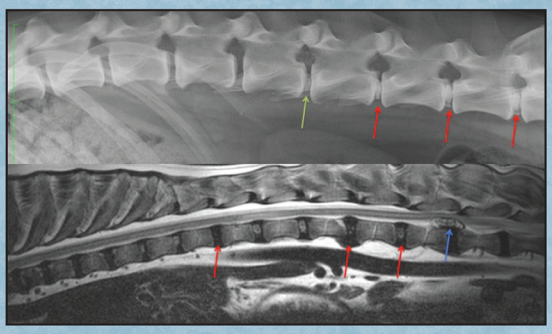
GENE AND CELL DELIVERY FOR INTERVERTEBRAL DISC DEGENERATION



EDITED BY

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Gene and Cell Delivery for Intervertebral Disc Degeneration

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Series Preface

Gene and cell therapies have evolved in the past several decades from a conceptual promise to a new paradigm of therapeutics, able to provide effective treatments for a broad range of diseases and disorders that previously had no possibility of cure.

The fast pace of advances in the cutting-edge science of gene and cell therapy, and supporting disciplines ranging from basic research discoveries to clinical applications, requires an in-depth coverage of information in a timely fashion. Each book in this series is designed to provide the reader with the latest scientific developments in the specialized fields of gene and cell therapy, delivered directly from experts who are pushing forward the boundaries of science.

In this volume of the Gene and Cell Therapy book series, *Gene and Cell Delivery for Intervertebral Disc Degeneration*, the editors have assembled a remarkable team of outstanding investigators and clinicians, each one of whom is an expert in a specific area of IVD, to give us an integrated approach to the most current and controversial aspects of IVD and the forefront research that is set to reform the way IVD management/treatment is approached.

This highly innovative and timely book brings together aspects pertaining to developmental and stem cell biology of the Nucleus Pulposus; cell recruitment, chemoattractants, immunology, and inflammation of disc degeneration; molecular-, cellular-, and biomaterials-based therapies targeting the degenerated disc; and the current therapeutic challenges that clinicians face when treating patients with IVD.

We would like to thank the volume editors, Raquel Gonçalves and Mário Barbosa, and all the authors, all of whom are remarkable experts, for their valuable contributions. We would also like to thank our senior acquisitions editor, Dr. C.R. Crumly, and the CRC Press staff for all their efforts and dedication to the Gene and Cell Therapy book series.

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Preface

Low back pain (LBP) is the global leading disorder in terms of number of years lived with disability. It is also a social problem with a heavy economic burden, and tendency to increase as long as the population ages. Intervertebral disc (IVD) degeneration is one of the major causes of LBP, for which common therapeutic interventions are not efficient. The current clinical approaches, either conservative or nonconservative, are determined by the degree, severity, and persistence of pain, but the outcome of these solutions is often transient, some of them affecting patients' mobility, and others causing adjacent IVD degeneration, which in the end leads to chronic LBP symptoms in many patients.

A search for alternative therapies for LBP and particularly IVD degeneration has been encouraged, with special focus on cell-based therapies. However, contrary to many other tissues, the IVD has an avascular nature, maintained under hypoxia, low-glucose and is highly pressurized, which turns degenerated IVD into a hostile environment for cell survival.

Furthermore, cellular characterization in the IVD, and particularly in the nucleus pulposus, remains controversial, meaning that its molecular and cellular signature is not consensual among the scientific community, mainly due to a lack of specific markers and species variability. This impacts directly on the knowledge about the regenerative potential of this tissue by itself.

Overall, this book aims to contribute to increasing the knowledge on cellular and molecular therapies for degenerated IVD and associated LBP. The most relevant issues include the *ex vivo* and *in vivo* models of IVD degeneration, the types of cells, and cell sources for treating degenerated IVD, the current and alternative routes of therapies for degenerated IVD, the vehicles for cell delivery into degenerated IVD, and the intradiscal molecular therapies for degenerated IVD.

Finally, it is the goal of this book to approach current controversial aspects of IVD research and bring together the most recent advances in the field of molecular and cell therapies for degenerated IVD.

Editors

Raquel M. Gonçalves has a degree in chemical engineering and a PhD in biotechnology (University of Lisbon, Portugal). She gained expertise in human hematopoietic stem cell and mesenchymal stem cell expansion, with a period abroad in the University of Nevada, Reno, United States. Since 2009, she has been an assistant investigator and has been dedicated to intervertebral disc research. Presently, at I3S (Instituto de Investigação e Inovação em Saúde/INEB, Institute of Biomedical Engineering, University of Porto), she develops her work at the Microenvironments for New Therapies Group, whose main goal is to dissect the microenvironment elements that contribute to reestablish homeostasis upon disease and/or injury and to bioengineer therapeutic strategies to modulate host response. In this group, she has been involved in the establishment of IVD *ex vivo* and *in vivo* models, high-throughput tools to characterize IVD cells and extracellular matrix, and immunomodulatory strategies and stem cell recruitment to degenerated IVD. In parallel, she is involved in science dissemination activities at Porto high schools and in teaching at the University of Porto.

Mário Adolfo Barbosa is a full professor at Instituto de Ciências Biomédicas Abel Salazar (ICBAS), University of Porto, Portugal. For nearly 30 years, biomaterials science and technology has been the topic of Mário's research. He is internationally recognized for his contributions to biomaterials science, particularly in cell–biomaterial interactions. Mário was one of the founding members of the Instituto de Engenharia Biomédica (INEB, http://www.ineb.up.pt), created in June 1989. From 2000 to 2012, he was the scientific coordinator of the institute and its president from 2000–2006 and 2010–2012. Presently, he is the scientific coordinator of the I3S (Instituto de Investigação e Inovação em Saúde), of the University of Porto and leader of the Microenvironments for New Therapies Group at i3S. His research interests focus on the modulation of the microenvironment, in particular the inflammatory response to improve tissue repair and/or regeneration.

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1 Intervertebral Disc Degeneration in Clinics
Therapeutic Challenges

Pedro Santos Silva, Paulo Pereira, and Rui Vaz

CONTENTS

1.1 INTRODUCTION

For spine surgeons, lumbar degenerative disc disease (DDD) is an everyday challenge. In the last decades, this condition has raised significant questions and controversies that are far from being solved. From this contextual uncertainty, we can point two main sides of this problem that are relevant for interventional treatments: disc herniation as a cause of *radicular compression* and disc degeneration as a source of *discogenic pain*.

Lumbar discectomy is by far the most common surgical treatment for intractable sciatica caused by lumbar disc herniation. Although it has been an option for many years, this procedure remains an act of aggression to the disc itself. Like a dentist extracting a tooth, the spine surgeon treats a dislocated part of the intervertebral disc by removing it. There is no procedure in our days than can resolve a lumbar radicular compression in a physiologic and reconstructive way.

Degenerative changes in lumbar discs can be associated with low back pain (LBP) in a selected group of patients, but the definition and diagnosis of discogenic pain remain a disputed concept. Beyond the diagnosis, the treatment of patients who are presumed to have discogenic pain involves a spectrum of more or less destructive procedures, none of which, including percutaneous techniques and lumbar fusion, is established as the standard of care.

For patients, the major setback is the lack of adequate treatments that can restore the biologic and mechanical intervertebral disc structure and function. This difficulty leads to several different treatment proposals with disappointing results and high rates of disability.

1.2 IMPORTANCE OF DISC DEGENERATION AND LBP

It would be no exaggeration to say that lumbar DDD is ubiquitous in the aging population. In a recent report (Armbrecht et al. 2017) of a prospective cohort of 10,132 individuals aged more than 50 years, all the participants had some degree of radiologic DDD, and moderate or severe DDD was present in 47% of the cases. Following the same trend, pain located in the lumbar area is an almost universal experience during human life. LBP has an enormous health and economic burden and has been the leading cause of years lived with disability in the world, in the last two decades (Global Burden of Disease Study Collaborators 2015).

According to Waddell (2005), LBP can be related to a *specific pathology*, *nerve root pain*, and *nonspecific causes* (Table 1.1). Specific causes are potentially severe spinal pathologies (fractures, tumors, and infection) and correspond to only 1%–2% of cases.

In this classification, about 5% of patients have nerve root pain (associated with disc herniation or vertebral canal stenosis) (Waddell 2005). The estimated incidence of sciatica in Western countries is 5:1000 (Cherkin et al. 1994), and while most cases

TABLE 1.1
Possible Causes of LBP

Specific LBP	Tumor
	Infection
	Fracture
Nonspecific LBP	Myofascial syndrome
	DDD
	Facet syndrome
	Instability
	Sacroiliitis
Nerve root pain	Lumbar disc herniation
	Vertebral canal stenosis
	Foraminal stenosis

of radicular pain resolve spontaneously, about 30% of patients can have persistent symptoms (Weber, Holme, and Amlie 1993).

Hence, by far, the vast majority of cases (85%–95%) correspond to nonspecific LBP, a widely heterogeneous group, where accepted diagnosis criteria are absent and the treatment is mainly empirical and unproved. In this category, a wide variety of pain generators have been included, such as the following:

- Intervertebral disc degeneration (discogenic pain)
- Muscle and ligaments (myofascial syndrome, low back strain)
- Facet joint osteoarthritis (facet syndrome)
- Abnormal movement (segmental instability)
- Sacroiliac joint (sacroiliitis)

In a study based on computed tomography (CT) and discography, about 40% of cases of nonspecific LBP were attributed to intervertebral discs (Schwarzer et al. 1995). Despite the advances with magnetic resonance imaging (MRI) and its association with provocative discography, there is no consensus on how to diagnose discogenic pain and the contribution of this entity to LBP.

1.3 CLINICAL MANIFESTATIONS OF DISC DEGENERATION

In clinical practice, the differential diagnosis between specific, nonspecific LBP, and radicular pain is a primary concern. Specific causes of LBP are fractures, tumors, infection, and inflammatory diseases.

A *fracture* is commonly suspected when acute back pain that worsens with loading begins after trauma; however, elderly women with osteoporosis can suffer vertebral fractures without a history of significant trauma. In adults older than 50 years, a slow-onset and progressive pain that wakes the patient at night suggests a *tumor*, particularly if there is cancer history. LBP in the presence of fever can be associated to infectious causes. Ankylosing spondylitis, psoriatic spondylitis, or Reiter syndrome are inflammatory diseases that affect the spine, mostly in young adults. These rheumatologic conditions are characterized by an inflammatory back pain that is more significant in the morning and is accompanied by stiffness with limitation of spine movements.

Nonspecific LBP can be related to the mechanical structures of the spine, such as the vertebrae and their articulations (intervertebral discs and facet joints), apposed joints (hip or sacroiliac joint), muscles, and ligaments. Injury or inflammation of these structures can cause a mechanical type of pain, which exacerbates with movement and exertion and tends to increase to the end of the day, and there is some relief with resting. The pain can radiate to the groin, buttocks, and thigh, which is call referred pain, a pain perceived at a different location from the site of the painful stimulus; this form of pain typically has a proximal radiation above the knee and is less well localized than a pain originating from a nerve root. There are some clinical aspects that can suggest an intervertebral disc origin for a LBP (Tonosu et al. 2017): a *discogenic pain* the can be triggered after sustained loading (sitting too long) and lumbar flexion, especially with knee extension (washing one's face), and can radiate

TABLE 1.2
Common Lumbar Nerve Root Compression Syndromes

Nerve Root	Pain/Numbness	Motor Weakness
L4	Inner side of the leg and foot	Extension of the knee
L5	Anterior and outer side of the leg and dorsal side of the foot	Dorsiflexion of the foot
S1	Outer and plantar side of the foot	Plantar flexion of the foot

to the anterior thigh. This condition should be differentiated from facet syndrome, a condition that results from facet joint osteoarthritis, in which the back pain may exacerbate with lumbar extension or rotation and radiate to the posterior thigh.

Radicular pain, also known as nerve root pain or sciatica, is caused by nerve root compression, usually in the lateral recess of the vertebral canal or in the intervertebral foramen. This compression can be originated by osteophytes, facet joint, or yellow ligament hypertrophies, but the most common cause is a lumbar disc herniation. Radicular pain runs from the lumbar region to the lower limb, is usually unilateral and sharp, and sometimes is associated with numbness. The topography of the pain is usually well defined and depends on the affected nerve root and its respective dermatome. Since the compression is more common in L4, L5, or S1 nerve roots, the pain typically radiates below the knee, affecting the foot. Neurological examination can reveal motor weakness and sensitive alterations, depending on the myotome or dermatome of the compressed root (Table 1.2). The straight leg raising test, also called *Lasègue's* test, is positive when the radicular pain is recreated by lifting the patient's leg while the knee is extended.

1.4 INTERVERTEBRAL DISC DEGENERATION IN IMAGING STUDIES

Lumbar DDD findings in imaging studies are well recognized, and there are several classifications of disc degeneration for radiographs, CT scans, and MRI. There are three progressive markers of DDD in radiography images and CT scans: disc height loss, osteophyte formation, and sclerosis of vertebral bodies (Lane et al. 1993; Wilke et al. 2006). The progression of the disease also leads to intervertebral disc vacuum sign, intervertebral disc space collapse, degeneration of the facet joints, subluxation (spondylolisthesis), and deformity in sagittal or coronal planes. The neural elements can be compressed by stenosis in the vertebral canal, lateral recess, or intervertebral foramen (Thalgott et al. 2004).

Pfirrmann et al. (2001) developed the most widely used classification of MRI findings of lumbar DDD. It is a grading system that describes the degenerative process based on T2-weighted MRI sequences. The higher the grade is, the greater the severity of degeneration. Throughout the degeneration process, the nucleus pulposus loses its water content and its hyperintense signal on T2-weighted images,

the distinction between nucleus and annulus is lost, and there is a reduction in the disc height (Table 1.3).

Degeneration of vertebral body endplates and subchondral bone on MRI was classified into three types (Modic et al. 1988). Modic type I changes are hypointense on T1-weighted and hyperintense on T2-weighted images, and indicate bone marrow edema. These are thought to represent acute changes of the vertebral body and can be related to discogenic back pain (Weishaupt et al. 2001). Type II changes are hyperintense on both T1 and T2 sequences and represent chronic degenerative changes with bone marrow replacement by fat. Modic type III changes are hypointense on both T1 and T2 sequences, indicating sclerotic vertebral endplates. The intervertebral disc can herniate through a disruption in the vertebral body endplates, causing an intravertebral disc herniation (Schmorl nodes).

Lumbar disc herniation can assume various forms, depending on the volume of the dislocated tissue and the integrity of the annulus. In 2014, an American consensus (Fardon et al. 2014) defined disc herniation as a localized or focal displacement of disc material beyond the limits of the intervertebral disc space. This disc material may be nucleus, cartilage, fragmented ring apophysis, or annular tissue. A disc *bulge or bulging* is the presence of disc tissue extending beyond the edges of the ring apophyses, throughout the circumference of the disc. This is not considered a form of herniation. A disc herniation is called *protrusion*: if the greatest distance between the edges of the disc material presenting outside the disc space is less than the distance between the edges of the base of that herniated disc material. When any distance between the edges of herniation is greater than its base, an *extrusion* is present. When no continuity exists between the herniation and the disc space, the extrusion is subclassified as *sequestration*. The term *migration* is used to describe the displacement of disc material away from the site of extrusion. Another classification of disc herniations, as *contained* or *uncontained*, depends on the displaced material being covered or not by annulus fibers, and/or the posterior longitudinal ligament.

TABLE 1.3
Pfirrmann Classification of Lumbar Disc Degeneration on MRI

Grade I	Disc is homogeneous, with a bright hyperintense white signal intensity and normal disc height.
Grade II	Disc structure is inhomogeneous, with a hyperintense white signal, with or without horizontal gray bands; distinction between nucleus and annulus is clear; and the disc height is normal.
Grade III	Disc is inhomogeneous, with an intermediate gray signal intensity; distinction between nucleus and annulus is unclear; and the disc height is normal or slightly decreased.
Grade IV	Disc is inhomogeneous, with a hypointense dark gray signal intensity; distinction between nucleus and annulus is lost; and the disc height is normal to moderately decreased.
Grade V	Disc is inhomogeneous, with a hypointense black signal intensity; distinction between nucleus and annulus is lost; and the disc space is collapsed.

In 2006, a lumbar degenerative disease severity score was proposed (Mirza et al. 2006), based on nine imaging features that evaluate disc and endplate degeneration on MRI, disc height loss, osteophytes, disc herniation type, stenosis, spondylolisthesis, instability, and deformity. This system is very complete and is scored from 0 to 39 points, and there was an excellent interrater agreement for this severity scale.

Provocative *discography* is an invasive diagnostic procedure that involves a pressurized injection of fluid into an intervertebral disc to elicit pain. It has been developed to identify the cases where the disc was the primary source of back pain. Dye extravasation from the injected annulus site indicates annular fissure, which may be interpreted as an abnormal finding; however, typical pain reproduction is essential to classify the discogram as positive. Currently, this procedure is less commonly used and the test is considered controversial due to its low specificity and the concerns that it can increase the risk of clinical disc problems by inducing iatrogenic degenerative changes (Cuellar et al. 2016).

1.5 RELATION BETWEEN DISC DEGENERATION AND PAIN

There are some controversies about the relation between pain and pathologic findings of the lumbar discs in imaging studies. Several studies revealed abnormal MRI disc findings in asymptomatic subjects: disc protrusion (25%–50%), disc degeneration (25%–70%), signal changes in the vertebral body endplates (10%), and annular fissures (14%–33%) (Boden et al. 1990; Carragee, Paragioudakis, and Khurana 2000; Jensen et al. 1994). On the other hand, these alterations of intervertebral discs, annulus, and vertebral endplates on MRI findings have been associated with pain intensity during provocative discography. Despite disc degeneration having a significant relation with age in asymptomatic individuals, in younger ages (younger than 50 years old), a strong association was found between disc degeneration and LBP, and similar findings were reported for disc bulges (Brinjikji et al. 2015). Furthermore, Pfirrmann grades ≥3 are strongly associated with a history of previous LBP (Tonosu et al. 2017). Posterior *annular tears* on discography and a high-intensity zone on T2-weighted MRI are likely to produce pain since its prevalence is higher in symptomatic patients, but the validity of these signs is limited because their prevalence in asymptomatic individuals is also elevated, so they are not clinically reliable as pain predictors (Carragee, Paragioudakis, and Khurana 2000; Ito et al. 1998). Regarding *endplate abnormalities*, moderate and severe type 1 and 2 Modic changes were related to pain during discography (Weishaupt et al. 2001).

A meta-analysis of 14 high-quality case control studies including more than 3000 individuals (Brinjikji et al. 2015) demonstrated that MRI findings of disc bulge (odds ratio [OR]: 7.54), degeneration (OR: 2.24), extrusion (OR: 4.38), protrusion (OR: 2.65), Modic 1 changes (OR: 4.01), and spondylolysis (OR: 5.06) are more prevalent in adults up to the age of 50 with back pain, when compared with asymptomatic individuals; annular fissures, high-intensity zones, spondylolisthesis, and central canal stenosis demonstrated no association with LBP.

Concerning radiographic abnormalities, a systematic review of the literature found a positive association between radiographic disc space narrowing and LBP (Raastad et al. 2015).

1.6 PROGNOSIS

The prognosis of LBP is variable, with a great proportion of patients undergoing remission but also with high rates of recurrence. Back pain episodes are typically transient, with improvements seen within a few weeks to a few months. Episode remission at 1 year ranges from 54% to 90% and recurrence at 1 year is estimated in a range from 24% to 80% (Hoy et al. 2010).

The prognosis of *sciatica* is good, and most patients will experience improvement in pain and disability in the short run without treatment. However, about 30% of patients refer persistent significant symptoms at 1 year (Weber, Holme, and Amlie 1993). Another study suggested that recovery from sciatica is less frequent than expected: 55% of patients still had symptoms of sciatica 2 years later, and 53%, after 4 years (25% who had recovered after 2 years had relapsed again by 4 years) (Tubach, Beaute, and Leclerc 2004).

1.7 THERAPEUTIC CHALLENGES FOR DISCOGENIC LBP

Interventional treatments for LBP are still controversial and should be reserved only for patients who failed to improve with time and appropriate conservative management. However, clear diagnostic criteria for discogenic pain are not established. Pain topography, characteristics, and worsening factors may suggest the anterior column as a pain generator. Spine imaging may show disc degeneration that can be related to pain, but these features are also found in asymptomatic individuals. In the last decades, several procedures to treat lumbar DDD emerged, with meaningful mechanisms of action and potentially favorable outcomes. In most of them, however, after some initial promising reports, randomized trials failed to prove unquestionable efficacy of the treatments. It seems that unclear and inadequate selection of patients is a determinant factor for failure of treatment and waning in generalized use of the techniques.

1.7.1 Conservative Treatment

Guidelines for the management of LBP (Chetty 2017) strongly recommend conservative treatments as the first approach. Initial management includes medication and paracetamol, nonsteroidal anti-inflammatory drugs, and muscle relaxants that may be used for short-term treatment. For severe pain, stronger analgesics, such as opioids, are next in the recommendations.

For chronic pain, a different approach is proposed, and medication may include opioids and anti-depressants. *Cognitive behavioral therapy* (CBT) is recommended for chronic pain in most guidelines.

The efficacy of *passive physiotherapy modalities*, such as traction, ultrasound, massage, acupuncture, transcutaneous electrical nerve stimulation, and heat and cool therapies is unclear, with conflicting results in the literature. *Exercises* are usually indicated, which include aerobic, muscle conditioning, and back exercise classes.

1.7.2 Percutaneous Techniques

Several techniques have been developed to treat the initial stages of lumbar DDD, having in common the insertion and manipulation of catheters or electrodes within the disc space. They are appealing for the patient and for the physician because they are minimally aggressive and have much lower complication rates than operative treatment, particularly considering spine fusion. Whether they are injections or ablative techniques, delivering some type of energy, all these procedures produce some degree of destruction of the disc.

Thermal annular procedures involve delivering energy to the posterior annulus fibrosus. The rationale is that coagulation of nerve fibers occur in the annulus and that denaturation of collagen fibers results in shrinking of the annulus and promotes the healing of annular tears (Lu et al. 2014). As mentioned, there is little evidence that annular fissures are related to discogenic pain.

In intradiscal electrothermal therapy (IDET), a flexible electrode is steered in a circumferential fashion inside the annulus fibrosus of the disc and then it is heated to 90°C. Two randomized controlled trials (RCTs) (Freeman et al. 2005; Pauza et al. 2004) compared IDET with sham procedures and reported poor results with the procedure. One study showed no significant benefit from IDET over placebo, and in the other study, substantial numbers of patients benefited from the sham treatment, so the apparent efficacy of IDET was considered to be related to nonspecific factors and not to the procedure itself.

Another form of thermal annular procedure is percutaneous intradiscal radiofrequency thermocoagulation (PIRFT). The efficacy of this technique was assessed in two RCTs and there were no significant differences between sham and treated groups (Barendse et al. 2001; Kvarstein et al. 2009).

A third form of thermal annular procedure, *biacuplasty*, involves the use of two cooled radiofrequency electrodes placed on the posterolateral sides of the annulus fibrosus. One RCT compared biacuplasty with sham procedure and reported clinical benefits in the intervention group at 6 months after the treatment (Kapural et al. 2013). Another multicenter RCT compared biacuplasty with conventional medical management and reported superior performance in the procedure group in all study outcomes (Desai et al. 2016).

All in all, regarding thermal annular procedures, IDET and PIRFT are likely ineffective for patients with discogenic pain, and intradiscal biacuplasty showed some promising results, but further studies are needed to confirm its effectiveness (Lu et al. 2014).

Electrothermal ablation of ramus communicans, a possible neuropathway for discogenic pain, was evaluated in only one study in 2004, with promising results, but no additional studies were published (Oh and Shim 2004).

Methylene blue can be used to chemically ablate nerve endings. The intradiscal injection of methylene blue was evaluated in an RCT (Peng et al. 2010): patients who underwent the treatment reported significantly better outcome scores than the sham group. In a small prospective clinical series of 15 patients (Kallewaard et al. 2016), 40% of the patients claimed at least 30% pain relief. An additional retrospective observational study (Zhang et al. 2016) stated that intradiscal methylene blue might be an effective therapy in short-term follow-up.

Two RCT studies investigated the clinical success of *intradiscal steroid injections*. One study with 1-year follow-up failed to detect significant differences between intradiscal steroid and saline injections (Khot et al. 2004). The other study found that patients who received intradiscal injections of steroid or steroid plus an anti-inflammatory herbal had significantly improved outcomes at their 3 and 6 month follow-up, compared to the saline injection (Cao et al. 2011). A recently published RCT (Nguyen et al. 2017) compared the results of an intradiscal steroid injection performed during discography versus discography alone. One month after the intervention, the percentage of responders (reduction in LBP intensity) was higher in the steroid than control group (55.4% versus 33.3%), but the groups did not differ in pain intensity at 12 months.

1.7.3 Operative Treatment

Lumbar segment arthrodesis, or *fusion*, is the reference treatment for patients with lumbar DDD who failed all other treatments and in whom the intensity of pain and reduction of quality of life are so severe that surgical intervention is considered. Lumbar fusion can be performed using several techniques. Posterolateral fusion involves promoting bone fusion between the adjacent facet joints and transverse processes, usually using screws and rods as an internal fixation device. Interbody fusion requires a radical discectomy, removal of the cartilaginous endplates of the adjacent vertebrae, and usually the insertion of a cage and bone or a bone substitute inside the disc space to promote interbody bone growth. In most cases, a construct with pedicle screws and rods is also used. The variations of interbody fusion techniques depend on the approach to the disc space: posterior, posterolateral, lateral, or anterior, and besides the arthrodesis, decompression of neural elements may also be performed during surgery, depending on the clinical picture and the option of the surgeon. Minimally invasive surgical techniques were developed to reduce the soft tissue damage related to the approach, and these techniques have been reported to reduce the blood loss and the need for analgesic medications during the postoperative period and to decrease the length of hospitalization and complication rates (Khan et al. 2015).

The rationale for fusion in patients with discogenic pain is to remove the pain generator, and reduce the nociceptive input from loading of the disc and the facet joints from painful motion.

There is limited evidence for the use of fusion techniques in patients with discogenic back pain. Lumbar fusion has been compared to nonoperative management. A systematic review and meta-analysis of five RCTs included data from 707 patients (Bydon et al. 2014): there was an overall improvement of 7.39 points in the

Oswestry Disability Index in favor of lumbar fusion, but this difference was not statistically significant. In 2014, a guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine was published (Eck et al. 2014) regarding fusion for intractable LBP without stenosis or spondylolisthesis. This study found a Level II evidence supporting the use of either intensive rehabilitation programs, incorporating cognitive therapy, or lumbar fusion.

Although lumbar fusion may benefit selected patients with discogenic pain, the fusion of a lumbar segment could lead to accelerated degeneration of adjacent disc segments. A recent study (Cho et al. 2014) reported that 66.8% of the patients have radiographic evidence of adjacent segment degeneration and 6.4% require a second operation at least 2 years after surgery.

Lumbar arthroplasty or *total disc replacement* was developed as a motion-preserving technique to lower the rate of adjacent segment disease, while keeping the rationale of lumbar fusion of removing the pain generator. There are various devices in the market, all of them including articular surfaces that tolerate loading and conserve the range of motion. Typically, they are inserted through an anterior approach. Most authors agree that adequate selection is the most important factor affecting arthroplasty outcomes and that ideal candidates are young patients with relatively preserved disc height, without any significant deformity, instability, or facet degeneration; in these patients, total disc replacement can be a suitable alternative to lumbar fusion (Salzmann et al. 2017). A review of five meta-analysis, about lumbar arthroplasty versus fusion, concludes that lumbar total disc replacement may be an effective technique for the treatment of selected patients with lumbar DDD, with at least equivalent results to lumbar fusion in the short-term; however, long-term studies are needed to address clinical outcomes, complications, and adjacent segment disease rates (Ding et al. 2017).

Surgery for discogenic pain may be only marginally superior to best conservative treatment, with the addition of significant complications and cost. The main limitations of operative treatment for DDD are the lack of pathoanatomical diagnosis in most patients and the absence of good-quality literature. Despite that, there has been an increase in the number of patients treated with spinal fusion for nonspecific LBP over the last two decades, which raised concerns about financial conflicts of interest among spine surgeons (Dhillon 2016).

1.7.4 Regenerative Techniques

Novel technologies with regenerative objectives have been proposed as an alternative to ablative procedures or operative treatment. The challenge is to stop or reverse disc degeneration. The use of biomolecular strategies, cell transplantation, and tissue-engineering technology is under investigation to attempt that purpose.

Biomolecular strategies are suitable for early degrees of disc degeneration, when cell growth and anabolic responses may be stimulated. Recombinant proteins and genes have been used to regenerate the expression of target molecules, facilitating the production of extracellular matrix. Members of the families of bone morphogenetic proteins and transforming growth factor were shown to increase proteoglycan content and disc height in several *in vivo* studies (Moriguchi et al. 2016). Gene vector systems

are being developed to regulate the transcription of growth factors, extracellular matrix degrading enzymes, and chondrocyte transcription factors (Woods et al. 2011).

Platelet-rich plasma has a high content of a variety of multifunctional growth factors. A recent RCT (Tuakli-Wosornu et al. 2016) studied intradiscal injection of platelet-rich plasma in 47 patients, and significant improvements in functional outcome were observed in the treatment group up to 1-year follow-up.

Introducing *stem cells* in the intervertebral disc has emerged as an attractive strategy for patients who have discs with intermediate structural damage, where the disc cell content is reduced. Several *in vivo* studies showed that these mesenchymal stem cells maintained viability and proliferate, and they can be induced to a chondrogenic pathway and then produce proteoglycans and collagen, increasing extracellular matrix and disc height (Moriguchi et al. 2016).

Intervertebral disc injection of autologous mesenchymal bone marrow cells was studied in 10 patients (Orozco et al. 2011), and the feasibility of the procedure was confirmed, with good clinical results despite unrecovered disc height.

Furthermore, after promising results in a canine model, a human trial was designed (Eurodisc) involving an autologous disc chondrocyte transplant into postdiscectomy patients. The study reported that in the intervention group, LBP was decreased and disc height was preserved at 2 years follow-up (Hohaus et al. 2008).

The impaired nutrient supply in degenerated discs is an obstacle to the feasibility of cell therapy. Furthermore, any injection inside the disc may induce additional degeneration.

Tissue-engineering technology is being developed for the treatment of advanced stages of disc degeneration. Scaffolds can be combined with cells, growth factors, and mechanical conditioning. The goal is an intervertebral disc construction *in vitro*, which can be implanted *in vivo*. Many studies have evaluated tissue-engineered components and whole-disc constructs, but no clinical study in lumbar spine was done (Moriguchi et al. 2016).

1.8 THERAPEUTIC CHALLENGES FOR SCIATICA

Most individuals with nerve root pain caused by intervertebral lumbar disc herniation have a high likelihood of recovery, spontaneously or with *conservative management*. As for discogenic back pain treatment, the initial approach can include pharmacological interventions and nonpharmacological strategies, such as physical therapy. In case of persistent pain or neurologic deficits, invasive treatments are the next step.

The evidence for caudal, interlaminar, and transforaminal *epidural glucocorticoid injections* in managing pain associated with lumbar disc herniation is good. These modalities may be an alternative to surgery, particularly in patients with contained disc herniations or moderate spinal stenosis (Manchikanti et al. 2013).

Lumbar discectomy is the standard surgical treatment for disc herniation. There is general agreement to indicate surgery in patients with good correlation between clinical picture and imaging studies, with progressive neurologic deficits or selected patients with persistent sciatica. There is still some controversy about the effectiveness of surgery in relation to conservative management. Studies that compared the