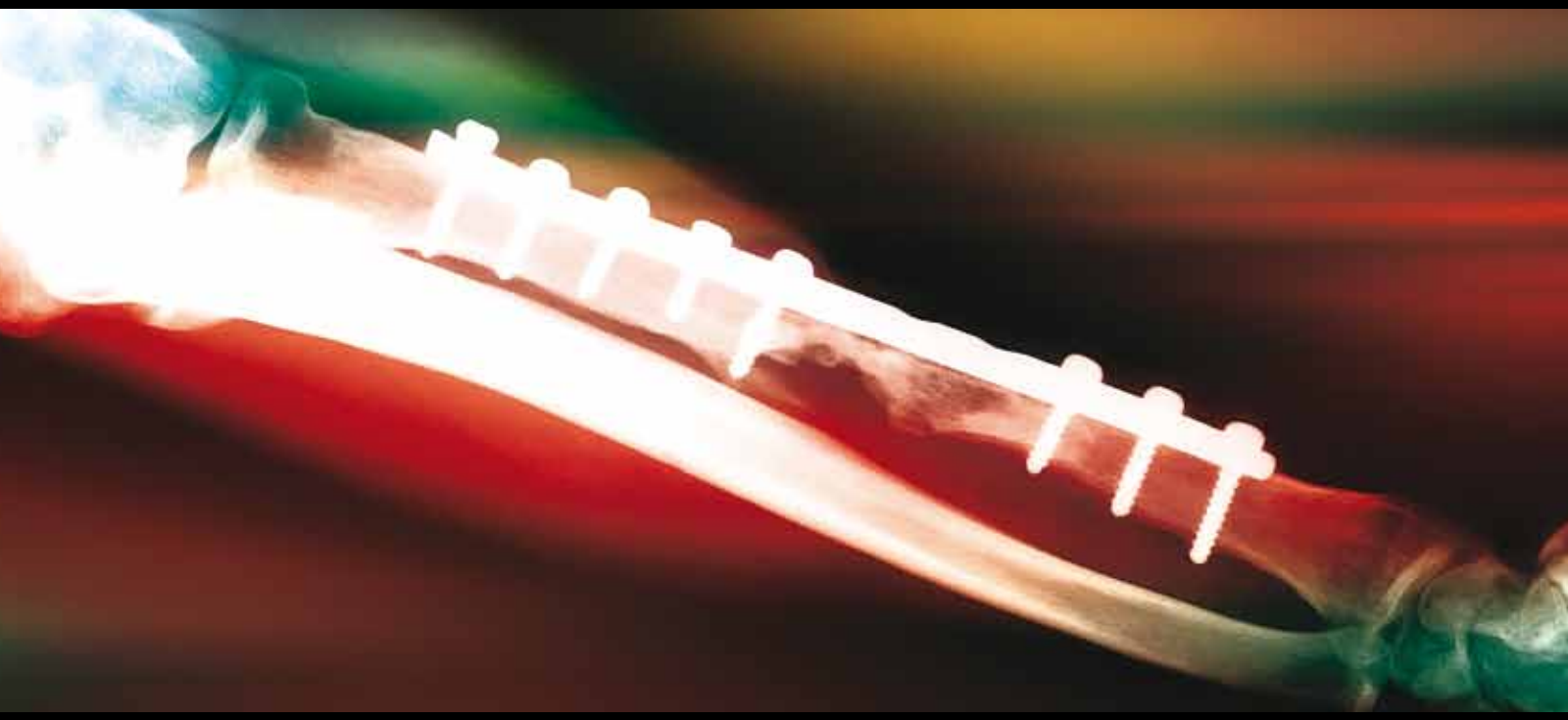
Advances in Orthopedics

Discogenic Lumbar Disease

Guest Editors: Brian R. Subach, Thomas C. Schuler, Mark R. McLaughlin, Paul J. Slosar, Christopher H. Comey, and Najeeb M. Thomas



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Editorial Board

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Editorial

Discogenic Lumbar Disease

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The treatment of discogenic lumbar disease is a major challenge faced by physicians throughout the world. This condition affects many patients and will inevitably become more prevalent with a rapidly aging population. Disc degeneration tends to increase rapidly with age so that 10% of 50-year-old and 60% of 70-year-old discs are severely degenerated [1]. The current special issue explores several crucial angles related to the pathology, diagnosis, and treatment of discogenic lumbar disease.

The mechanism of lumbar disc disease is elucidated in an article by V. K. Goel et al. which outlines the molecular processes involved in disc degeneration and the physical and chemical changes reducing disc integrity. The diagnosis of this condition is extensively explored in two related articles. The first article by A. C. Breen et al. "*Measurement of intervertebral motion using quantitative fluoroscopy: report of an international forum and proposal for use in the assessment of degenerative disc disease in the lumbar spine*" presents the case for using quantitative fluoroscopy application to the measurement of intervertebral motions and degenerative disc diagnosis. In the second article, M. W. Hasz provides a review of the diagnostic procedures for degenerative disc disease. He also provides a succinct explanation of how radiography, computed tomography, magnetic resonance, and discography are utilized in degenerative disc disease diagnosis.

Disc disease treatment is extensively addressed in four articles. The articles by D. Kok et al. and by L. Marchi et al. explore the application of interbody fusion as treatment for severely degenerated discs. V. Popov and D. G. Anderson provide an insightful review of treatments for lumbar disc degeneration and the application of ipsilateral and bilateral decompression with a tubular retractor system under microscopy. D. Drazin et al. provide a review of stem cell injection therapy for the intervertebral disc.

Evaluation of the outcomes of patients with lumbar disc disease is critical to the assessment of treatment efficacy. C. Lozano-Alvarez et al. describe the use of the Core Outcome Measures Index (COMI) in daily clinical practice for assessing patients with degenerative lumbar disease.

The current issue covers disc disease from several angles. Our intention is to provide a resource which can enlighten readers as to the mechanism, diagnosis, and the present state of intervertebral disc disease therapy and its treatment advances.

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Review Article

Diagnostic Testing for Degenerative Disc Disease

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The diagnostic of degenerative disc disease should be reached with the help of various diagnostic studies. This article briefly review the information gained by the following tests: radiographs, computed tomography, magnetic resonance, and discography. The article explains how each modality provides a piece of the diagnostic puzzle and how discography confirms the origin of the patient's pain.

1. Introduction

In the diagnosis and treatment of a patient with ongoing predominantly midline low-back pain (axial back pain), degenerative disc disease must be kept high amongst the possible diagnoses. In addition to the appropriate patient history, examination, and patient response to nonoperative conservative treatment, various diagnostic studies can aid in the diagnosis of degenerative disc disease and the exclusion of other diagnoses.

Common studies used to aid in the diagnosis of patients with axial back pain include lumbar radiographs, computed tomography (CT) scan, magnetic resonance imaging (MRI), and provocative discography. These studies should be used in conjunction with the patient history and physical examination. They are useful to aid in the diagnosis but are not in and of themselves definitive studies for the diagnosis of pain. However, using the studies in conjunction with the patient's clinical status and response to treatment is very useful for the overall diagnosis of degenerative disc disease.

2. Lumbar Radiographs

Lumbar X-rays should include a full series with standing or weight-bearing views: standing anterior-posterior (AP) pelvis and lateral flexion-extension views. These weight-bearing and dynamic studies can help identify many diagnoses which may otherwise be overlooked by a pure supine or non-weight-bearing X-ray: instability, increased angular motion on flexion-extension lateral views, anterolisthesis or retrolisthesis (each of which can be either subtle or direct indications of local instability), or indirect findings of lumbar disc degeneration.

Radiographs are more often used to exclude other diagnoses rather than directly diagnose degenerative disc disease. Diagnoses that can be more directly excluded with appropriate X-rays include scoliosis, spondylolisthesis, fractures, and gross instability. The actual radiographic findings of lumbar disc disease encompass a range of findings used to infer disc disease (Figure 1).

The radiographs are primarily used for assessing bony anatomy and alignment. They do not directly view the discs and soft tissues. In the early stages of lumbar disc disease, the disc heights may be unchanged. There may be annular tears identified and painful discs, but radiographs may not give any significant indication of disc injury, particularly in the acute setting of a disc injury. The flexion-extension lateral views may hint to muscle spasm and decreased excursion of range of motion. Therefore, muscle spasm or restriction can be inferred but not directly attributed to disc disease (Figure 2).

Some patients may have instability related to insufficiency of the lumbar disc. Some authors have defined 11° or greater of angular change on flexion-extension views to suggest the disc to be unstable [1]. Additionally lumbar retrolisthesis identified on radiographs has also been used to infer instability at lumbar levels [2] (Figure 3).

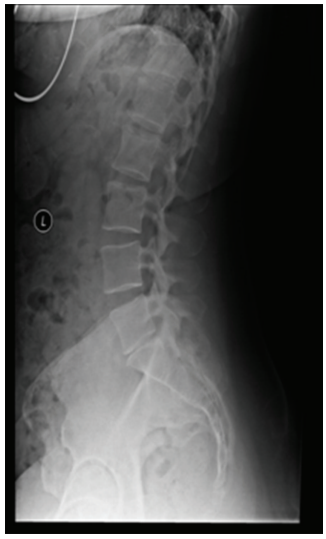


Figure 1: A lumbar radiograph with narrowing of the L5–S1 disc space. This narrowing is suggestive of disc degeneration.

The angular changes as well as retrolisthesis in the degenerative model of disc disease should not be confused or associated with the trauma model associated with White and Panjabi studies [1]. These studies were performed on cadavers where acute injury models and structural defects were made in order to assess instability in a trauma model. Applying these criteria in the degenerative disc disease model would be inappropriate.

Further suggestion of degenerative disc disease along the degenerative cascade would lead toward the formation of osteophytes along the edges of the endplates, narrowing of the disc space height, increased sclerosis along the endplates at the disc segment level, and possible osteophytes or sclerosis of the facet joints. In conjunction with the loss of disc space height, the foramina can be observed to narrow on the lateral and oblique studies [3] Toward the end of the degenerative cascade, a vacuum disc element can frequently be observed [4] (Figure 4).

Many of these degenerative changes in the lumbar spine may not be symptomatic and are only suggestive of the diagnosis of degenerative disc disease. In symptomatic patients, these radiographic findings are definitely suggestive of degenerative disc disease although further studies would be indicated.

3. Computed Tomography Scan

Overall a CT scan by itself is of limited value in the correct diagnosis of degenerative disc disease. Often a CT scan can be normal in the face of this disease. A CT scan has little direct value beyond the lumbar radiographs in the direct assessment of degenerative disc disease.

A CT scan is used to help exclude other diagnoses, as previously mentioned on the section on plain radiographs. A CT scan is very useful to help assess a pars defect or spondylolisthesis for example. Additionally, a CT scan can demonstrate findings that are also found on radiographs as well. A CT scan may be able to better demonstrate osteophytes as well as endplate sclerosis and vacuum disc sign, all related to findings of degenerative disc disease [4].

A CT scan is performed in a non-weight-bearing position and is of limited use to assess any dynamic instability in the lumbar spine. The CT scan can be used to assess the spinal canal and vertebral bony anatomy, as well as the posterior joint complex. It can further assess potential foraminal stenosis, and, when used in conjunction with myelography, it can assess possible nerve compression and indirectly disc protrusions (Figure 5).

4. Magnetic Resonance Imaging

MRI scanning, like CT scanning, can be used to evaluate the spinal canal and space available for neural structures. It can evaluate the overall bony alignment and the lumbar facets, but it has the additional benefit of allowing the direct assessment of the neural structures as well as the disc structures. This direct evaluation of neural and disc structures is not possible by CT scan [5].

An MRI is capable of evaluating the hydration within the discs based on increased signal on the T2-weighted images. Increased disc signal on T2-weighted images is associated with dehydration of the lumbar discs. Change in the disc signal, or darkening of the signal, is associated with dehydration or loss of hydrogen ions within the disc. This is often associated with lumbar disc degeneration. Decreased hydration leads to a loss of signal intensity on the T2 images which leads to darkening of the disc on the image (Figure 6). An area of increased signal may be identified within the disc or along the annulus of the disc. This area of increased signal is called a high-intensity zone. This high-intensity zone is thought to be correlated with an area of increased inflammation, thought to be associated with a disc tear or annular tear, and often is associated with axial back pain [6].

In addition to the changes within the disc, changes at the endplate adjacent to the disc have been described [7]. Modic noted reactive endplate changes at the endplates of the discs and graded them as Modic 1, Modic 2, and Modic 3 changes.

(i) Modic 1 reactive endplate changes demonstrate decreased disc signal on T1 images and increased disc signal on T2 images. These changes are associated with disruption and fissuring of the endplate and vascular fibrous tissue adjacent to the endplate. Modic 1 reactive endplate changes are infrequently associated with axial back pain (Figure 7).

(ii) Modic 2 reactive endplate changes are represented by increased signal intensity on T1 images and neutral signal on T2 images. These changes are associated with degenerative disc changes on plain radiographs. These changes represent yellow marrow replacement in the adjacent vertebral body at the endplates. This increased lipid content has been suggested to be an inflammatory response associated with a painful disc.

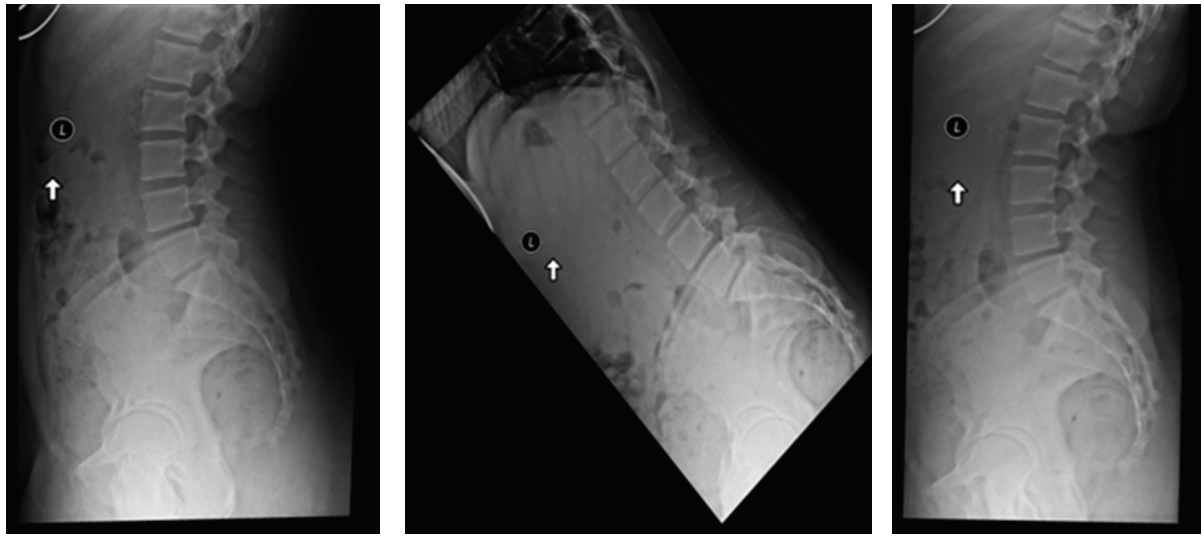


Figure 2: Lateral standing, flexion and extension X-rays are important to identify motion and/or instability in the spine. Some patients have unremarkable lateral upright X-rays but demonstrate a mobile spondylolisthesis upon dynamic testing.

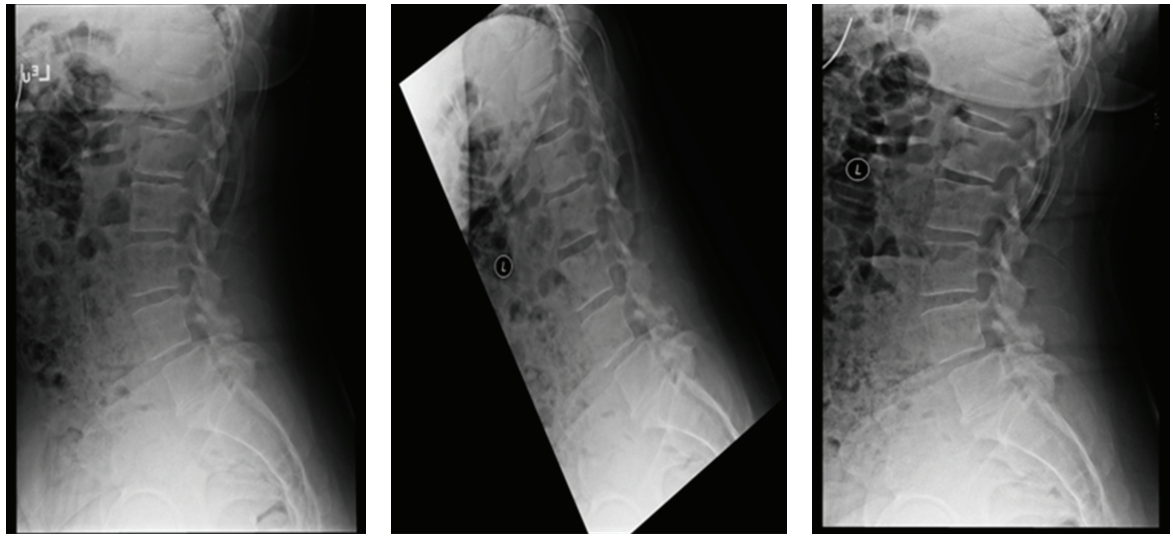


Figure 3: Lateral X-rays demonstrating a L4-L5 grade 1 spondylolisthesis. The standing lateral dynamic flexion and extension X-rays are used to determine motion at this segment.

(iii) Modic 3 reactive endplate changes demonstrate decreased disc signal on both T1 and T2 images. This represents bony sclerosis at each endplate. There are sclerotic endplate changes representing near-end-stage disease at the endplates. These are also associated with decreased blood supply at the endplates.

As mentioned earlier, the discs themselves have a range of intensity from high signal on the sagittal T2 images to a loss of signal. This represents a range from the normal hydration of the disc to gradual loss of hydration which is represented by a breakdown of the proteoglycans within the disc space and gradual degeneration of the disc.

A dark disc on MRI does not necessarily mean it is a symptomatic disc. Disc abnormalities are frequently seen on MRI in an asymptomatic patient. Up to 30% of asymptomatic volunteers have an approximately 30% rate of abnormal signal intensity within the discs. These abnormalities include disc protrusions and herniations, as well as decreased disc signal. Additionally as a patient ages, the frequency of decreased disc signal on MRI increases.

However, in a clinically symptomatic patient, an MRI that demonstrates decreased disc signal, particularly along the posterior annulus known as a high intensity zone, is highly associated with axial back pain. In symptomatic patients, lumbar discography can be of further use to help determine whether or not a disc is symptomatic.

In summary, an MRI plays an important but not exclusive role in the diagnosis of degenerative disc disease. In a symptomatic patient who has failed nonoperative conservative treatment and has normal X-ray findings, an MRI can

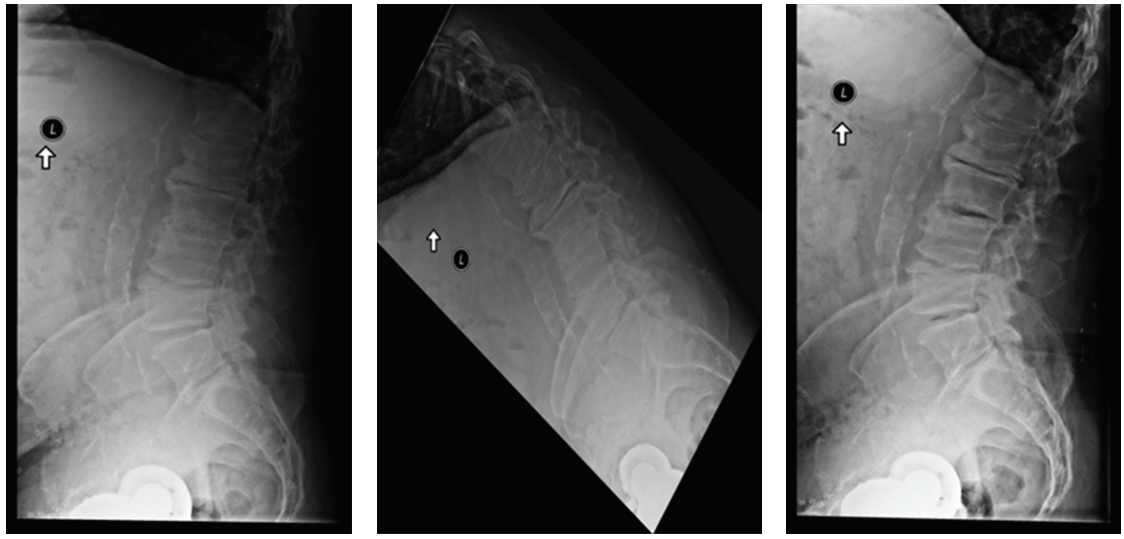
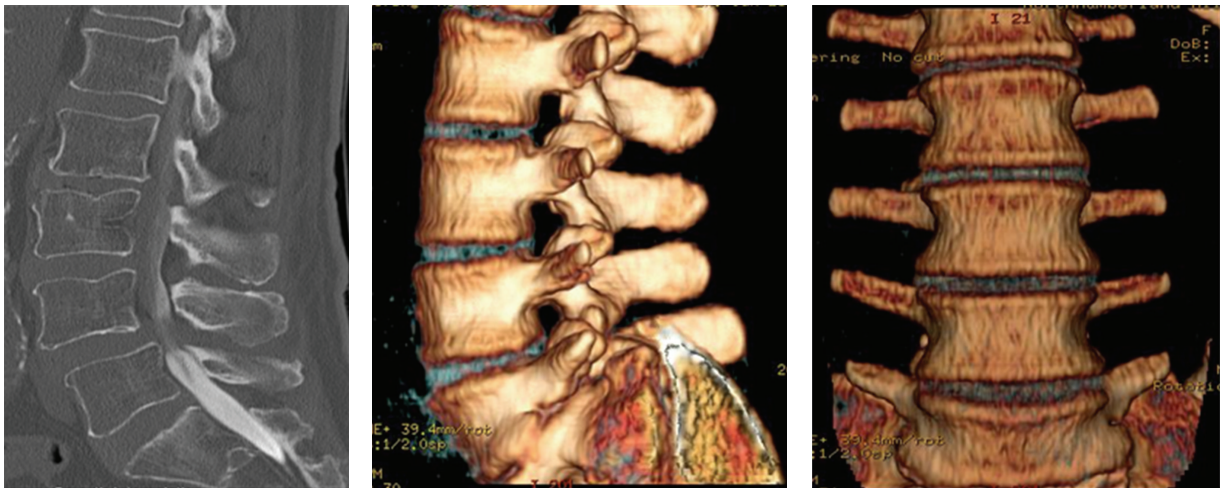


Figure 4: Lumbar X-rays. Standing lateral, flexion, and extension views. Disc degeneration suggested by vacuum disc (on extension) and osteophyte formation.



(a) (b) (c)

Figure 5: CT scans. (a) Grade I spondylolisthesis. ((b) and (c)) 3D reconstruction, lateral and anterior views.

be a very useful tool for further evaluation of a patient with axial back pain. A dark disc can be a tool to diagnosis of symptomatic degenerative disc disease.

5. Discography

Discography, particularly provocative discography, is the single most important diagnostic tool of degenerative disc disease. Lumbar discography is a test that would be appropriately performed in symptomatic patients who have failed nonoperative conservative treatment and whose X-rays and MRI studies suggest no other obvious pathology leading toward their diagnosis (Figures 8 and 9). Since the patient's chief complaint is pain and since no imaging studies actually see pain, lumbar discography can be used to potentially provoke and reproduce the patient pain [8].

There are four important pieces of information obtained in an appropriately performed discography: the subjective pain response, the volume and/or pressure of the fluid injected into the disc (a normal disc accepts 0.5 to 2.5 cc), the morphology of the disc injected (http://www.ncpainmanagement.com/InfoLumbarDiscography.htm), and the lack of a pain response in the adjacent controlled disc levels tested. All four of these criteria can be used and evaluated in an appropriately performed discography.

The discography should be performed under fluoroscopic guidance and using standard aseptic technique. Fluoroscopic guidance is used and radiopaque dye is injected within the disc space. This contrast enables the imaging of the actual disc, and its morphology can be evaluated. A normal disc has a biloped or globular pattern within the center of the disc. An abnormal pattern demonstrates leakage

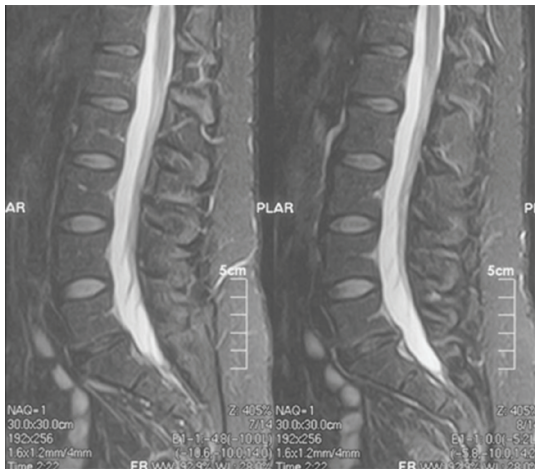


Figure 6: MRI sagittal T2-weighted demonstrating decreased disc signal at L5-S1. This indicates decreased hydration of the disc space. It does include or exclude patient symptoms of back pain.

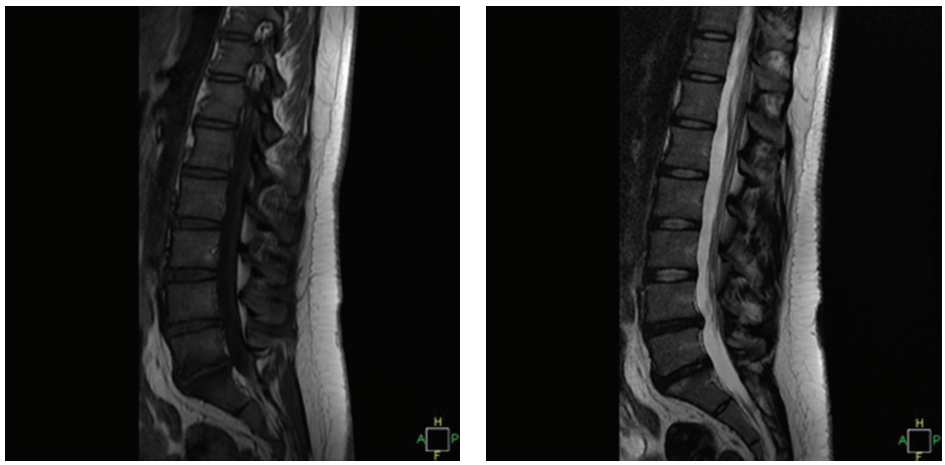


Figure 7: This MRI has two levels of decreased disc signal: L4-5 and L5-S1. There are early reactive endplate changes at L5-S1 as well (Modic type 1).

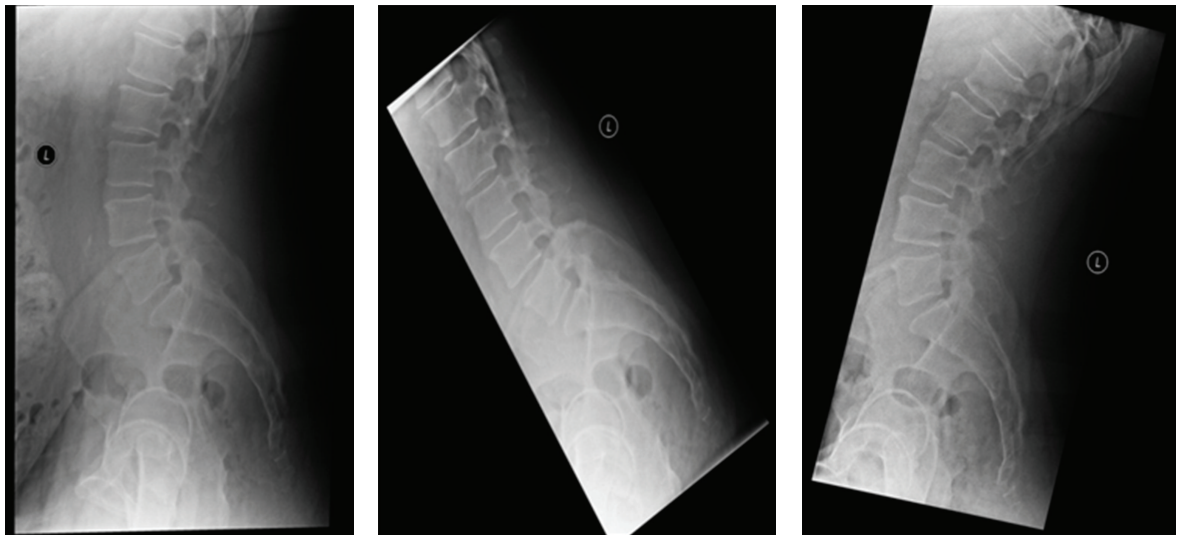


Figure 8: This patient's X-rays, including the upright lateral flexion and extension, are overall unremarkable.

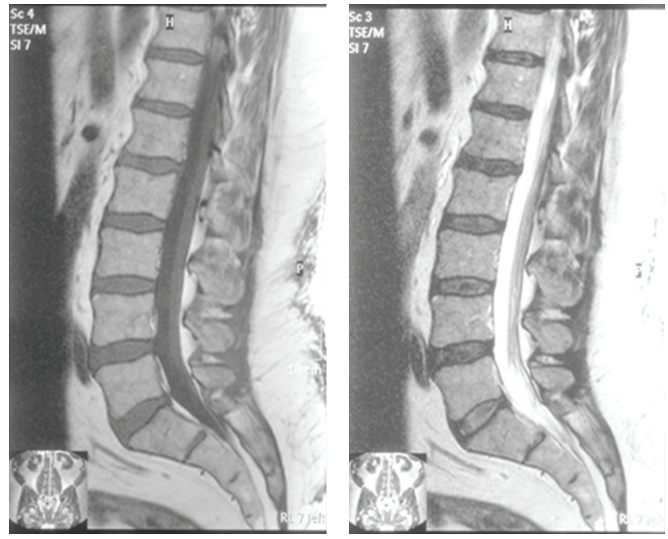


Figure 9: The same patient's T1 and T2 MRI demonstrates decreased disc signal at L4-5.

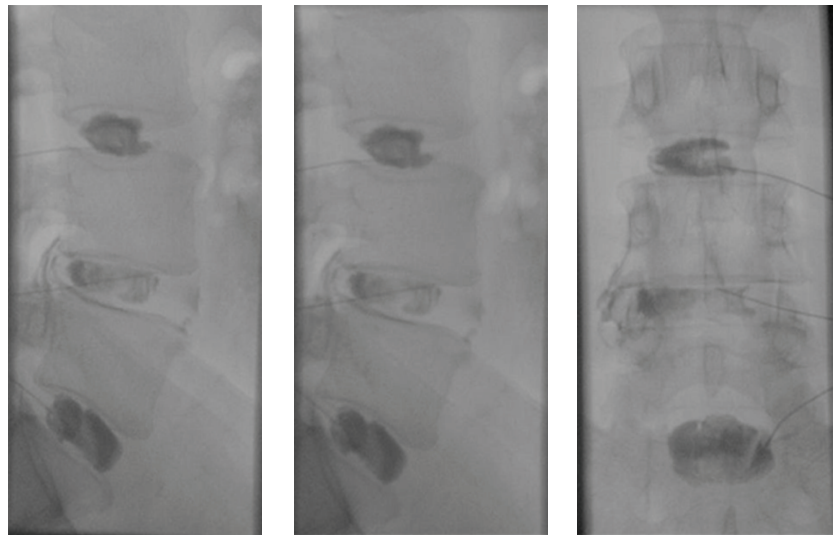


Figure 10: The discography performed on the same patient demonstrated tears at L4-5 and reproduced the patient's pain. The other levels were pain free and morphologically normal.

of the dye to the various layers of the annulus and possible leakage into the epidural space (Figure 10). Additionally multiple discs need to be tested in order to identify lack of pain response in adjacent disc levels tested [9].

The most important portion of the discography is the actual pain response of the patient. It is important to identify discs adjacent to the symptomatic level to be painfree or minimal pressure sensation. The quality of the pain should be reported by the patient using self-reported pain intensity visual analog scale. Observation of the patient by the discographer can also determine the patient's pain response and behaviors. The patient needs to be alert and cooperative for the procedure in order to monitor these responses.

Postdiscography CT scan has been reported by some to increase the ability to diagnose radial tears in the annulus. Based on current treatment options of degenerative disc disease, including lumbar fusion and/or prosthetic disc placement, this additional information may not be of any clinical significance. The specificity and location of the annular tear may become useful information for future treatment options.

In summary, the provocative discography evaluation is the only test currently available to evaluate the actual pain response of a patient, as other imaging studies such as CT scan, X-rays, and MRI can only infer anatomic changes and cannot evaluate pain directly. It is useful to identify levels of degenerative disc disease that recreate the patient's pain. It

is significantly useful to identify levels adjacent that do not recreate their pain.

6. Conclusion

When evaluating a patient with ongoing axial back pain with predominantly back pain as opposed to radicular pain, many studies such as X-rays and an MRI are the initial imaging studies to obtain. If more specific information is needed, lumbar discography is the most direct study available to further evaluate pain with the diagnosis of degenerative disc disease.

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Review Article

Biomechanics of Disc Degeneration

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Disc degeneration and associated disorders are among the most debated topics in the orthopedic literature over the past few decades. These may be attributed to interrelated mechanical, biochemical, and environmental factors. The treatment options vary from conservative approaches to surgery, depending on the severity of degeneration and response to conservative therapies. Spinal fusion is considered to be the "gold standard" in surgical methods till date. However, the association of adjacent level degeneration has led to the evolution of motion preservation technologies like spinal arthroplasty and posterior dynamic stabilization systems. These new technologies are aimed to address pain and preserve motion while maintaining a proper load sharing among various spinal elements. This paper provides an elaborative biomechanical review of the technologies aimed to address the disc degeneration and reiterates the point that biomechanical efficacy followed by long-term clinical success will allow these nonfusion technologies as alternatives to fusion, at least in certain patient population.

1. Introduction

Low back pain (LBP) remains the second most common symptom for a visit to a physician in the United States [1]. The associated costs may exceed $100 billion per year and are allied with lost wages and reduced productivity [2]. The pain may arise from any of the spinal structures (discs, facets, ligaments, vertebrae, and muscles), but one of the leading causes is spinal instability resulting from the degeneration of inter vertebral disc [3, 4]. Degenerative disc disease (DDD) encompasses disc herniation, spinal stenosis, and degenerative spondylolisthesis, among other changes. DDD becomes a source of chronic pain. Over 90% of spine surgeries are performed because of the DDD [5].

Intervertebral disc (IVD) is composed of nucleus pulposus in the central region surrounded by annulus fibrosis and cartilaginous end plates [6]. Nucleus is a hydrostatic fluid like structure, and it has a mixture of water and aggrecan-proteoglycan gel in combination with the collagen type II and elastin fibers network. Annulus, the other component of the disc, forms a structure of 15 to 25 "concentric" lamellae around the nucleus [6]. Each lamella is composed of collagen type I fibers, which is oriented at $\pm 30^{\circ}$ to the horizontal in consecutive layers. The IVD resists compression because of the osmotic properties of the proteoglycans [7]. Ability of the disc to resist anterior and lateral shears along with compression and flexion makes IVD the most important load bearing component of spine, beside the facets [8].

DDD is a part of aging, and it can occur due to many other factors as well. Mechanical factors like heavy lifting leading to abnormal loads, vibrations, immobilization, and trauma may implicate unfavorable distribution and transmission of stresses to adjacent spinal structures resulting in structural failures. Degeneration is attributed to structural failures such as annulus tears, disc prolapse, internal disc disruption, end-plate damage, and narrowed disc space [7, 9, 10]. Due to poor nutrition supply, water content of the nucleus decreases and the content of proteoglycans also changes (biochemical factors). This reduces the hydrostatic pressure and disc height altering the load distribution. The annulus and facet joints are overloaded to meet this demand. The annulus becomes "less" flexible in response to the increased compression, causing annulus fibers to tear. Annulus tears may cause a bulged or herniated disc, which further decreases the disc height. These may pinch the spinal cord or a nerve resulting in radiculopathy. The decreased disc

height may trigger osteophyte formation across adjoining vertebrae and/or facet joint arthritis due to the increased loading on the neural arch by 40% [9]. End-plate damage that occurs decompresses the nucleus; the nucleus may protrude in to the vertebral bodies. The nucleus herniated through the end plate known Schmorl's node may cause inflammation [7]. Structural or mechanical damages also depend on loading history. These damages are irreversible in older population because of a decrease in the healing potential with age.

Although the degeneration of the disc takes place as a part of aging and other factors which are interrelated, the underlying mechanisms for the initiation of disc degeneration and its progression are still being pursued [5, 9].

2. Biomechanics of Disc Degeneration

A few of the pertinent biomechanical studies which emulate the mechanical factors that might affect the intervertebral disc and the concomitant spinal structures are presented in the following paragraphs.

Wilke et al. [11, 12] reported that the nucleus pulposus in the early life or in slightly degenerated discs acts like a gelatinous mass. A compressive load decreases disc height due to a decrease in the volume of gelatinous mass. This also increases the hydrostatic pressure which leads to a bulging of outer annulus. During the day, the compressive load reduces the disc height mainly because of water being squeezed out of the disc, and in part due to the creep of the viscoelastic annulus collagen fibers. Both effects are reversible in healthy discs like unloading of the spine during a night's bed rest [11]. The longer the load acts on spine, the more the annulus bulges and the more the facet joints are loaded. Disc degeneration alters the structure and function [13, 14]. Finite element (FE) studies showed that the risk of prolapse is highest in the posterior and posterolateral annulus, especially in normal and mildly degenerated discs, while moderate or strongly degenerated discs have a lower risk for a prolapse [15].

Prolonged sitting results in sustained axial compressive loading which may alter the viscoelastic properties of the disc and vertebra [16, 17]. Goel et al. found that an increase in load occurs across the disc at the resonant frequency of the spine 5 to 8 Hz range [18]. The resonant frequency can occur during driving and postures that are common in occupational workplace [19, 20]. This study found that at resonating frequency, the corresponding increase in nucleus pressure was about 150% of the static case, which implies that the spine would be exposed to excessive loads.

Kong et al. conducted an FE study in which muscle dysfunction due to quasistatic backlifting conditions was simulated and found that muscle dysfunction destabilized the spine, reduced the role of facet joints in transmitting load, and shifted loads to the discs and ligaments [21].

Wang et al. [22] conducted a study on ten symptomatic patients with DDD and reported that the discs at the adjacent levels experienced higher tensile and shear deformations during end ranges of lumbar motion, compared to the healthy subjects. The authors also evaluated the effect of lumbar DDD on *in vivo* motion of the facet joints under functional weight bearing activities and concluded that the DDD alters the facet joint motion at the degenerated and adjacent levels. They also observed the hypermobility in coupled rotations implying a biomechanical mechanism leading to further adjacent level degeneration [23].

Disc degeneration at one or multiple levels may affect the other spinal component of that level or other levels [3, 24]. Panjabi et al. [24] found that any damage to disc alters the biomechanics of facet joints by disproportionately sharing the facet loads.

The relationship between the intervertebral disc degeneration and nonlinear multidirectional spinal flexibility was investigated by Mimura et al. [25]. They studied 47 lumbar discs under sagittal, frontal, and transverse plane loadings (pure moments) and found that the range of motion (ROM) decreased in flexion-extension and lateral bending. The neutral zone-to-range of motion (NZ/ROM) ratio increased for all the three rotations, indicating greater joint laxity with degeneration.

Another study measured the stress distribution *in vitro* in normal, healthy discs and degenerated discs under compression [26]. They found that the stress distribution was uniform, isotropic for normal disc; nonuniform and anisotropic for the degenerated disc.

Shirazi-Adl et al. [27] performed a FE study in which they simulated a characteristic of the degenerated disc, that is, 50% loss of disc pressure than that of normal disc and subjected the motion segment to sagittal plane pure moments up to a maximum of 60 Nm. They found that a 50% reduction in intradiscal pressure had a decrease in the segmental stiffness. Additionally, they reported that the flexion rotation had lower intradiscal pressure in a disc with pressure less than in a normal disc, indicating that the portion of load transmitted through the nucleus decreases with degeneration.

Some authors have devised ways of grading the level of disc degeneration (Figure 1; Table 1) in the lumbar spine based on the MRI images [28].

The level of disc degeneration varies among patients and so does the type of treatment. The treatment may range from conservative treatment such as bed rest and prescription of pain relievers for mild disc degeneration to surgical intervention in severe chronic degeneration cases.

It is essential to treat DDD to relieve pain and possibly prevent further degeneration at index level and adjacent levels. Conservative treatment includes chiropractic adjustments, physical therapy, yoga, acupuncture, and medication. If conservative treatment fails, surgery would be the next option. Spine surgery involves different surgical techniques, using appropriate instrumentation to relieve pain. There are many surgical treatments such as fusion with or without rigid instrumentation and nonfusion techniques like dynamic stabilization, total disc arthroplasty, and implanting interspinous devices [3].

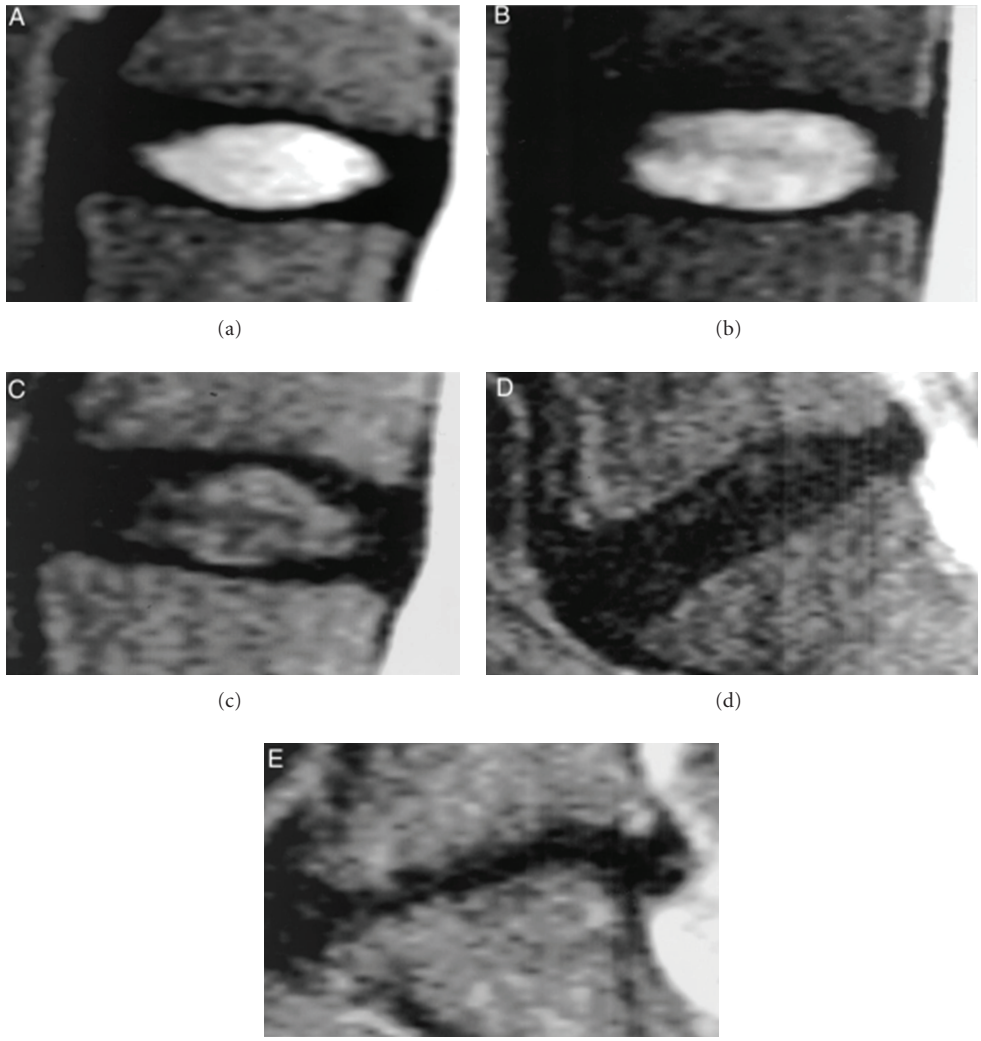


Figure 1: (a–e) pictures depict the grading system for the assessment of lumbar disc degeneration. Grade I: the structure of the disc is homogeneous, with bright hyperintense white signal intensity and a normal disc height. Grade II: the structure of the disc is inhomogeneous, with a hyper intense white signal. The distinction between nucleus and annulus is clear, and the disc height is normal, with or without horizontal gray bands. Grade III: the structure of the disc is inhomogeneous, with intermediate gray signal intensity. The distinction between nucleus and annulus is unclear, and the disc height is normal or slightly decreased. Grade IV: the structure of the disc is inhomogeneous, with hypointense dark gray signal intensity. The distinction between nucleus and annulus is lost, and the disc height is normal or moderately decreased. Grade V: the structure of the disc is inhomogeneous, with hypo intense black signal intensity. The distinction between nucleus and annulus is lost, and the disc space is collapsed. Grading is performed on T2-weighted midsagittal (repetition time 5000 msec/echo time 130 msec) fast spin-echo images [28].

3. Biomechanics of Spinal Implants

Biomechanics of the spine is altered by the implantation of spinal devices used to stabilize the segment [29]. Along with many devices currently available in the market to treat spinal disorders, many new designs are also being developed in the hope to improve clinical outcomes. It is essential to evaluate their biomechanical efficacy among other issues, prior to clinical use [30]. The spinal implants can be evaluated by comparing the stability of the construct to the intact spine stability and/or stability provided by a predicate device. The biomechanical effects of decompression and stabilization provided by implants can be assessed using *in vitro* studies [31, 32]. *In vitro* studies involving ligamentous spine specimens from human cadaver or other species like sheep, calf, and rabbit are carried out using standard test protocols [30]. Finite element analysis (FEA) in spine biomechanics is very helpful to perform the structural analysis of bone and bone implant composites of complicated geometry. Since it is difficult to get all the parameters from experimental studies, finite element models can be used to address the remaining issues [33, 34]. Thus, *in vitro* and FE-based biomechanical studies provide valuable information on implants safety and effectiveness prior to their clinical use [30].

Table 1: Table lists the classification of levels of disc degeneration. Adapted from Pfirrmann et al. [28].

Grade	Structure	Distinction of nucleus and annulus	Signal intensity	Height of intervertebral disc
I	Homogeneous; bright white	Clear	Hyperintense; isointense to cerebrospinal fluid	Normal
II	Inhomogeneous with or without horizontal bands	Clear	Hyperintense; isointense to cerebrospinal fluid	Normal
III	Inhomogeneous; gray	Unclear	Intermediate	Normal to slightly decreased
IV	Inhomogeneous; gray to black	Lost	Intermediate to hypointense	Normal to moderately decreased
V	Inhomogeneous; black	Lost	Hypointense	Collapsed disc space

3.1. Fusion Systems. Fusion restricts the motion of involved segment. It may reduce progressive degeneration and relieve the patient from back pain. The main clinical indications for fusion are failed conservative treatment, prolonged back pain more than a year, and advanced degenerated disc [3]. Fusion surgeries are performed with or without supplement instrumentation. Segment fusion is achieved through the use of autograft, allograft, bone graft substitute, demineralized bone matrix (DBM), ceramic-based bone graft, recombinant human bone morphogenetic proteins (rhBMP-2), β-tricalcium phosphate (TCP), calcium sulphate (CaS), and hydroxyapatite (HA) [3, 35]. Fusion has been the gold standard in treating DDD and practiced since the beginning of the 20th century. Fusion without instrumentation has often led to nonunion of bone known as pseudoarthrosis. To overcome this complication, many spinal implants have been developed which are now used in fusion surgeries. The usage of spinal instrumentation provides segmental stability and facilitates high fusion rates.

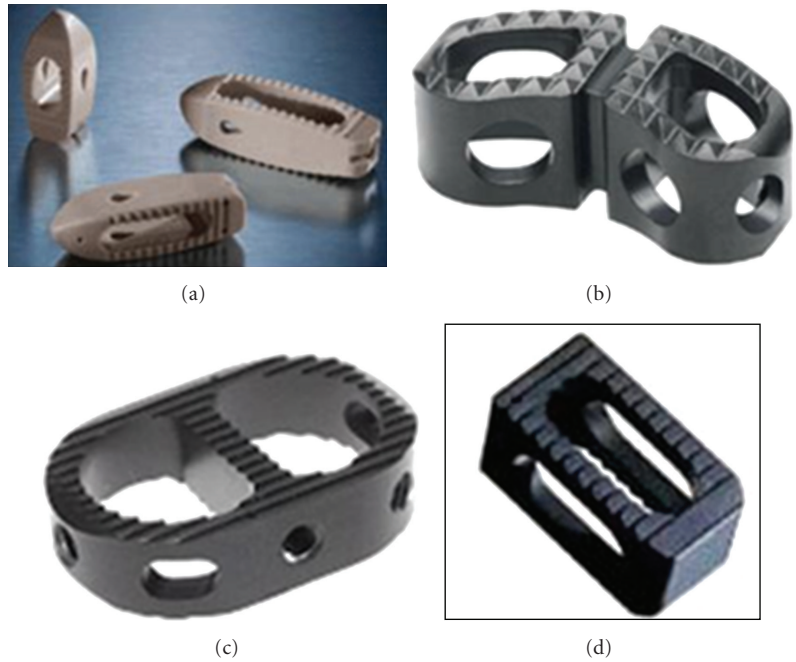
Lumbar interbody fusion (LIF) was introduced by Cloward, and currently, it is being used widely [3, 36]. In LIF, cages filled with bone graft are placed in the disc space, supported by instrumentation to stabilize the spine and thereby enhance the fusion process. The bone grafts placed in between the vertebrae experience 80% of compressive loads, which enhances the fusion process. The grafts in LIF occupy 90% of bony area in between the vertebrae, which has rich vascular supply leading to enhanced fusion [36]. The cages were initially designed as rigid systems (Figure 2) in cylindrical, rectangular, and other shapes. However, to overcome the problems associated with these rigid cages [37], expandable cages (Figure 3) have been developed in recent times.

There are several implants used as spinal instrumentation in fusion procedures like pedicle screw system and rods, plates (Figure 4), clamps, and wires. Pedicle screw system is considered to be an effective supportive instrumentation in achieving highest fusion rates [38]. Interspinous fixation systems (Figure 5) are also currently being developed and are gaining some popularity as their performance is similar to standard pedicle screw system [39, 40]. Interspinous devices are implanted by minimally invasive procedures in the posterior region, and they are also used in conjunction with interbody fusion procedures.

There are both anterior and posterior approaches for fusion surgery. The posterior approaches include posterolateral fusion (PLF), posterior lumbar interbody fusion (PLIF), and transforaminal lumbar interbody fusion (TLIF). Anterior approach includes anterior lumbar interbody fusion (ALIF) and extreme lateral inter body fusion (XLIF). XLIF, which is gaining popularity recently, involves lateral accessing of anterior column using sophisticated imaging technology to avoid neural disruption [41]. This procedure has the advantage of overcoming the complications associated with PLF, PLIF, TLIF, and ALIF. Combination of both anterior and posterior approach is called anteroposterior fusion, also known as 360° fusion. Depending on the level of surgery, sex of the patient, anatomic variations, and history of spine surgery, one or combination, of the aforementioned procedures is selected to treat LBP, and it is surgeon-specific [42].

A biomechanical study was performed by Kiapour et al. [43] using finite element (FE) technique to evaluate the effect of VariLift expandable and BAK cages on biomechanics of the lumbar spine motion segment. The cages were simulated at the L4-L5 level using PLIF surgical approach. The VariLift cage depicted comparable biomechanical effects on the lumbar segment with those of BAK cage. The expansion mechanism led to a relatively larger contact area between the cage and the endplate improving the chances of solid fusion to occur after surgery. The expansion of the cage also follows the lordotic angle of the treated segment ensuring a better contact between the cage and endplates.

The footprint size of the interbody fusion device is an important factor that determines the biomechanical stability afforded by these implants. Moreover, occurrence of subsidence is also influenced by the cage's footprint. A finite element (FE) analysis was conducted by the same group [44] to compare the loading and stresses at vertebral endplates following implantation with AVID TLIF cage of a larger foot print compared to regular TLIF cage in different configurations (Figure 6). A follower load of 400 N was applied to the spine to simulate compression (at standing posture), and then, a 10 Nm bending moment was applied to the segment to simulate physiological flexion and extension loadings. They found that the double TLIF and AVID cases observed slightly higher normal loads at the endplates compared to other cases in all loading modes due to their



(a) (b) (c) (d)

Figure 2: Rigid interbody cages. (a) Ardis (Zimmer spine, Minneapolis, MN, USA), (b) Leopard (DePuy, Raynham, MA, USA), (c) Cougar (DePuy, Raynham, MA, USA), and (d) Jaguar (DePuy, Raynham, MA, USA) (website).

(a) (b) (c)

Figure 3: Expandable interbody cages. (a) Varian (Medyssey spine, Skokie, IL, USA), (b) VariLift-L (Wenzel spine, Austin, TX, USA), and (c) StaXx XDL (Spine wave, Shelton, CT, USA) (website).

higher contact area at the interface. The larger footprint interbody device (AVID) resulted in lower stresses in the endplate immediately after surgery. AVID implant may be able to lower the incidence of subsidence, as compared to regular TLIF devices.

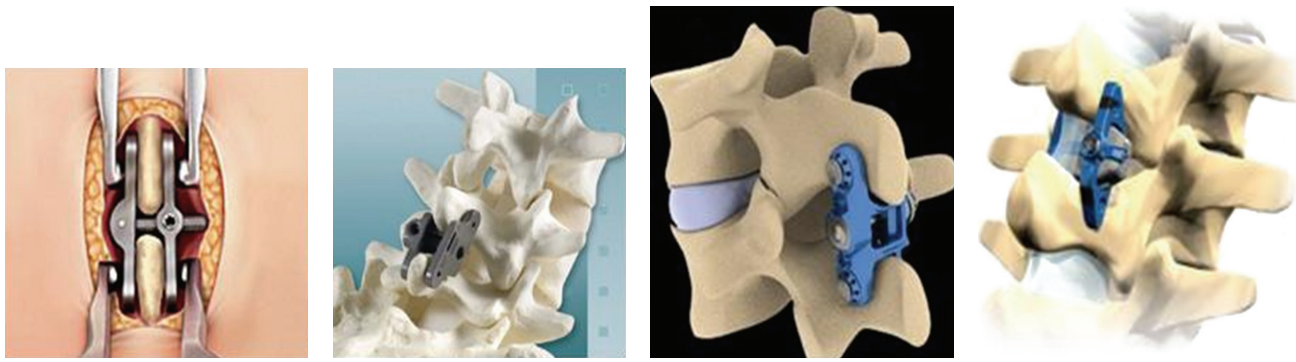
Oxland et al. [45] and Rathonyi et al. [46] conducted cadaver biomechanical studies in which they evaluated anterior lumbar interbody fusion (ALIF) cages and observed a decrease in stability in extension. In flexion, lateral bending, and axial rotation, the stabilization was significant compared with the intact spine (the median value for motion was 40, 48, and 29 percent of the value for the intact condition, resp.; $P = 0.002$ for all three directions). In this study, stabilization was defined as a decrease in motion after insertion of an implant.

Tsantrizos et al. performed a cadaver study with Ray TFC and contact cages using posterior approach (PLIF) and reported that the stability in axial rotation decreased significantly, more with Ray TFC than with the other cages [47].

Another study performed by the Kiapour et al. [48] simulated the cadaveric experiment of Kanayama et al. [49] using FE technique. The load-displacement behavior and stresses in compression (500 N), flexion (5 Nm), left bending (3 Nm), and left rotation (50 N + 3 Nm) were computed for 4-WEB cage followed by comparison with two titanium (BAK and TITAN) cages and one PEEK interbody cage. The maximum pressure on the bone graft was 123.5, 304.5, 58.6, and 145.8 KPa in the WEB cage with smaller foot print (comparable to other cages) compared to 113.7, 144.1, 64.1

(a) (b) (c)

Figure 4: Anterior plate system. (a) Aegis (DePuy, Raynham, MA, USA), (b) Aspida (Alphatec spine, Carlsbad, CA, USA), and (c) Trinica (Zimmer spine, Minneapolis, MN, USA) (website).



(a) (b) (c) (d)

Figure 5: Interspinous fusion devices. (a) CD Horizon spire (Medtronic, Memphis, TN, USA), (b) Aspen (Lanx, Inc., Broomfield, CO, USA), (c) Prima LOK (OsteoMed, Addison, TX, USA), and (d) Axle (X-Spine, Miamisburg, OH, USA) are currently being studied (website).

and 121 KPa in PEEK, 146.4, 132.6, 57.5, and 160 KPa in TITAN, and 30.7, 82.7, 17.7, and 36 KPa in the BAK device. The 4-WEB implanted segment had lesser peak stress at the interface with bony endplates.

The XLIF surgical procedure was simulated in a FE study by Kiapour et al. [50] on lumbar-pelvis segment to compare the biomechanics of interspinous fixation device with traditional screw-rod fixation system. Segmental motion and loads on sacroiliac joint (SIJ) and vertebral endplates were computed for all cases after applying a 400 N of compressive load and 10 Nm moment. They reported that the placement of fixation constructs leads to a significant decrease in range of motion of all index levels (L2–L5) in all loadings. At each of implanted levels the motion decreased by about 95% (Flex), 93% (Ext), 80% (LB), and 90% (LR) in interspinous device implanted model compared to intact case. The reductions in motion were 97%, 95%, 96%, and 94% for screw fixation and 51%, 48%, 68%, and 86% for cage alone cases, for same loadings, respectively. Also, the maximum load at SIJ decreased by 4% in Flex and increased by 8% in Ext, 8% in LB, and 7% in LR for all implanted cases compared to intact case. In the posterior plate model, the shear load at endplates of the most superior implanted segment increased and decreased in extension and left bending loadings, respectively compared to other fixation constructs.

Both cadaver and FE studies evaluated standalone cages and reported less stabilization of the spine in the literature. Anterior or posterior instrumentation systems along with cages are essential to have proper stability at the implanted

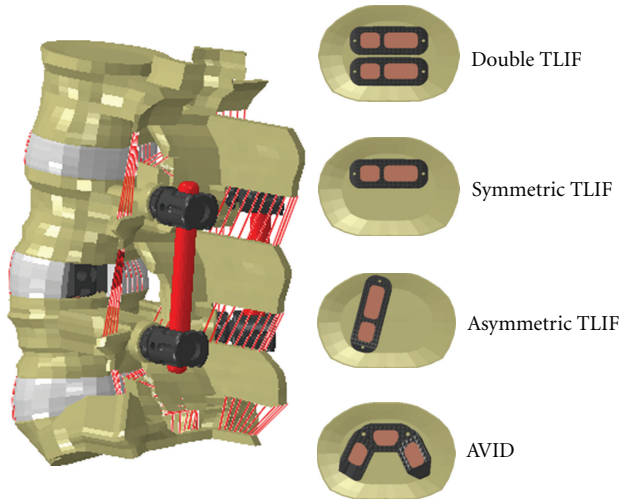


Figure 6: Four configurations of the interbody devices implanted at L4-L5 level in the FE model. (a) double cage TLIF; (b) regular TLIF Symmetrically placed; (c) regular TLIF asymmetrically placed; (d) large footprint TLIF (AVID) [44].

level. However, expandable cages may provide enough stability without additional instrumentation [43].

The main complication associated with fusion is adjacent segment degeneration. The reason for this has not yet been clear and has become the point of debate. Some people argue that degeneration at adjacent level is part of aging spine, and others argue that it is due to reduced motion resulted from fusion. The reasons for adjacent level degeneration can be hyper mobility, increased disc pressure, increased facet joint pressure, and alteration in histological properties of ligaments at adjacent level to the index level [51]. Many *in vitro* and FEA studies showed the adjacent level hyper mobility after fusion [34, 52–56], but there are very few *in vivo* studies [51], which showed that the adjacent hyper mobility was not significant.

The success of the fusion surgery is defined as achieving arthrodesis across index level to provide stability and relieve pain. The modern techniques are successful in achieving fusion in 95% of the cases; however, the pain in the low back is relieved in less than 70% of the cases [52]. In spite of its wide application, fusion has varied clinical outcomes [3, 52, 53]. The causes of adjacent segment degeneration were not clear, though they are attributed to reduced motion at index level and increased motion at the adjacent level. In order to overcome morbidity associated with fusion, motion preservation devices were developed [52, 57].

The literature review of fusion systems enumerates major drawbacks like restricted (or) lack of motion, pseudoarthrosis, adjacent level degeneration, and donor site pain. The above shortcomings of fusion have led the researchers to develop an alternative approach for the treatment of disc degenerative disease.

Many non-fusion techniques have been investigated and have emerged in recent times to replace the conventional fusion techniques in treating degenerative discogenic pain. These techniques include spinal arthroplasty (artificial disc and nucleus) and dynamic stabilization systems. These systems aim to provide a more physiologic solution.

3.2. Total Disc Replacement. Disc arthroplasty or total disc replacement is one such option that is being seen as a potential alternative to fusion. As the name suggests, the goal of disc arthroplasty is to completely replace the degenerated intervertebral disc by an artificial implant which has capability not only to treat the pain causing symptoms but also promises to restore the lumbar motion and create a proper load balance with surrounding tissue without compromising patient safety.

The first human implantation of lumbar artificial disc was performed by Fernstrom in 1966 [58]. He used a metal ball (SKF ball bearing) to reproduce the mechanism of the disc. However, the obtained results were poor, and the implant was withdrawn. The SB Charité prosthesis, the first FDA-approved artificial disc for clinical use in USA, was designed in the former East Germany in the early 1980s by Schellnac and Buttner and was first implanted by Zippel in 1986 [59]. This event triggered the development of several variety of artificial discs aiming on parameters like restoring natural motion, biocompatibility, corrosion and wear resistance, stability, strength to sustain maximum expected loads, maintain intervertebral height, preserve lordosis, and to restore the energy absorptive qualities of the native disc. Table 2 lists and Figure 7 depicts some of the major lumbar artificial disc designs. The present lumbar disc designs can be classified into four groups:

(i) composite discs: comprise of several articulating parts; often with different materials (Charité, and-ProDisc);

(ii) hydraulic discs: these are designed for nucleus replacement and include an expandable fluid enclosed by a woven/porous bag (PDN);

(iii) mechanical discs: which are made of articulating parts made of single type of material (Maverick, Flexicore, and Kineflex);

(iv) elastic discs: include a deformable cores, usually made of elastomers or polymers attached to metallic endplates (Acroflex).

These artificial discs are also classified based on constraint parameter as constrained, semiconstrained, and unconstrained, respectively. The unconstrained design strategy allows for six-degrees-of-freedom segmental motion, with translations and rotations about three independent axes. Constrained devices typically permit rotation in all planes and include a fixed center of rotation, which limits segmental translation under flexion-extension and lateral bending conditions [61].

Biomechanical data from *in vitro* and mathematical modeling are presented. Different biomechanical parameters such as segmental motion, instantaneous axis of rotation, intradiscal pressure, facet loads, load/stress distribution at bone-implant interface, and wear at articulating sites, have

Table 2: Table lists different lumbar artificial discs and respective types of materials and features [60–63] .

Lumbar discs	Articulating surfaces and materials	Constraint	Center of rotation	Manufacturer
SB Charité	Metal-polymer-metal	Unconstrained	Mobile	DePuy Spine, Raynham, MA, USA
Prodisc-L	Metal-polymer-metal	Semiconstrained	Mobile	Synthes, West Chester, PA,USA
Maverick	Metal-metal	Semiconstrained	Fixed	Medtronic, Minneapolis, MN, USA
Flexicore	Metal-metal	Fully constrained	Fixed	Stryker, Kalamazoo, MA, USA
Mobidisc	Metal-metal	Unconstrained	Mobile	LDR medical, Troyes, France
Activ-L	Metal-polymer-metal	Semiconstrained	Mobile	Aesculap AG Tuttlingen, Germany
Kineflex	Metal-metal	Semiconstrained	Mobile	Spinal Motion, South Africa
Acroflex	Rubber core with titanium endplates (elastomeric disc)	Unconstrained	Mobile	DePuy Spine, Raynham, MA, USA

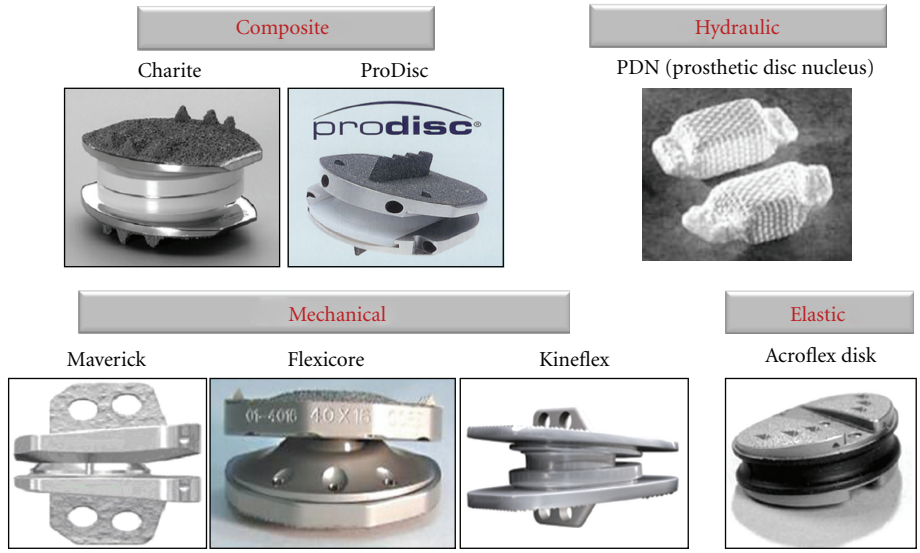


Figure 7: Different lumbar artificial disc concepts: Composite (Charité, Prodisc), Hydraulic (PDN), Mechanical (Maverick, Flexicore, Kineflex), and Elastic (Acroflex) [60].

been analyzed after disc replacements to understand device's ability to mimic the intact disc behavior and predict its durability in the long run.

3.2.1. In-Vitro Studies. The *in vitro* studies enable us to understand the effects of total disc arthroplasty (TDA) on the kinematics of the implanted and adjacent levels of the spine.

Hitchon et al. studied the biomechanics of Maverick anterior disc using an *in vitro* setup with 7 human lumbar specimens, in which pure moments of 6 Nm were applied in all planes of rotation after implanting the artificial disc at L4-L5 level [64]. They observed that the artificial disc decreased flexibility compared to discectomy, and the motion was comparable with the intact state.

Rousseau et al. did an *in vitro* study on twelve human lumbar spine segments after disc replacement with Prodisc II (6) and Charité III (6) versus intact. They measured the facet forces and instantaneous axes of rotation (IAR) for different spinal positions under simulated weight-bearing conditions. They concluded that the degree of constraint affects postimplantation kinematics and load transfer. With the Prodisc (3 DOF), the facets were partially unloaded, though IAR did not match the fixed geometrical center of the UHMWPE. The latter observation suggests joint surface incongruence is developed during movement. With the Charité disc (5 DOF), the IAR was less variable, yet the facet forces tended to increase, particularly during lateral bending. These results highlight the important role the facets play in guiding movement, and that implant constraint influences facet and implant synergy [65].

Ha et al. [62] conducted a study on five L2-S2 spines in which range of motion, facet strains and intradiscal pressures were monitored. A 400 N compressive load and 8 Nm moments in all three planes were applied to compare the intact, postimplantation of Semiconstrained Activ-L device at L4-L5 level. They reported that even though the device could not restore the normal motion of the intact spine, results of other parameters implicated

a reduction in the incidence of adjacent segment disease. Those parameters were insignificant decrease of intradiscal pressure at the inferior adjacent disc, and the statistically significant decrease of facet strains at the operative level during flexion and strains at the inferior facets in axial rotation.

Goel et al. studied the biomechanics of spine implanted with Charité disc using a hybrid loading protocol [66]. They employed both *in vitro* experiment and finite element modeling. Results indicated that the Charité artificial disc placement slightly increased motion at the implanted level, with a resultant increase in facet loading when compared to the adjacent segments. The motions and loads were less at the adjacent levels.

Most of the lumbar artificial discs are of articulating type. These have potential for wear, much like the hip and knee arthroplasties. Cyclic loading and relative motion at the bearing surface may increase the risk to surrounding spinal structures like spinal cord and blood vessels. Therefore, biotribological tests serve as an effective preclinical tool to investigate device wear characteristics. A wear rate of 1.1 mg/million cycles [67] has been reported for the Charité artificial disc. Paré et al. [68] reported a steady state wear rate of $0.33 \pm 0.12\,\text{mm}^3$/million cycles in flexion-extension and $0.43 \pm 0.06\,\text{mm}^3$/million cycles in combined motion tests for the metal-on-metal Maverick disc (constrained).

3.2.2. FE Analyses. A finite element study was conducted by Rohlmann et al. to understand the effects of ProDisc on lumbar spine kinematics. They loaded their model with the upper body weight and muscle forces to simulate standing, 30-degree flexion, 15-degree extension, and 6-degree axial rotation. The disc position was varied by up to 2 mm in both the anterior and posterior direction. Three different disc heights were investigated as well as the influence of removing different portions of the natural disc and resuturing the ALL ligaments. They observed that implant position strongly influenced intersegmental rotation for the loading cases of standing and flexion. Also, they found that a disc height 2 mm in excess of the normal disc space increased intersegmental rotation at implanted level during standing and extension. The intersegmental rotations were closer to the intact spine, when lateral portions of the annulus were not removed. Finally they concluded that when implanting an artificial disc, great care should be taken in choosing the optimal height and correct position for the implant. Lateral portions of the annulus should be preserved whenever possible. A perfect reconstruction of the ALL would help restore the biomechanics to normal [69].

Moumene and Geisler [70] performed a study to evaluate the loading on the facet joints and stress on the polyethylene core after implantation of Charité (unconstrained) and Prodisc (Semiconstrained) TDA. The unconstrained TDA unloads the facet joints and presents decreased core stress as compared to the fixed-core Semiconstrained TDA.

In a computational study performed by Dooris et al. [71], the effects of facet load sharing following TDA were

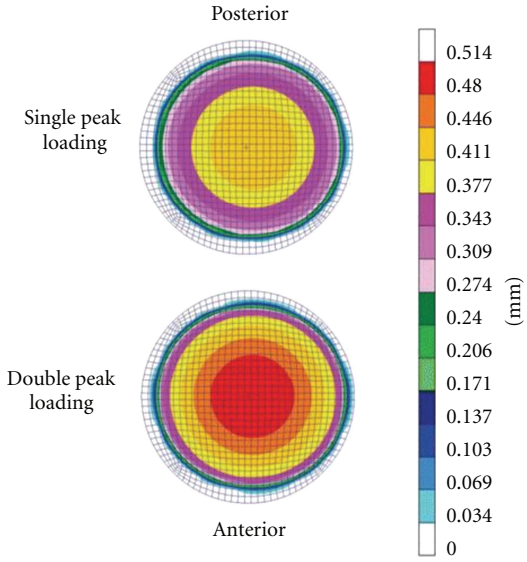


Figure 8: Linear wear contour predicted for ProDisc-L using finite element technique. Adapted from [62].

examined. Different annular window sizes and varied anteroposterior artificial disc placement was simulated for a ball-on-socket disc design by Medtronic. Findings demonstrated that an artificial disc can alter spinal bending stiffness in the sagittal plane. Changes in spinal stiffness were noted to be dependent on the position of the disc and degree of annular resection. Anterior placement of the device led to increased facet joint loads in compression and extension. These findings suggest that if the anterior longitudinal ligament is preserved and the implant is placed posteriorly within the disc, the spinal stiffness will be restored, and facet loads will be maintained at preimplantation levels.

A study performed by Denozière and Ku [72] to compare TDA and fusion at one level of lumbar spine indicated that the level implanted with the artificial disc showed excessive ligament tensions (greater than 500 N), high facet pressures (greater than 3 MPa), and a higher risk of instability. The mobility and the stresses in the level adjacent to the arthroplasty also increased. They concluded that there was a greater risk of instability and further degeneration for artificial disc implanted model than that predicted for the fused model.

FE models have also been utilized to understand wear characteristics of joint replacements in the hip and knee. FE-based wear study was conducted by Rawlinson et al. [73], which depicted a uniformly distributed wear pattern as per ISO 18192 which was not observed during the retrieval analysis (Figure 8). This study was validated against experimental wear simulation of ProDisc-L implant.

FE technique was also applied in cervical spine by Bhattacharya et al. [74] to evaluate wear in a simulated C5-C6 FSU. A predictive FE wear model of the artificial disc alone (TDR only) was developed, and it was implanted into C5-C6 FE model (TDR + FSU). Both of these models were subjected to a motion profile (rotation about three axes)

with varying preloads of 50 to150 N at 1 Hz, consistent with ISO 18192. A subroutine based on Archard law simulated abrasive wear on the polymeric core up to 10 million cycles. The TDR + FSU model was further modified to simulate facetectomy, sequential addition of ligaments, and compressive load. They reported more predicted localized wear in certain regions for TDR + FSU, in contrast to the uniformly distributed wear pattern of the TDR-only model. In addition, the cumulative volumetric wear for the TDR-only model was 10 times that of the TDR + FSU model. The TDR + FSU model also revealed a separation at the articulating interface during extension and lateral bending. After facetectomy, the wear pattern remained lopsided, but linear wear increased eight-fold, whereas volumetric wear almost tripled. This was accompanied by a reduction in observed liftoff.

Similar kind of studies in the lumbar spine may enable the scientists to pursue and understand the effects of clinical and other parameters (like surgical variables, different loading profiles, different disc designs, and bone quality) on wear of lumbar artificial discs.

3.2.3. In Vivo Studies. In the *in vivo* study of Siepe et al. [75], 175 patients with disc replacement with mean followup of 29.3 months were investigated. Facet joint pain, predominantly at the index level, was identified in 22 patients (12.6%). The sacroiliac joint was also a frequent cause of post-operative pain ($n = 21$; 12.0%). Pain from both structures influenced all outcome parameters negatively ($P < 0.05$). Patients with an early onset of pain ≤ 6 months) were 2–5 fold higher at risk of developing persisting complaints and unsatisfactory outcome at later stages in comparison to the entire study cohort ($P < 0.05$). They also observed that the level of TDR significantly influenced postoperative outcome. Best results were achieved for the TDRs at L4/5 (incidence of posterior joint pain: 14.8%). Inferior outcome and a significantly higher incidence of posterior joint pain were observed for TDR at L5/S1 (21.6%) and bisegmental TDR at L4/5/S1 (33.3%), respectively. Their study was unable to address that TDR will reduce the incidence of posterior joint pain, unlike the lumbar fusion procedures.

Zigler [76] did a clinical study on 78 patients with minimum 6-month followup replacement of ProDisc. Among the patients, 54 also had a 1-year followup, enrolled in a prospective randomized FDA study evaluating the safety and efficacy of ProDisc II versus control, a 360-degree lumbar spinal fusion. At 6-month follow-up, there were 55 ProDisc patients out of which 23 underwent fusion. Both fusion and disc replacement group had similar clinical outcomes. Also a trend was identified at 6 months in patient satisfaction rates favoring ProDisc versus fusion ($P = 0.08$), which were not significant at 1-year follow-up period. Similar clinical studies and randomized trials have been conducted in the past to evaluate the performance of an artificial disc in terms of safety and efficacy [77–83].

Based on the above studies, increased facet joint loading, increased lordosis at the implanted level, hyper mobility, and wear at articulating surfaces are the major issues with TDA and need further investigations. Even though the short-term results are promising [76], the long-term complications and benefits of TDA are yet to be realized, especially in terms of preventing adjacent level disc degeneration [84, 85]. Hence, it cannot be concluded that total disc replacement is superior to spinal fusion in terms of clinical outcome, at least at present.

3.3. Dynamic Stabilization Systems. Spinal fusion surgeries aim at limiting the motion of the segment and restoring the stability. Anterior lumbar disc replacements are used to restore spinal alignment and kinematics of a degenerated segment. Compared to fusion of the segment, disc replacements may prevent adjacent segment degeneration. To resolve some of the deficiencies of anterior lumbar arthroplasty, such as the approach itself, difficulty of revision, and postoperative facet pain, 360° motion preservation systems based on posterior disc and posterior dynamic stabilization system (PDS) designs are being pursued [86].

Dynamic stabilization systems aim at altering favorably the movement and load transmission through the spinal motion segment [87]. The hypothesis behind dynamic stabilization system is that control of abnormal motion and more physiologic load transmission would relieve pain and prevent adjacent segment degeneration.

The biomechanical action of a dynamic stabilization system is two-fold: (i) permit or restore "normal" motion and (ii) share load with the disc and the facets. The load sharing should be more or less uniform during the entire range of motion. This implies that the kinematics of the segment stabilized with a dynamic system should be similar to the intact spine. This is achieved when the location of the instantaneous axis of rotation of the construct lies close to the intact segment [87]. There are two types of dynamic stabilizations systems currently available: dynamic pedicle screw-based systems and interspinous spacers.

3.3.1. Dynamic Pedicle Screw-Based Systems. Some flexible stabilization systems consist of pedicle screws threaded into adjacent segments and a member spanning between the heads of the pedicle screws to limit the movements of the spinal segment.

In 1994 Henri Graf, (Lyon, France) introduced the Graf ligament, designed to provide less stressful load sharing. It consists of a nonelastic band as a ligament to connect the pedicle screws across the segment to be stabilized to lock the segment in full lordosis. The concept was that abnormal rotatory movement causes instability and locking the facets would control the rotation movement. The system would allow for limited flexion and no rotatory motion. The ligaments get lax in extension; hence there is no restriction in the motion [88].

The fulcrum assisted soft stabilization system (FASS system) was developed to address the disadvantages of the Graf ligament. In this system, a fulcrum is placed between the pedicle screws in front of the ligament. The fulcrum distracts the posterior annulus. When the elastic ligament is placed posterior to the fulcrum to compress the pedicle screw

heads, the fulcrum transforms this posterior compression force into an anterior distraction force, which distracts the anterior annulus. The lordosis is not dependent on the patient's ability but is created by the tension in the ligament. Experimental studies have shown that the implant unloads the disc, but the flexibility of the segment is lost as greater unloading of the disc occurs by the adjustment of the tension in the ligament and the fulcrum [88].

The Dynesys system (dynamic neutralization system) was developed by Gilles and Müller. Dynesys system comprises of three components: (i) pedicle screws, (ii) polyethyleneterephthalate (PET) ligaments, and (iii) polycarbonate urethane (PCU) spacers. The spacers are bilaterally placed between the pedicle screw heads to withstand compressive loads. The ligaments are run through the hollow core of the spacers. A tensile preload of about 300 N is used to stabilize the construct [88]. The plastic cylinder between the screw heads limits the degree of lordosis that can be created. As the ligament is not elastic, flexion compresses the disc, and the axis of flexion is the posterior ligament, which is well posterior to the normal axis of flexion [88]. Active extension will open up the anterior annulus without compression of the posterior annulus. Theoretically, lordosis can be achieved by the action of the spinal extensor muscles; in extension the cylinder will take increasing load [79]. Thus, the principle of the system is its ability to create load sharing and restoration of disc height, not necessarily motion preservation because the system is rigid [87].

The Cosmic system is a pedicle screw-based dynamic instrumentation system (Ulrich, Ulm, Germany) equipped with a hinge between the screw head and threaded portion. Cosmic is a load sharing system which reduces mechanical stress on the implants. Thus, protection against implant failure and loosening is achieved. The hinged screw allows only for axial load, due to this, it is important to have a largely intact anterior column for implantation of this system. While Dynesys stabilizes by neutralizing motion, Cosmic corrects the sagittal plane and maintains motion in flexion/extension.

The Isobar TTL is another novice device in this category, comprised of a titanium alloy rod and a dampener element. The dampener element is formed of a series of helical springs that allow linear and angular motion and serve as a shock absorber. This instrumentation allows flexion-extension and axial rotation, while lateral bending is restricted. A lordotic angle is also incorporated into this system. Benefits associated with this device include ease of implantation, motion segment stabilization, maintenance of lordotic angle, load sharing, and conformance to the IAR of the motion segment [89]. Other notable devices in this category include the Axient, BioFlex, TalinRod, CD Horizon Agile, and Stabilimax systems. Figure 9 depicts some of these implants.

In Vitro Studies. The Dynesys stabilization system has been widely studied. Freudiger et al. tested the Dynesys system on four cadaveric spine specimens on a lumbar spine simulator, which allowed the simultaneous application of bending moments, and compressive and shear loads. They concluded that the Dynesys reduces flexion and extension angles significantly [90].

Aylott et al. investigated the stresses of the intervertebral discs at the instrumented and the adjacent segments under compressive loading (1 kN) in flexion (6°) and extension (4°), in an *in vitro* study. The effects of spacer height on the intradiscal pressure distribution were also evaluated. They observed that Dynesys eliminated the peak stresses in the anterior annulus in flexion and in extension. The peak annulus stresses increased with decrease in the spacer height. However, there was no change in the stresses in the adjacent segment discs [91].

Niosi et al. (2004) conducted an *in vitro* biomechanical study to investigate the effect of spacer length of Dynesys on the range of motion. The test conditions included intact, injury at L3-L4, and Dynesys at L3-L4 (standard spacer, long spacer, and short spacer). They quantified range of motion and facet contact loads for a pure moment of ±7.5 Nm with and without a preload of 600 N. The trends in motion were similar with and without preload. Long spacer reduced the motion more than other two cases, the contact loads of the long and short spacer were 150% and 64% of the standard spacer, respectively [93].

Wilson et al. investigated 10 cadaveric lumbar spine specimens, subjected to pure moments of ±7.5 Nm (axial rotation, flexion, and extension) to compare range of motion and facet loads of intact specimens with those of injured specimens stabilized with Dynesys. The facet loads were measured using thin film electroresistive pressure sensors. They found that the facet loads decreased in axial rotation after implantation of Dynesys. In extension, they were similar to the intact spine, and no significant difference compared to the intact case. They, however, found that the facet loads were significantly higher in flexion with the Dynesys due to device compression. It was found that the Dynesys system reduced spinal motion from intact and decreased peak facet loading [94].

In addition to this, Schmoelz et al. [95] compared Dynesys to a rigid fixation system. They concluded that Dynesys provides substantial stability in case of degenerative pathologies and can replace conventional fusion surgery in these indications, while the motion segment is preserved.

FE Analyses. Rohlmann et al. studied the intersegmental rotations and intradiscal pressures in a degenerated disc after implanting the posterior dynamic implant in a FE-based study [96]. Motion at the implanted level decreased, and it slightly increased at the adjacent level. Intradiscal pressure was also decreased at the injured level with the implant. There is no much effect on IDP at the adjacent level with the implant.

In a study performed by Parepalli [97], rigid rod (fusion) system was compared with AXIENT to evaluate the parameters like range of motion, intradiscal pressure, and facet loads of the implanted and adjacent levels. They found that AXIENT restored kinematics of the degenerated spine close to normal thanthat with the fusion device (for grade I and grade II degenerated spine). AXIENT was able to restore the kinematics of degenerated spine at the adjacent levels where as fusion increased segmental motion beyond the intact. Also, stresses in pedicle screws were more for rigid

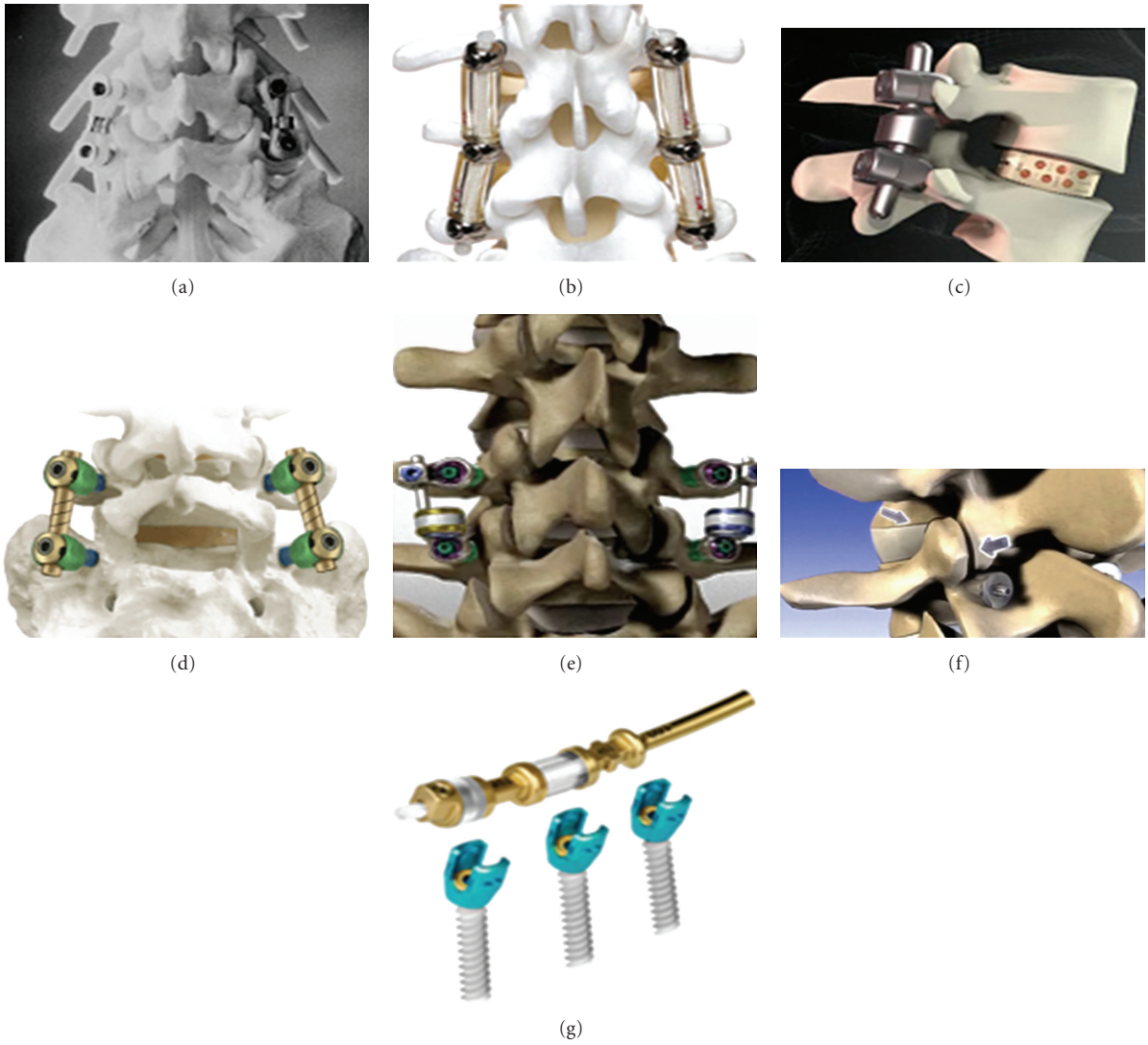
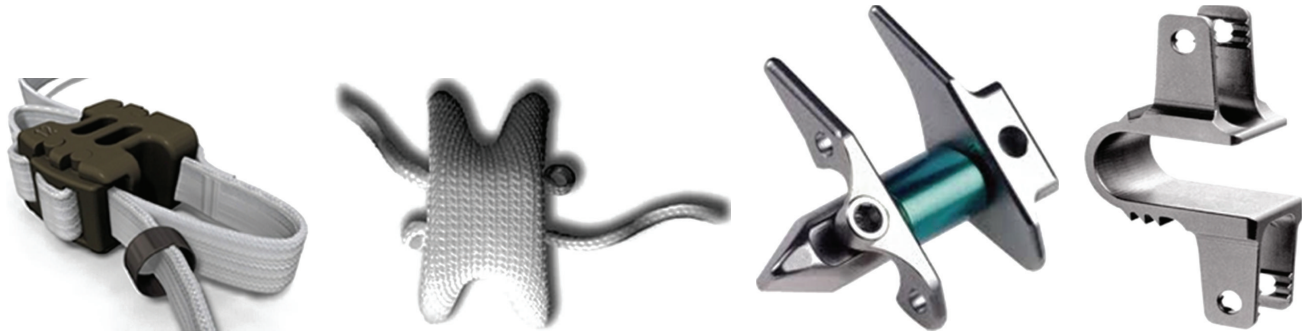


Figure 9: Posterior dynamic stabilization systems. (a) Graf system; (b) Dynesys; (c) IsoBar; (d) AccuFlex; (e) Stabilimax; (f) PercuDyn; (g) Transition [92].

system compared to the AXIENT system implicating less risk of screw breakage for AXIENT system. Vishnubhotla et al. [98] performed a study in which FE analysis has been used to assess the kinematics of a motion segment instrumented with (i) Rigid screw rod system (used infusion), (ii) Rigid screw system with flexible rod (Nitinol; super elastic), (iii) Dynesys (Zimmer, Inc.) a pedicle screw-based dynamic stabilization system, (iv) Cosmic (Ulrich, Ulm. Germany) a pedicle screw based hinged dynamic stabilization system, and (v) Wallis (Spinal Concepts, Inc.) an interspinous based dynamic stabilization system. They reported that the dynamic stabilization systems are more flexible than rigid systems but not flexible enough to say that they preserve motion. However, the evaluation of the IAR indicates that the Dynesys system achieves kinematics closer to that of the intact spine while restricting motion.

Another study was performed by Goel et al. [99] to evaluate the biomechanical performance of the Dynesys dynamic stabilization system as a function of graded facetectomies, including complete bilateral facetectomies. An experimentally validated FE model was used to compare the biomechanics of L3-S1 lumbar spine with graded facetectomy (50%, 75%, and total bilateral medial facetectomy) at L4-L5 before and after placement of Dynesys versus intact. A 400 N compressive follower load plus a 10 Nm bending moment were applied to all models to simulate physiologically relevant motions in all planes. Results depicted the Dynesys dynamic stabilization system constrains the motion of the decompressed segment similar to a rigid system. They reported that multiple grades of facetectomy show minimal effects on the kinematics of the stabilized segment in all loading cases, except in axial rotation (AR). In total facetectomy case, increased motion and elevated pedicle screw stresses were observed in AR as compared to the intact-stabilized case. Higher screw stresses in AR for 50% facetectomies may accelerate screw loosening/failure



(a) (b) (c) (d)

Figure 10: Interspinous spacers. (a) Wallis system; (b) DIAM system; (c) X-stop; (d) Coflex [92].

especially in combination with other motions like flexion/extension during daily activities.

3.3.2. Interspinous Spacers. The interspinous distraction devices are floating devices, which are not rigidly connected to the vertebrae. The interspinous spacers are designed to off load the posterior disc and the facet joint, by distracting the spinous processes [98]. There are several interspinous-based devices.

The Weiss springs consist of springs anchored to the lamina; the indication for the usage of this system is for fracture and deformity applications [100]. This system was modified further to consist of a rod portion attached to the spinous process using bands; these rods were meant to control rotation. A comparison study with the Harrington distraction rods concluded that modified Weiss springs often maintain better spinal stability [101].

The X-stop is intended to provide a minimally invasive, nonfusion, alternative to current treatments for degenerative lumbar spinal stenosis from L2–L5 levels, which include medical management, epidural steroid injections, and decompressive laminectomy with or without fusion. The X-stop is made of high strength titanium alloy and consists of two parts. The device is introduced between the spinous processes of adjacent level vertebral bodies and is held in place by the supraspinous ligament keeping the segment in a slightly flexed position. Due to the slightly flexed position, the nerves get decompressed thus providing relief from pain.

French orthopedic surgeon Jean Taylor developed this device. The device for intervertebral-assisted motion (DIAM) system consists of a polymeric interspinous spacer, with extended wings to act as a posterior shock-absorbing device. It consists of a flexible spacer and dual independent ligaments, which attach the spacer to the spinous process above and below, transferring some of the axial load to the posterior elements in flexion and extension (Figure 9). The flexible spacer is made with an inert medical-grade silicone core material, and the ligament is made of Graf/Senegas ligament. The surgical procedure involved for the DIAM device is to distract the spinous process to place the spacer and then to insert each ligament into the adjacent interspinous space. There is minimal wear debris seen in the DIAM, since there are no articulating surfaces. Other notable devices in this category include Coflex. Figure 10 depicts some of these spacers.

There are few biomechanical and clinical studies showing the effectiveness of these kinds of devices. Wilke et al. did a biomechanical study on X-stop, Wallis, Coflex, and DIAM devices to assess the flexibility, stability provided, and the effect on intradiscal pressure after implanting these devices. They found that all the devices provided stability in extension, but there was no difference for flexion, lateral bending, and axial rotation. The intradiscal pressure dropped in extension and led to no difference in other mentioned loading modes [102].

Six human cadaveric motion segments were subjected to complex cyclic loading to determine the risk of interspinous spacer (Superion, VertiFlex Inc, CA, USA) device migration and to assess damage on the device and specimen under extreme coupled motion [103]. Motion segments with interspinous spacer were tested for 5-degree extension/10-degree flexion coupled with an axial rotation of $\pm$3-degree up to 57600 million cycles. CT images were taken for specimens in neutral, 5-degree extension, and 10-degree flexion before and after the implantation of the spacer. Vertebral foramen and canal dimensions were quantified. Results have shown no device migration or subsidence. Specimens did not sustain any significant injury during testing. Canal area was minimally altered and foramen height, width, and area increased in extension and were statistically significant as compared to intact. It was concluded that interspinous spacer effectively prevents the motion at the implanted level and does not change the anatomy significantly.

Kabir et al. conducted a review study to find out the clinical and biomechanical evidences of interspinous device safety, effectiveness to suggest the clinical indications for these kinds of devices. They reviewed articles related to the aforementioned 4 interspinous spacers. They found that most of the studies were conducted related to X-stop, and a few studies, both biomechanical and clinical, were conducted related to other devices. In biomechanical points of view, all the devices have a beneficial effect on the kinematics of spine. The authors found these implants to be very effective in comparison to conservative treatments. They could not suggest clinical indications for interspinous

devices because of varied outcomes, and a small number of studies conducted so far [63, 104]. In spite of the varied results of these interspinous devices, the author found these implants are effective in treating stenosis when compared to conservative treatment. The authors suggested the need for randomized controlled studies to evaluate these devices and to revise clinical indications for these kinds of devices [104].

4. Conclusion

In contrast to the previous paradigms of rigid fixation, new technologies aim to restore and preserve motion while enabling a proper load sharing. In theory, proper load sharing and restoration of physiologic motion will reduce the probability of adjacent segment disease. Current focus of research efforts emphasizes long-term evaluation of devices and validation of theoretical and experimental benefits in a clinical setting. In addition to bench-top testing, well-designed, randomized clinical trials are needed to achieve these goals.

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Research Article

Measurement of Intervertebral Motion Using Quantitative Fluoroscopy: Report of an International Forum and Proposal for Use in the Assessment of Degenerative Disc Disease in the Lumbar Spine

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Quantitative fluoroscopy (QF) is an emerging technology for measuring intervertebral motion patterns to investigate problem back pain and degenerative disc disease. This International Forum was a networking event of three research groups (UK, US, Hong Kong), over three days in San Francisco in August 2009. Its aim was to reach a consensus on how best to record, analyse, and communicate QF information for research and clinical purposes. The Forum recommended that images should be acquired during regular trunk motion that is controlled for velocity and range, in order to minimise externally imposed variability as well as to correlate intervertebral motion with trunk motion. This should be done in both the recumbent passive and weight bearing active patient configurations. The main recommended outputs from QF were the true ranges of intervertebral rotation and translation, neutral zone laxity and the consistency of shape of the motion patterns. The main clinical research priority should initially be to investigate the possibility of mechanical subgroups of patients with chronic, nonspecific low back pain by comparing their intervertebral motion patterns with those of matched healthy controls.

1. Introduction

The need to be able to measure intervertebral motion in the diagnosis of problem back pain has been recognised for over a century. Attempts began with plain X-ray studies [1–5] and were followed by cineradiography [6–10], videofluoroscopy [11–16], roentgen stereophotogrammetry [17, 18], and magnetic resonance imaging [19, 20]. All have been found impractical for routine clinical use for a variety of reasons, ranging from poor image quality to low computing power, poor reliability and accuracy, laboriousness of multiple image registrations, X-ray dosage, invasiveness, cost and problems with sequential image acquisition. Until the emergence of quantitative fluoroscopy technologies, the standard approach to evaluating the mechanics of intervertebral linkages *in vivo* has remained a pair of plain radiographs taken at the end of bending range [21].

Quantitative fluoroscopy (QF) is an objective assessment of the spine in motion using fluoroscopy (moving video X-rays) and automated computer processing algorithms which calculate intersegmental kinematic parameters throughout the motion. It overcomes the above obstacles by automatically processing low-dose digital fluoroscopic image sequences from live subjects in motion [16, 22–25].

The method uses modern conventional image intensifiers and requires little specialist knowledge to operate. However, differences between the techniques of different research groups have made comparison of results difficult; therefore a consensus is needed if it is to benefit patients.

By 2008, three independent teams from across the world had published methods and results from their individual studies. Their varying approaches to acquisition, analysis, and interpretation meant that combining or comparing data was impractical and a more standardised approach, building on the strengths of the different methods was desirable. In August 2009, with support from the British Council in the form or a grant under the International Networking for Young Scientists Scheme, these three teams met in San Francisco for the First International Forum on Quantitative Fluoroscopy of the Lumbar Spine. This International Forum was a networking event of the three research groups (UK, US, Hong Kong), over three days. Its aim was to reach a consensus on how best to record, analyse, and communicate QF information for research and clinical purposes.

2. Materials and Methods

Three research teams led by Professor Alan Breen (AB) (UK), Dr Deidre Teyhen (DT) (US), and Dr Kris Wong (KW) (Hong Kong) met over three days to attempt to reach consensus on a proposal for optimal QF methodology for clinical and research studies. The Forum was also attended by representatives from the medical devices company Ortho Kinematics Inc., also of the US. After discussion on the rationale for quantitative fluoroscopy, the teams considered 4 subject areas: (1) choice of intervertebral motion measurement, (2) image sequence acquisition protocols, (3) image analysis methods, (4) future research priorities. Each team, in turn, described its methodology, followed by group discussions on a consensus in each area.

All sessions were recorded and transcribed to note form by FM. Two drafts of the proceedings were compiled by AB and circulated for comment and amendment. Further drafts of some sections were written by DT and FM. A final compressed version for publication was edited by AB with input from all groups. Updates on reliability and accuracy were obtained from FDA studies in 2011 and for radiation dosage from the masters' degree dissertation of one author (ACB).

3. Results and Discussion

3.1. Choice of Intervertebral Motion Measurement. There is a range of options for acquiring intervertebral motion data for measurement, for example, in the coronal or sagittal plane (the transverse plain not being assessable); in lying, sitting, or standing orientations; using free or controlled bending protocols and using various methods for patient stabilisation. There are also options for what to measure to best inform clinical decisions. These traditionally include overall angular rotation and translational range of intervertebral motion (IV-ROM), the position(s) of the instantaneous axis of rotation (IAR) [26, 27], and laxity in the form of the size of the Neutral Zone [28]. QF acquires continuous motion data, offering possibilities to measure all of these, plus others, such as the proportions of lumbar motion shared by the various levels [29], "phase lag" (the tendency for different levels to commence or end at different points in the trunk motion sequence) [30] and the measurement of disc height [31]. Other important choices include those of vertebral landmarks and their use to calculate these. The technique as a whole also depends on the minimisation of radiation dosage, the reduction of movement blurring and the avoidance of out-of plane image distortion.

The Forum agreed on the following 7 priorities for measurement by QF:

(1) Range of intervertebral rotation.

(2) Range of intervertebral translation.

(3) Directional coherence.

(4) Motion commencement sequence.

(5) Neutral zone laxity.

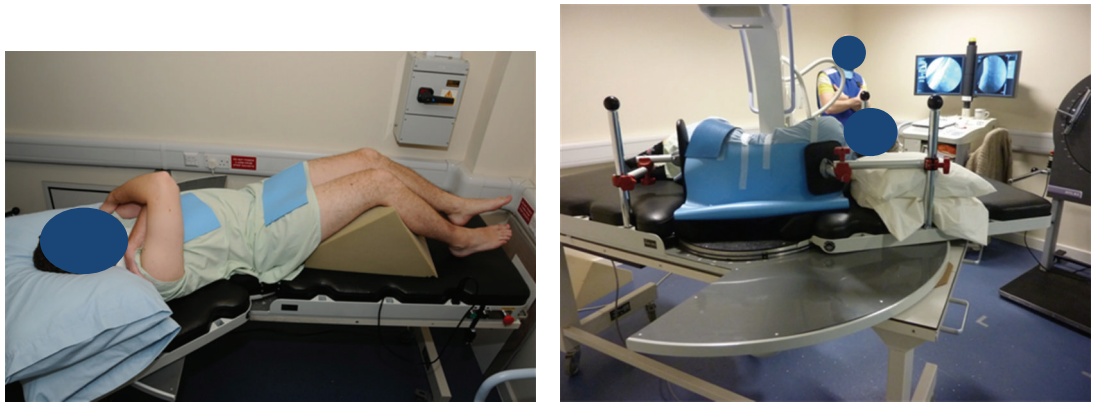
(6) Instantaneous axis of rotation (IAR).

(7) Disc height.

3.2. Image Sequence Acquisition Protocols. The US method [22] assessed lumbar flexion and extension in the upright posture. The subjects move through their full range of motion and are instructed to slowly bend forward and return to the upright posture in about 4-5 seconds. This pace was selected based on patient comfort and that faster movements could result in blurring of the images. Subjects complete four cycles of flexion, and extension, with the third cycle captured for analysis. To help maintain the lumbar spine within the field of view and minimize hip and knee flexion a stabilization device that included a climbing harness and belts was used to stabilize the patient. The Hong Kong method [32] also acquired flexion-extension images in the standing position with an electrogoniometer strapped to the back [15, 23, 32] and the pelvis unconstrained. Subjects voluntarily extend and flex maximally and then return to neutral. The intensifier was made to follow and keep the vertebrae of interest in the middle of the field. This may result in movement blurring.

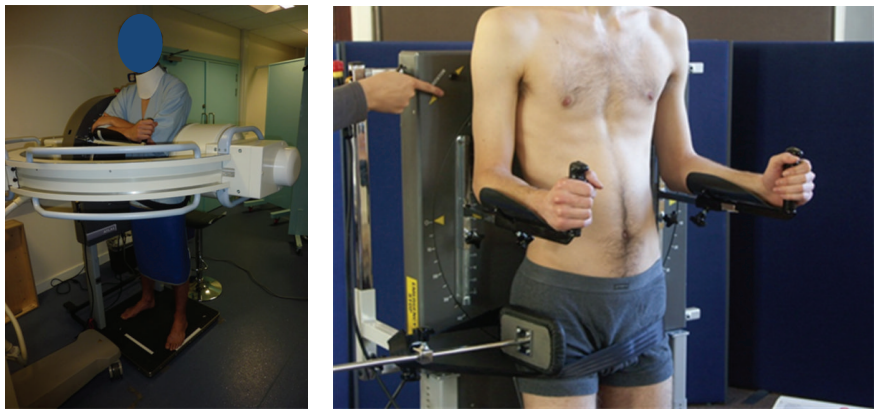
The UK method screened subjects in either passive, controlled recumbent motion on a specially designed motion table (Figures 1(a) and 1(b)) [24] or standing against a special motion frame (Figures 2(a) and 2(b)) (Atlas Clinical Ltd.). This method measured both flexion and extension, used lead masking to reduce intensifier flare during motion, and controlled for rate and range. This was conventionally 40 degrees in each outward direction over 10–15 seconds for each direction.

Consensus: The Forum agreed that imaging procedures should include both the standing and lying patient orientations and both the coronal and sagittal planes, with the sacrum stabilised during weight bearing investigations with the patient following an upright motion frame to control the rate and range of trunk motion (Figures 2(a) and 2(b)).



(a) (b)

Figure 1: (a) Passive recumbent supine right lateral flexion acquisition. (b) Passive recumbent flexion acquisition.



(a) (b)

Figure 2: (a) Weight-bearing flexion-extension image acquisition following an upright motion frame. (b) Weight-bearing side-bending acquisition: position of motion frame.

No restraint is needed for lying acquisitions (Figure 1) where knee support in the supine position and antiroll pads in the lateral recumbent position can provide adequate stabilisation.

All image capture should be preceded by "warmup" motion (without fluoroscopic screening). The simultaneous recording of trunk motion is inherent in all three methods as continuous global motion data are needed to make comparative calculations with kinematic measurement. The UK method imposed preset global motion on the trunk, whereas the Hong Kong method used surface goniometry which may be unreliable [33] and the US method measured from the vertebral images over a short section of the lumbar spine. It was decided to recommend the UK method; however, this may not challenge all segments in very flexible subjects. Therefore, it was also recommended that free, end-of-range and neutral fluorograbs are obtained to check that any fixed segments have been adequately challenged before accepting a finding of immobility.

It was agreed that the range and velocity of trunk motion should be standardized, and all image acquisition should start from the neutral position. This reduces the global range variability making possible the collection of normative intervertebral motion information and allowing follow-up studies to have standardised comparators. A neutral position start also ensures that Neutral Zone information can be obtained. However, it is recognised that, in the lying positions the flexing of the patient's knee and hips means that the lumbosacral spine is also slightly flexed.

It was also recommended that the standardised range for recumbent motion is 40 degrees in left, right, and flexion directions for both standing and lying investigations, with the exception of 20 degrees of extension and 60 degrees of flexion for flexion-extension motion in weight bearing, which takes account of the natural lumbar lordosis in the erect postures. In order to avoid "aliasing" or movement blurring if acquisition is too slow or too fast, it was recommended that each motion direction duration is of 8–12 seconds, with ramp-up, ramp-down, and motion reversal intervals of 0.5–1 seconds to avoid lost image registration at the beginning and patient "wobble" at the end of ranges.

A single unidirectional fluorosequence should involve around 20 seconds of exposure, including positioning and use factors between 70–90 kVp and 50–70 mA. A whole

examination involving flexion-extension and left-right lateral flexion should give an average effective dose of between 0.80 and 1.5 mSv. (This can be compared to 1.3 mSv which is the reported average dosage for an AP and lateral single plain radiographic series of the lumbar spine [34, 35]).

The US method captures images at 30 fps using a digital frame grabber and the UK method at 15 fps taken directly from a digital fluoroscope. It was recommended that at least 8-bit images acquired at 15 fps over 6–20 seconds of motion would be acceptable and that image acquisition speed should be not less than 12.5 fps and digital image bit-depth and pixel densities not less than 8-bit and 512×512, respectively.

3.3. Image Analysis Methods. QF image sequences can provide several hundred images per examination. To use these for kinematic measurement therefore requires automated methods. The steps involved are image registration, image tracking, recording of serial intervertebral spatial relationships throughout the motion, transformation of these spatial relationships as data outputs, and the summarisation of these outputs into graphic or numerical form for interpretation.

In the US method, images were enhanced to help detect the borders of the vertebral bodies from the surrounding soft tissue using digital filters (Image Pro Plus software, MediaCybernetics, Silver Springs, MD). Images were then imported to MATLAB (The Math Works, Natick, MA) for vertebral body detection and kinematic analysis. Vertebral body detection consisted of manually defining the vertebral body corners and specific midpoint locations using a modified technique originally developed by Frobin et al. [36] (Figure 3). Following this, computer algorithms were used to verify these corner locations and calculate the specific midpoint locations. Four iterations of the vertebral corner selection process were used to enhance reliability. Once these locations were determined for each frame (approximately 200 frames per flexion-extension cycle), the key points to detect the vertebral body were smoothed across frames using a fourth-order Butterworth filter to minimize error.

In the Hong Kong, method the 4 corners of the vertebral body images are marked. This is referred to as the "active contour method," or "Snake." The active contour program fits a template, and an image processing program then fits this to the edges of subsequent vertebral images by learning the outline and predicting the position of the next template in the sequence. This is thought to be highly reliable over the same images because the active contour method always finds the same edges. This is true for measuring rotation, but translational motion is error-prone because, unlike the Frobin et al. method, this method does not compensate for image distortion. From acquisition, intervertebral motion is measured for every degree of trunk motion from 20 degrees extension to 40 degrees flexion as measured from L1 to S1. This method is not significantly inhibited by the presence of bowel gas or intensifier flare.

In the UK method, images are also enhanced (Figure 4(a)). The resultant images are marked by placing cursor lines around each vertebral body five times (tracking templates). These are registered from frame-to-frame automatically throughout the sequence using cross-correlations and a rolling average over each 2 images as the sequence progresses to reduce noise. During marking, additional templates (reference templates) are placed using only the four body corners and are linked to the tracking templates as coordinates in order to verify tracking and to obtain coordinates for calculating translation, disc height, and IAR using the Frobin et al. method [36, 37]. (Rotation is calculated from the vertebral tracking templates individually).

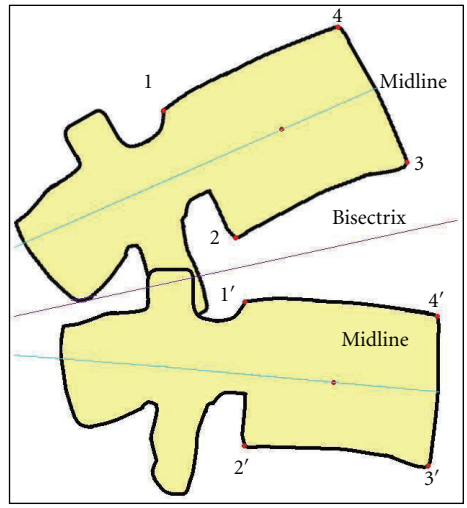
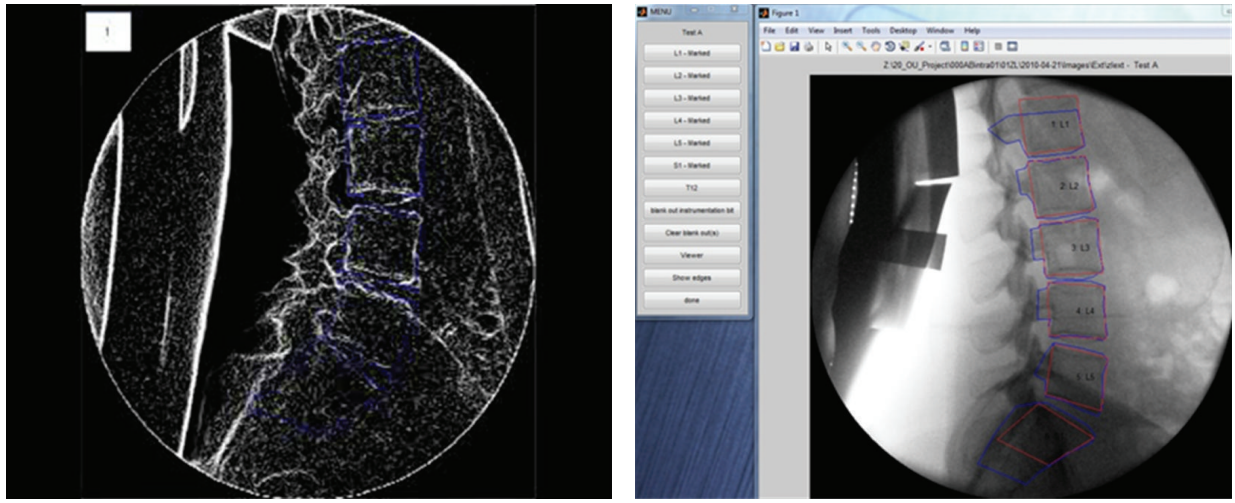


Figure 3: Frobin et al.'s [36] method for registering the positions of vertebrae.

Areas of implanted metal within the vertebral images can be removed by marking around them and subtracting out the enclosed area. The ability of the templates to track all images is checked both by viewing the overlay of the vertebral motion graphs and the adherence of the templates to the vertebrae during video playback. For intervertebral rotations, the 5 trackings for each vertebra are subtracted from those adjacent to them for each combination of vertebrae and vertebral tracking to give 25 intervertebral angle sequences per pair. Mean and median values of these 25 are very similar and either can be used to display rotational results. Failed trackings may be remedied by remarking vertebrae.

Consensus: Although each research team addressed QF differently, a combination of best practices across the techniques has the possibility of improving the technology. This may be achieved by using the US method for more reliably locating corners in the initial images, followed by the Hong Kong method for fitting the templates to the vertebrae and then the UK method for tracking them. It should then be possible to combine the advantages of automated tracking with more precise template fitting to obtain more reliable results with less operator interaction. The Hong Kong method for tracking could also be used as an alternative in individual patients.

It would also be useful to try to test these multiple methods with the same patient. This would involve first, corner marking, then corner detection, then marking reference



(a) (b)

Figure 4: (a) Lateral view of lumbar spine image with enhancement. (b) User interface output showing lateral view of lumbar spine image with tracking and reference templates.

templates based on the Snake, then placing these reference templates in the Snake for one of the five tests and tracking the rest with cross-correlations. The cross-correlation method is based on the rigid-body assumption, and this should give better results than the Snake method (which changes shape during tracking) for calculating translation, disc height and IAR, whereas using the Snake method for one of the trackings should give better results for rotations.

This should also accommodate the need to blank out metallic implants; however, the Snake method is as yet untried for A-P images and may also not track S1 in the lateral projection. To optimise image analysis using a combination of these methods will require optimal image acquisition and an understanding of the effects of body type on the different image processing technique combinations.

3.4. Indices of Motion. All groups had used QF to determine rotational IV-ROM, but it was recognised that various geometric transformations of the data would provide access to many more kinematic parameters.

It was decided to prioritise rotational and translational range, regularity, symmetry, laxity, and IAR location in recumbent passive and active weight-bearing configurations as useful measurements in people with chronic, nonspecific low back pain. Continuous rotational and translational range data provides the measurement of maximum range, wherever it is attained during trunk motion, while enabling, by data extrapolation, the display and measurement of phase lag, motion sharing, regularity, and laxity (Figures 5(a) and 5(b)).

The measurement of Neutral Zone laxity has been subject to some preliminary testing using recumbent lateral bending studies [25]. The ratio of the slopes of intervertebral and global motion is measured in the accompanying 10 degrees of trunk motion. The higher the ratio of intervertebral motion slope to global motion slope, the less restraint is acting in the Neutral Zone (Figure 6).

IAR is also computed from the same reference template information as the other motion parameters (Figures 7(a) and 7(b)). This can be displayed as x-y coordinates, equivalent mm from a nominated anatomical landmark, graphically on the user interface or as a location on the image (Figure 8). Multiple IARs can also be computed serially and displayed as moving or accumulating points on a video sequence of the images.

3.5. Repeatability and Accuracy. All groups at some time have also reported on the reliability and/or accuracy of QF for intervertebral range measurement. The most recent accuracy calculations come from a 2011 FDA study (Ortho Kinematics 2011) which used 60 image sets from two *in vitro* calibration models made of human vertebrae. The QF images were distorted by rotating half of them 10 degrees out of plane, and all were degraded by interposing animal soft tissue. The results for intervertebral rotation report an error of less than 0.70 degrees for rotational measurement and less than 2.60% of vertebral body depth for translation (<0.91 mm for a standard vertebra of 35 mm depth) (Table 1).

The repeatability part of this study compared three measurement methods: QF, digitisation of X-rays at maximum voluntary bending angles (MVBA), and measurement of X-rays at MVBA by ruler and protractor. Intervertebral rotation and translation were recorded in 63 patients' image sequences by 3 trained observers. The mean RMS errors for all patients and intervertebral levels are shown in Table 2, reflecting repeatability errors of less than 1.30 degrees and 1.92% of vertebral body depth (0.7 mm) for QF compared to substantially larger errors for the other two methods.

3.6. Radiation Dose. QF uses low-exposure durations compared to what is traditionally expected of fluoroscopy.

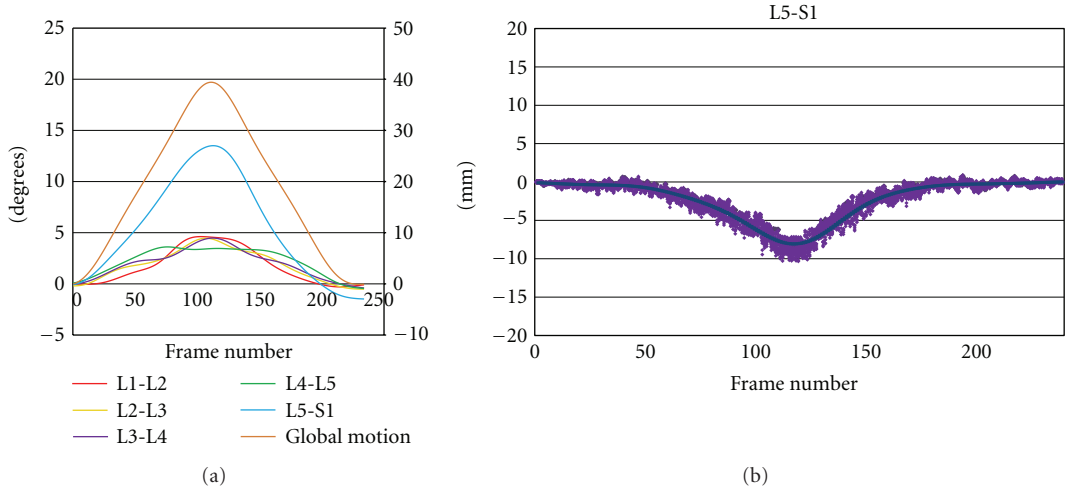


Figure 5: (a) Continuous intervertebral angles for 5 levels (left y-axis) and global (trunk) motion (right y-axis) in a patient with unstable L5-S1 spondylolytic spondylolisthesis. (Passive recumbent extension motion, note excessive motion at L5-S1, with irregular motion at L3-4 and L4-5. Maximum L4-5 range attained before maximum global motion range). (b) Translational motion path at L5-S1 extension in the same image sequence as in 5(a). (Solid line is mean translation and shaded area is all data). Note translational range of 8 mm.

Table 1: Accuracy: combined results from two calibration models for four bending modes.

	RMS error			
Study	Flexion	Extension	Left	Right
Rotation (degrees)	0.69	0.57	0.1	0.22
Translation (% body depth)	2.44	2.59	N/A	N/A

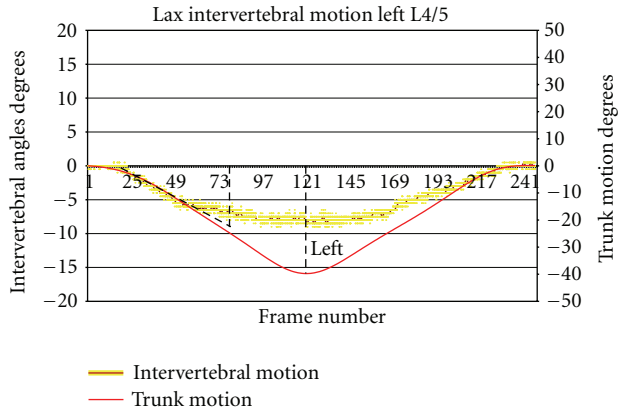


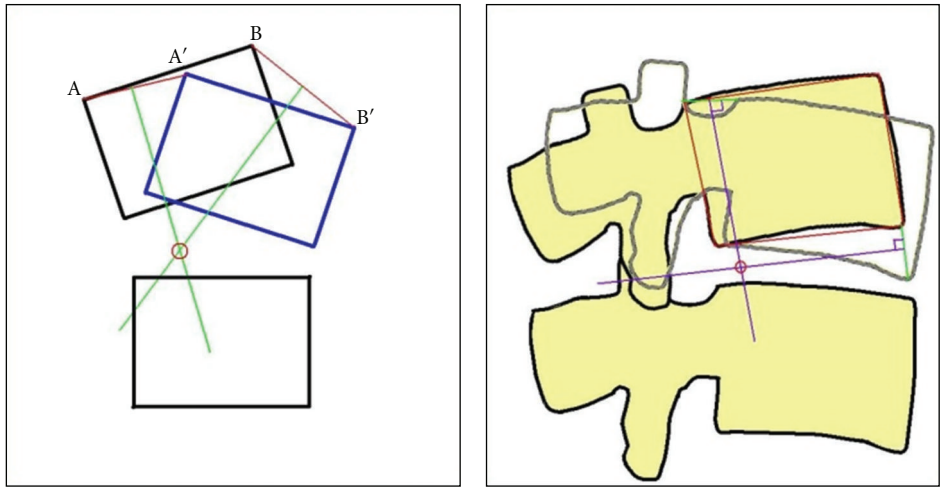
Figure 6: Example of use of intervertebral versus trunk motion graphs for the calculation of laxity by ratio of their slopes in the first 10 degrees of global motion (slope of global motion = −0.536).

This and improved image intensifier technologies keep the radiation dosages low. The average dose across 53 subjects who underwent QF examination in the UK in 2011 (passive motion flexion-extension and right and left lateral bending) was 0.89 mSv, with a standard deviation of 0.25 mSv. This is equivalent to approximately 22 weeks of UK average background radiation [34] (where the UK average is 2.2 mSv per year). As a comparison, the typical dose received during an X-ray examination of the hip is 0.3 mSv, equivalent to 7 weeks background radiation or additional lifetime risk of 1 in 67,000 fatal cancer per examination. An X-ray examination of the thoracic spine is 0.7 mSv (4-month background radiation or 1 in 30,000 lifetime risk of fatal cancer per examination) and an examination of the lumbar spine is 1.3 mSv (7-month background radiation, 1 in 15,000 lifetime risk).

3.7. Future Research Priorities. Multiple authors have researched fluoroscopy as a method for measuring intervertebral motion *in vivo* [6, 7, 9, 10, 12, 14, 15, 38–48], but it has only recently been developed as a diagnostic technology. The reasons for this include a lack of a suitable methods for standardising patient motion, assuring adequate image quality, achieving frame to frame image registration and obtaining adequate computer online storage and processor speed to handle the required volume of image data. However, once these began to appear, QF became a viable method and its reliability, validity, X-ray dosage [24], and clinical utility [25, 29, 32, 49] began to be investigated.

The benefits to patients from QF will be principally in the conservative care arena, where most people remain, but also in the world of spinal surgery, where the more severe cases are often found and where many implantable devices that are intended to influence intervertebral motion require evaluation.

The Forum identified, as a priority for future QF research, the investigation of mechanical subgroups within



(a) (b)

Figure 7: Illustration of geometric determination of IAR: (a) on a simple block diagram, (b) on vertebral body images. The IAR is located in the posterior half of the disc space.

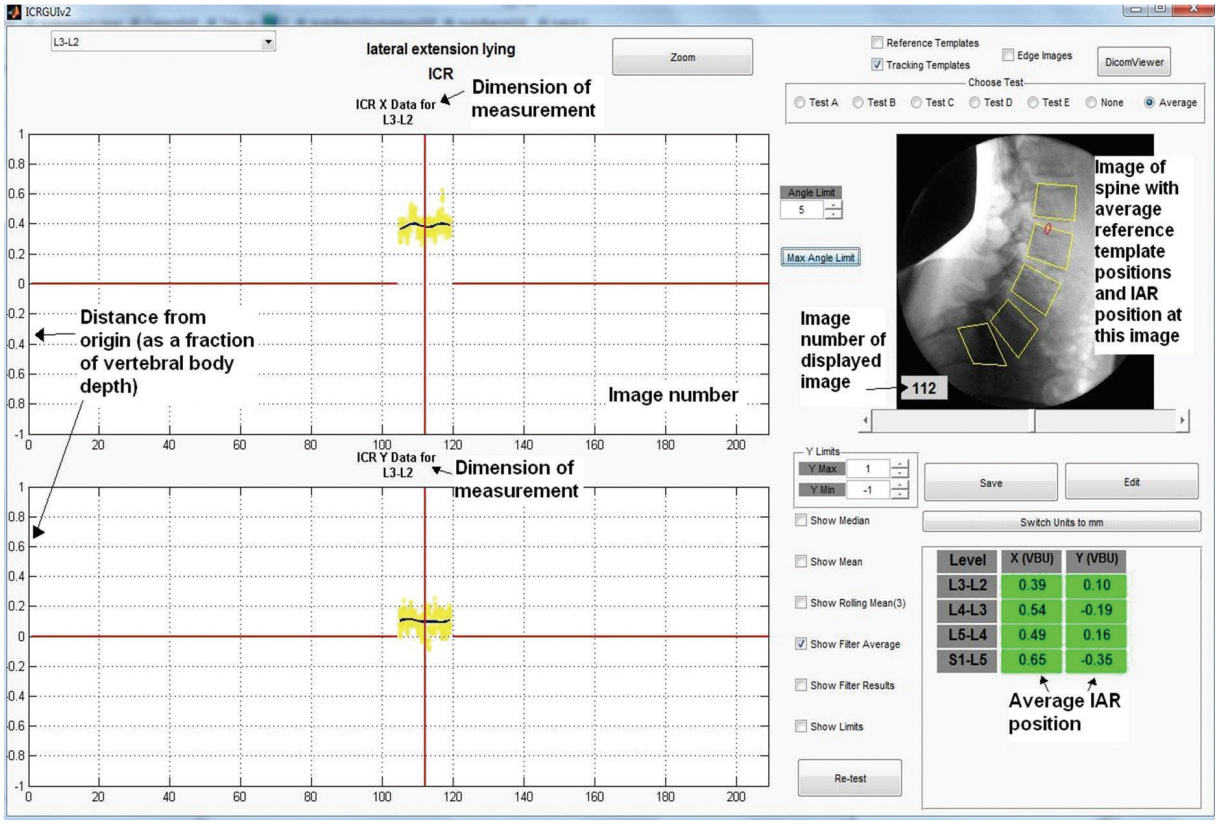


Figure 8: User interface image showing graphical and numerical output of overall IAR position and as the location of this position on the image.

Table 2: Observer repeatability for three measurement methods (mean RMS).

	Intraobserver errors			Interobserver errors		
Study	QF	MVBA	Ruler	QF	MVBA	Ruler
Rotation (degrees)	0.77	2.66	4.22	1.26	3.14	4.50
Translation (% body depth)	1.19	3.83	5.83	1.92	4.35	6.61

chronic nonspecific low back pain and disc degeneration. However, large subject populations are needed to establish subgroups. This is not only because the main beneficiaries will be the minority of patients who have chronic pain, but also because the consequences of ligament subfailure involve combinations of abnormalities [50] of the passive, active, and control systems of the spine [28, 51–53]. In conservative treatment, for example, strength alone may not be enough to rehabilitate if motor control is not improved. It is therefore necessary to find methodologies that will disaggregate these for clinical purposes. This anticipates combining QF with other technologies, such as electromyography and algometry to investigate more thoroughly these patient subgroups.

One promising entry point into these lines of investigation of data may lie in studies of the lumbar multifidus muscle and the changes in its function and structure that occur in chronic back pain [54–56]. We also need to understand the role of other trunk musculature, notably the transversus abdominus in these syndromes [54]. Using QF and other technologies in combination, it may be possible to discover when and to what extent chronic back pain may be associated with recordable abnormalities in the passive, active, and control systems as separate entities.

It is also recognised that psychosocial factors can play a part in prognosis [57, 58] and patient populations in QF subgrouping studies should take account of the extent to which these are present. For example, in terms of intervertebral function, the role of fear-avoidance behaviours [59] is unknown.

4. Conclusion

People with chronic, nonspecific low back pain are likely to be a very heterogeneous group. However, an objective diagnostic test that could help guide its management would be valuable for individual patients and society as a whole. These benefits would lie in being able to better predict who will benefit from spinal manipulation, exercises, and flexible stabilisation surgery. It may also predict who will return to work, who will need to leave their jobs, and who will become dependent on social support. Previous research has identified a number of weak to moderate predictors of these outcomes, but none have been able to objectively assess an intervertebral site that is suspected of being mechanically involved. In the future, QF technology may be used to determine which patients with chronic nonspecific back pain had a mechanical basis for it.

It will also be necessary to know the intrasubject variation in pain-free subjects over a treatment period. These intrasubject reliability studies in control subjects will be necessary to ascertain the smallest change over time that could be attributed to a treatment intervention. Clinicians from both the surgical and conservative care will then be able to investigate the role of mechanics in patient outcomes.

Conflict of Interests

The authors declare that they have no competing interests.

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Review Article

Stem Cell Therapy for Degenerative Disc Disease

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Low back pain is widely recognized as one of the most prevalent pathologies in the developed world. In the United States, low back pain is the most common health problem for adults under the age of 50, resulting in significant societal and personal costs. While the causes of low back pain are myriad, it has been significantly associated with intervertebral disc (IVD) degeneration. Current first-line therapies for IVD degeneration such as physical therapy and spinal fusion address symptoms, but do not treat the underlying degeneration. The use of tissue engineering to treat IVD degeneration provides an opportunity to correct the pathological process. Novel techniques are currently being investigated and have shown mixed results. One major avenue of investigation has been stem cell injections. Mesenchymal stem cells (MSCs) have shown promise in small animal models, but results in larger vertebrates have been mixed.

1. Introduction

1.1. IVD and Low Back Pain. Intervertebral discs act as the main joints of the spinal column, providing both stability and flexibility. In addition to facilitating bending, flexion, and torsion, they also help to transmit loads applied to the spine. In the normal course of aging, the intervertebral disc (IVD) and in particular the nucleus pulposus (NP) undergo extensive morphological and cellular changes resulting in hardening of the NP and a decrease in structural integrity, disc height, and flexibility of the IVD as a whole [1, 2].

Low back pain has been strongly associated with such IVD degeneration [3, 4]. Numerous epidemiological studies suggest that such back pain is widespread, frequently debilitating, and costly. Approximately 25% of American adults reported low back pain occurring in the past 3 months. This corresponds to over 54 million individuals [5]. Over a lifetime, 70% to 80% of people will at some time experience back pain [6]. Accordingly, in the United States, low back pain is the fifth most common reason for physician visits, constituting approximately 2.3% of all appointments [5, 7].

Low back pain is frequently debilitating and as such is responsible for significant productivity losses. Accounting for 149 million lost work days annually, back pain is the second most common reason for sick leave, behind only the common cold [8–10]. In a given year, 8% of the entire working population will be disabled by back pain [11]. This results in significant economic losses. As of 1997, it was calculated that back pain resulted in an aggregate productivity loss of $28.17 billion in the US, although by some estimates this figure may have been as high as $87.8 billion [12, 13].

At least one recent study suggests that the incidence of low back pain is increasing. Freburger et al. [14] found a 6.3% increase—from 3.9% to 10.2%—in reported chronic low back pain between 1992 and 2006. Given the costs and discomfort associated with chronic low back pain, this increase is concerning and underscores the import of exploring new treatment modalities.

In this paper, we discuss the potential of using MSCs to treat IVD degeneration. We comment on current research and conclude with recommendations for further study.

2. The IVD: Structure and Degeneration

2.1. Disc Morphology. The IVD is avascular and consists mainly of a macromolecular extracellular matrix (ECM) with a low-density population of cells that help to maintain this ECM. Grossly, a normal IVD consists of a central

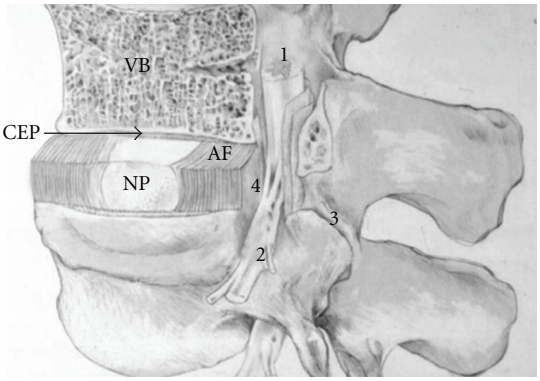

Figure 1: Illustration of the main intervertebral disc structures and vertebral column. CEP: cartilage endplate; AF: annulus fibrosus; NP: nucleus pulposus; VB: vertebral body; 1: spinal cord; 2: nerve root; 3: apophyseal joint; 4: site of NP protrusion and nerve root compression after IVD degeneration.

NP surrounded by the annulus fibrosus (AF), all of which is sandwiched between two cartilaginous endplates (EPs) (Figure 1). The NP is relatively fluid, composed primarily of an ECM of collagen type II and proteoglycans. Functionally, the collagen imparts tensile strength, while the proteoglycans attract and bind water, providing resilience to compression. Suspended throughout this ECM are chondrocyte-like cells. Commonly, the consistency of the NP is described as "gel-like." In turn, the AF is composed of a series of concentric rings (lamellae) which are primarily collagen I. The high-percentage of collagen makes the AF rigid, a property that helps it to contain the more fluid NP and contribute to the integrity of the disc. Finally, the endplates separate the NP and AF from the adjacent vertebral bone.

2.2. The Aging Disc. Histologic assessment has shown that disc degeneration definitively begins in the early teenage years [2, 15]. The discs of the lumbar spine bear a disproportionate amount of this wear [2]. Far from being static, the disc ECM is subject to continuous synthesis and degradation [16]. In IVD degeneration, the rate of matrix anabolism slows, while matrix catabolism increases. This results in a number of changes. Proteoglycan content in the NP drops significantly, and with it the ability of the ECM to attract and retain water [16]. The number of chondrocytes in the ECM decreases [15, 17]. Macroscopically, fibrous tissue forms in the NP, resulting in a loss of gel-like character and ultimately leading to a dissolution of the distinction between NP and AF [2]. Repeated mechanical loading [1, 18] and declining nutrition [1, 19, 20] have been implicated as the two most critical factors in degeneration.

Mechanical overloading of the IVD has been shown to induce catabolic activity associated with degeneration [21]. It has also been suggested that the routine cycle of disc deformation and recovery caused by normal activity could eventually lead to fatigue failure of the disc [1].

Insufficient nutrition is significant in slowing matrix anabolism. Because the IVD is avascular, it must receive nutrients through diffusion. Blood vessels terminate at the EP and nutrients then move down concentration gradients across the plate and through the ECM to reach embedded cells. It is well established that the EPs become less permeable with age [20, 22], and Boos et al. [15] found histologic evidence that a decrease in endplate blood vessels coincides with an increase in disc ECM breakdown. Studies on disc nutrition have suggested that glucose is the critical nutrient for maintaining cell viability, with oxygen and pH acting as secondary factors [19, 23]. When nutrition of the disc is sufficiently impaired, disruption of matrix synthesis and cell death can occur [24, 25].

The other component in disc degeneration is breakdown of the matrix. Matrix metalloproteinases (MMPs) and aggrecanases are two classes of enzymes involved in both normal matrix turnover and degeneration. These enzymes degrade the components of the ECM and have been found at elevated levels in degenerated discs [26, 27].

3. Treatments: Present and Future

3.1. Current Treatments. Current treatments for disc degeneration fall into two categories. Conservative, nonsurgical management entails analgesics, rehabilitation programs, and lifestyle adjustments such as weight loss. Surgical intervention involves spinal fusion and disc arthroplasty [28, 29]. While conservative management is the preferred treatment method for most cases of IVD degeneration, patients not benefiting from such management can realize benefits from surgical fusion [30]. Nevertheless, neither conservative nor surgical management addresses the underlying process of IVD degeneration, and for many patients neither is effective at relieving low back pain. Furthermore, fusion surgery has significant downsides. Beyond the loss of flexibility between fused vertebrae, fusion can also increase stress and strain on adjacent discs and thus accelerate their degeneration, necessitating further surgical intervention [31–33].

3.2. Emerging Treatments. A growing understanding of the molecular changes associated with IVD degeneration has led to a burgeoning exploration of various treatments designed to directly address these changes [17]. In recent years, therapies targeting several molecular and cellular aspects of degeneration have been explored. One approach has been the direct injection or stimulation through gene therapy of a number of growth factors involved in regulating matrix anabolism [34, 35]. This technique has shown promising results *in vitro* and *in vivo* in small animal models [36–40]. Another major avenue of investigation has been cell therapy. The goal of cell therapy is to increase ECM synthesis by repopulating the degenerate NP. To accomplish this, one of several types of cells is injected directly into the NP (Figure 2). Cell types utilized thus far include NP cells [41–43], chondrocytes [44–46], and MSCs [44, 47–55], all of which have exhibited potential for slowing and repairing degeneration. In this paper, we focus on research regarding MSCs.

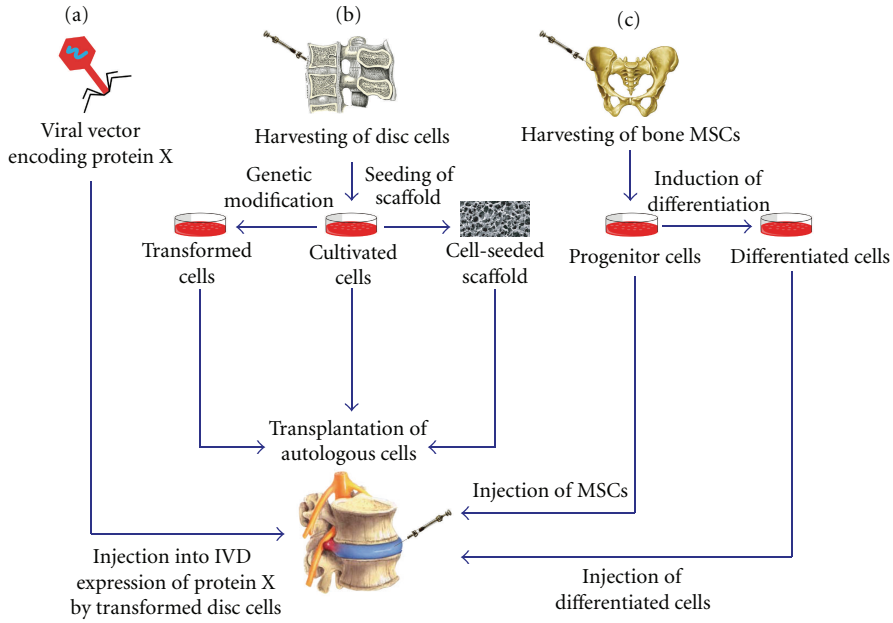

Figure 2: Different treatments for IVD degeneration are illustrated. (a) Injecting a viral vector into the IVD causes expression of the coded protein by the transformed disc cells. (b) Cells from the NP are harvested and then can be cultivated, genetically modified, or seeded into a scaffold before being transplanted into the IVD. (c) Bone MSCs are harvested and injected into the IVD as MSCs or as differentiated cells.

4. Mesenchymal Stem Cells

4.1. Background and General Therapeutic Use. MSCs are undifferentiated cells found in several adult tissues. The multipotent nature of individual MSCs was first demonstrated by Pittenger et al. [56], and since then they have been found to be pluripotent, giving rise to endoderm, ectoderm, and mesoderm cells [57]. MSCs are well suited to therapeutic application because they can be easily cultured and have high *ex vivo* expansive potential [58]. They are also capable of robust, persistent engraftment [57]. Furthermore, use of MSCs avoids the ethical issues raised by embryonic stem cell harvesting [59, 60]. MSCs have shown therapeutic promise in a number of diverse applications including regenerating infracted myocardium [61, 62], improving functional recovery from ischemic stroke [63], and rescuing liver failure [64].

A number of mesenchymal tissues have been investigated as MSC sources in adults (Table 1). Chief among these are bone marrow [56], periosteum [65], synovial membrane [66], and adipose tissue [67]. Two recent studies have suggested that MSCs isolated from different tissues exhibit different levels of expandability, chondrogenesis, osteogenesis, and adipogenesis, with synovium-derived MSCs being generally superior [68, 69].

4.2. Use in IVD Degeneration: In Vivo Studies. A number of *in vivo* studies have examined the use of MSCs to slow the process of IVD degeneration and regenerate the matrix. In 2003, Sakai et al. [51] conducted the first study exploring the use of MSCs to repair IVD degeneration *in vivo* using a rabbit model. Partial aspiration of the NP was used to induce degeneration, and autologous MSCs embedded in an Atelocollagen gel were then injected into discs. This procedure was found to prevent histological and morphological disc degeneration when compared to a nontreated, degeneration-induced control. Overall NP and AF structure, cell volume, and matrix formation (in particular proteoglycan content) were maintained up to 8 weeks after injection, and implanted MSCs were found to have differentiated into cells resembling original disc cells.

A number of other studies examining the use of MSCs in small animals have demonstrated the ability of these cells to survive, differentiate towards disc cells, and produce matrix components including collagen II and proteoglycans. This has been shown both with and without a number of cellular scaffolds (Atelocollagen gel, hyaluronan gel, and PuraMatrix) using autologous, allogenic, and xenogeneic (specifically, human) MSCs, and with follow-up times ranging from approximately one month to four months [47, 52–55]. Using a rabbit model, Zhang et al. [55] found that transplanted allogenic MSCs survived and increased proteoglycan and collagen II synthesis in the NP. Wei et al. [53] used a rat model to assess the ability of human MSCs to proliferate and function within the IVD. After 6 weeks, MSCs demonstrated survival and differentiation towards disc cells. Widespread success using allogeneic and xenogeneic MSCs may reflect the immune privilege of the IVD [70], as well as the immunosuppressive capabilities of MSCs [71].

While small animal models have yielded universally positive results, the results of large animal studies have been mixed. Henriksson et al. [48] injected human MSCs into

Table 1: Review of stem cell intervertebral disc therapy reported in the literature, including the animal model, cell type, and treatment outcome.

Study year	Animal model	Cell type	Cellular scaffold	Result
Nishimura and Mochida, 1998 [41]	Rat (nucleus aspiration)	Autologous NP tissue	NA	NA
Okuma et al., 2000 [42]	Rabbit (nucleus aspiration)	NP cells	No	Delayed formation of clusters of chondrocyte-like cells, the destruction of disc architecture, and the elaboration of type-II collagen
Nomura et al., 2001 [43]	Rabbit (nucleus aspiration)	Allograft NP tissue	No	Decreased IVD
Gruber et al. 2002 [77]	Sand rat	Autologous disc chondrocytes—AF cells	No	Engrafted cells integrated into the disc and normal ECM was synthetized
Ganey et al., 2003 [45]	Canine (disc material removal)	Autologous disc chondrocytes—NP and AF cells	No	Viable proliferating chondrocytes that synthetized ECM (collagen I and II) were found and retention of disc height
Gorensek et al., 2004 [46]	Rabbit (nucleus aspiration)	Autologous cartilage chondrocytes	No	Only Hyaline-like cartilage was found
Sakai et al. 2003 [51], Sakai et al. 2005 [78]	Rabbit (nucleus aspiration)	Autologous BMSCs—genetic marking with LacZ	Atelocollagen gel	Improved annular structure and proteoglycan preservation
Crevensten et al., 2004 [47]	Rat (no injury)	BMSCs	Hyaluronan gel	Increased disc height and matrix synthesis
Sakai et al. 2005 [78]	Rabbit (nucleus aspiration)	Autologous BMSCs—genetic marking with GFP	Atelocollagen gel	Proliferation and site-dependent differentiation
Zhang et al., 2005 [55]	Rabbit (no injury)	Allogeneic BMSCs—genetic marking with LacZ	No	Increased proteoglycan and collagen type II synthesis
Leung et al. 2006 [79]	Rabbit (nucleus puncture)	Allogeneic BMSCs	NA	NA
Sobajima et al., 2008 [52]	Rabbit (no injury)	Allogeneic BMSCs—genetic marking with LacZ	No	Transplanted BMSCs migration and engraftment into the inner annulus fibrosus
Hiyama et al., 2008 [49]	Canine (nucleotomy)	Autologous BMSCs	No	Suppression of disc degeneration and preservation of immune privilege
Hoogendoorn et al. 2008 [80]	Goat (ABC chondroitinase)	None		Mild slowly progressive degeneration
Yang et al., 2009 [54]	Murine (annular puncture)	BMSCs from EGFP transgenic mice	No	Increased matrix synthesis by both autonomous differentiation and stimulatory action on endogenous cells
Henriksson et al., 2009 [48]	Porcine (nucleus aspiration)	Human BMSCs	Hydrogel	Cells survival and disc-like differentiation
Wei et al., 2009 [53]	Rat (no injury)	Human BMSCs labeled with tracker orange	No	Cells survival and chondrocytic differentiation
Acosta et al., 2011 [44]	Porcine (nucleotomy)	Juvenile Chondrocytes/Allogeneic BMSCs	Fibrin	JC survival, proliferation, and synthesis of ECM. MSCs were not observed

NP: nucleus pulposus, AF: annulus fibrosus, ECM: extracellular matrix, MSCs: mesenchymal stem cells, BMSCs: bone marrow mesenchymal stem cells, and IVD: intervertebral disc.

porcine discs which were then harvested at up to 6 months. At followup, MSCs were found to have survived and differentiated toward disc cells, exhibiting matrix-producing functionality. Similarly, Hiyama et al. [49] found MSC injection into degeneration-induced canine discs to increase proteoglycan content and effectively mitigate degeneration. While these results are encouraging, another recent large animal study casts doubt on the potential of MSCs to treat IVD degeneration clinically. Acosta et al. [44] injected injured porcine discs with allogeneic MSCs. Discs were then harvested at 3, 6, and 12 months. At all followups, no viable MSCs or proteoglycan synthesis as observed. One reason postulated for this includes the larger disc size and therefore greater nutrient restriction present in the porcine model as compared to small animal models. This larger disc size more closely mimics the conditions in adult human IVDs, where nutrients must travel up to 8 mm from the terminal end of the blood vessel to cells in the center of the disc [23].

5. Future Directions

5.1. Critique of Current Studies. A notable criticism of current studies involving *in vivo* implantation of MSCs is that they do not accurately replicate the environment of the human degenerate disc. This is true for several reasons. Firstly, in all *in vivo* studies to date, MSCs have been implanted either into unmodified, healthy, young discs [47, 52, 53, 55] or into discs where degeneration was simulated by aspiration of the NP [44, 48, 49, 51] or annular injury [50, 54]. While these techniques have been shown to induce degeneration of the NP and AF as evidenced through MRI [72], there is no evidence that they lead to the EP damage typical in painfully degenerated IVDs, damage which likely impairs nutrient diffusion. Lack of nutrients has been found to impair ECM synthesis [24, 25] and poor EP permeability is highly correlated with morphologic and biochemical degeneration [73]. The central role of nutrition in the efficacy of MSC treatment is further implicated in the results of Acosta et al. [44], where it was hypothesized that the relatively larger discs of minipigs compromised nutrient diffusion and prevented the survival of implanted MSCs. Based on current research, it is unclear whether repopulation without nutritional supplementation will lead to effective matrix anabolism. In the future, development of a standardized *in vivo* model that more accurately mimics disc degeneration in humans would allow for more meaningful study of all therapies targeting molecular and cellular components of degeneration.

It is also worth noting that the histological and morphological slowing and reversal of IVD degeneration may not necessarily relieve low back pain. In fact, this was the outcome of one clinical study using MSCs to repair cartilage in osteoarthritis patients. Although biopsy and arthroscopic observation demonstrated new cartilage growth, no significant clinical improvement was reported [74, 75]. At present there exists no animal model for low back pain, making the therapeutic benefit of NP regeneration challenging to study [76]. The clinical benefit of restoring matrix integrity must be further explored.

5.2. Obstacles in Translation to Clinical Use. Before stem cells can be adequately and efficiently used in IVD degeneration, it is imperative that the mechanisms of pathogenesis are more clearly understood in order to answer many questions that have been left from previous studies. The absence of an animal model for low back pain involving IVD degeneration makes it difficult to truly study and assess the effectiveness of cell therapy. It has previously been studied that the degenerating IVD creates a harsh environment by decreasing nutrient supply from the EP, increasing the acidity of the microenvironment and elevated inflammatory substances [19, 74]. This hardly is the ideal environment required for a successful graft, not only can cell survival be impaired but the MSC's differentiation may be altered in an unknown way.

Another difficulty is establishing which patients are candidates for MSC therapy. A patient with a Thompson of 4-5 most likely would not be a candidate due to the extreme microenvironment [67]. It should be considered that 20–50% of asymptomatic patients have radiological signs of IVD degeneration raising the question of the timing of the treatment [74]. Early treatment may perhaps be the difference from symptom relief and failed therapy, regardless of cell survival and proliferation. Two clinical trials show different results on symptomatic relief in patients with IVD degeneration after undergoing stem-cell transplantation. A Thompson score of 2-3 might be the ideal candidate for MSC therapy, but this remains to be studied.

Combination therapy, providing supportive matrix and bioactive substances, may possibly be the best treatment required, optimizing cell survival, proliferation, and differentiation [55, 74]. Several growth factors described in previous studies have been implicated in IVD degeneration and therapy. MSCs secreting transforming growth factor-beta (TGF-β), Insulin-like growth factor-1 (IGF-1), and platelet-derived growth factor (PDGF) have been found in cocultures with NP cells and have been shown to be an effective stimulator on matrix metabolism and cell proliferation during biological repair of IVDs [13, 67]. Growth and differentiation factor-5 has been shown to increase disc height and stimulate proliferation and matrix synthesis in the NP and AF. Furthermore, Henriksson et al. found endogenous stem cell niches in the AF border to the ligament zone and the perichondrium region [21]. The utilization of growth factors may stimulate proliferation of these endogenous stem cells. It is reasonable to assume that injection of naked growth factors within the scaffold containing the MSCs at time of transplantation may increase graft survival and cell proliferation and differentiation into NP. Bringing into question what type of scaffold if any is the most adequate for transplantation. Immunogenicity, architectural and mechanical properties along with biocompatibility, biodegradability, and method of graft delivery need to be considered when choosing the scaffold [76]. Dosing studies will also need to be done in order to determine the cell density and volume that will need to be transplanted in order to obtain the desired effect

while causing the least amount of side effects. Moreover, to be determined will be the need for subsequent treatments or if one time treatment will suffice.

Given that the IVD is considered immunoprivileged, the need to find an autologous cell origin might not be necessary [7, 67]. Although this should be studied further to ascertain if an immunosuppressive regimen will be needed and for how long.

One last consideration is the ideal culture conditions of the MSCs. First of all, in order to be used for clinical trials it must be done in GMP grade conditions with xeno-free reagents. Coculture of NP cells with MCS may be necessary in order to enhance the biological and metabolic viability of the cells [67]. It is important to consider that *in vitro* expansion can lead to an accumulation of genetic and epigenetic changes with an unknown effect *in vivo* once transplanted. The changes may lead to increased immunogenicity even when autologous or malignant transformation.

6. Conclusion

It is evident that there are many questions left unanswered. In order to move forward in finding an effective therapeutic option for IVD degeneration-associated back pain, they will need to be studied further. One of the main obstacles is creating an animal model that can adequately replicate the microenvironment seen in IVD degeneration. Once an animal model is established, more preclinical data will be able to be collected in a directed way with adequate conditions.

Authors' Contribution

D. Drazin and J. Rosner contributed equally to this paper. They are coauthors.

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Clinical Study

The Memory Metal Minimal Access Cage: A New Concept in Lumbar Interbody Fusion—A Prospective, Noncomparative Study to Evaluate the Safety and Performance

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Study Design/Objective. A single-centre, prospective, non-comparative study of 25 patients to evaluate the performance and safety of the Memory Metal Minimal Access Cage (MAC) in Lumbar Interbody Fusion. *Summary of Background Data*. Interbody fusion cages in general are designed to withstand high axial loads and in the meantime to allow ingrowth of new bone for bony fusion. In many cages the contact area with the endplate is rather large leaving a relatively small contact area for the bone graft with the adjacent host bone. MAC is constructed from the memory metal Nitinol and builds on the concept of sufficient axial support in combination with a large contact area of the graft facilitating bony ingrowth and ease in minimal access implantation due to its high deformability. *Methods*. Twenty five subjects with a primary diagnosis of disabling back and radicular leg pain from a single level degenerative lumbar disc underwent an interbody fusion using MAC and pedicle screws. Clinical performance was evaluated prospectively over 2 years using the Oswestry Disability Index (ODI), Short Form 36 questionnaire (SF-36) and pain visual analogue scale (VAS) scores. The interbody fusion status was assessed using conventional radiographs and CT scan. Safety of the device was studied by registration of intra- and post-operative adverse effects. *Results*. Clinical performance improved significantly ($P < .0018$), CT scan confirmed solid fusion in all 25 patients at two year follow-up. In two patients migration of the cage occurred, which was resolved uneventfully by placing a larger size at the subsequent revision. *Conclusions*. We conclude that the Memory Metal Minimal Access Cage (MAC) resulted in 100% solid fusions in 2 years and proved to be safe, although two patients required revision surgery in order to achieve solid fusion.

1. Introduction

Chronic low back pain is an insidious problem. Individuals suffer from prolonged discomfort, anxiety, and disability. Low back pain has been shown as the leading cause of man-hours lost to disease or injury. Degeneration of the intervertebral disc is the most common cause of low back pain [1].

Conservative treatment for low back pain may include rest, heat, physical therapy, medication, bracing, and education. Most individuals will find relief given conservative treatments. However, for those with significant continuing specific symptoms, surgical intervention may be appropriate. One of the interventions is posterior lumbar interbody fusion (PLIF). The goal of spinal fusion is to obtain a solid arthrodesis. There is a wide range of fusion rates (56–95%) reported after PLIF with varying techniques [2–14].

The PLIF procedure was introduced independently by Jaslow [15] and Cloward [2, 16–18] in the 1940s to treat painful intervertebral disc damaged by degeneration or herniation. A PLIF has the advantages over other types of fusion allowing neural decompression while in the meantime restoration of the disc height, and segmental alignment is maintained [19].

In order to eventually achieve a solid interbody fusion a bone substitute has to be applied to the disc space. Without a mechanical support, these grafts tend to collapse, displace, or

Figure 1: Memory Metal Minimal Access Cage (MAC).

extrude [20–22]. For this reason, various metal and carbon fibre interbody cages have been developed [3, 23, 24]. Interbody fusion cages aim to fulfil both mechanical and biological requirements for fusion, in that the cages are designed to withstand high axial loads [19, 25, 26], and in the meantime to allow ingrowth of vital host bone. Although cages have rapidly become popular, the mismatch in the modulus of elasticity between many available metal cages and the actual vertebral body may cause stress shielding, resulting in a delayed fusion and eventually pseudarthrosis [27, 28]. Carbon fiber cages better approximate this modulus of elasticity of the vertebral bone; however, there are some reports on carbon fiber release causing synovitis [29]. The titanium implants developed by Kuslich et al. [23] and Ray [24] offer a radio-opaque alternative to carbon fibre materials that also exhibit the necessary biomechanical strength as well as facilitating the cage to be located radiographically. Their open design means that the bone is exposed to a greater graft surface area that has been shown to facilitate good bony in growth. However, the problem with most cages is the small contact area of the bone graft and, therefore, a high rate of pseudoarthrosis.

The Memory Metal Minimal Access Cage (MAC) builds on the concept of sufficient axial support in combination with a large contact area of the graft facilitating bony ingrowth and ease in minimal access implantation due to its high deformability. The MAC cage is a horseshoe-shaped implant. It confers the ability for fast and solid fusion due to the large contact area. The MAC cage is constructed from the memory metal nitinol (Figure 1). This device has the same modulus of elasticity as the vertebral body [30], allows a large bone surface contact area from the graft, and its high deformability will facilitate less invasive implantation in the future (Figure 2). Earlier biomechanical testing revealed an adequate subsidence resistance in human lumbar spine, comparable to or even better than the Harms cage [30]. The use of memory metals and their biocompatibility has already been described in earlier medical applications [31], as are the safety considerations [32].

The purpose of this pilot study was to evaluate the performance and safety of this new interbody fusion device in a relatively small group of patients.

2. Materials and Methods

2.1. Patients. Twenty-five consecutive patients (11 male and 14 female) with a diagnosis of a symptomatic single level degenerative lumbar disc consented to participate in the study, following Research Ethics Committee approval. The average age of the patients was 41.3 (range 23.8–71.4) Inclusion criteria required all patients aged 18 years and over, with disabling back and/or refractory radicular pain who have had at least six weeks of conservative management, with moderate-to-severe degenerative changes in one or two lumbar disc levels based on MRI performed not more than three months prior to study entry. In addition, discography had been provocative for patients back pain. Exclusion criteria ruled out patients with more than two abnormal lumbar disc levels, evidence of infection in the disc or spine, spinal tumor(s), who are immunocompromised, pregnant, and/or have a condition which would compromised their participation and followup in this study. Conservative treatment mostly entailed a combination of appropriate analgesics, physical therapy, and epidural and/or facet injections.

2.2. Implant Features and Surgical Procedure. The Memory Metal Minimal Access Cage has a horseshoe shape and comprises a material strip of 1.08 mm thickness for the small sizes, and 1.25 mm for the medium and large sizes. All cages have diamond-shaped holes for bone through growth, spikes on the top and bottom edges for stability, and a wedged profile. The diamond-shaped hole design aspect of the MAC is in line with surgical titanium mesh for similar product appearance, and seats on the bony outer cortical rim of the vertebral body.

The cages are made of nitinol, a shape memory alloy, which enables the surgeon to un-curve the strip completely, put it into an inserter, and insert it into the disc space while pushing it out of the inserter. The flat strip will henceforth curve into the original horseshoe shape (Figure 2). All surgeries were performed by two experienced spine surgeons between January 2004 and Oktober 2006. A standard PLIF procedure was performed using the Monarch TM pedicle screw system (DePuy International) where after the MAC cage was placed anteriorly in the intervertebral disc space (Figure 2), and locally available decompressive autologous bone was subsequently grafted into the disc space.

2.3. Clinical and Radiological Outcome. Patients were evaluated preoperatively at 1, 3, 6, 12, and 24 month after surgery. Evaluation at each interval included physical and neurological examination, concomitant medication, additional surgical procedures, subject completed questionnaires (Oswestry Disability Index, Short Form-36 Health), and Visual Analogue Scale for Pain. Any adverse events and complications were recorded in the case report forms.

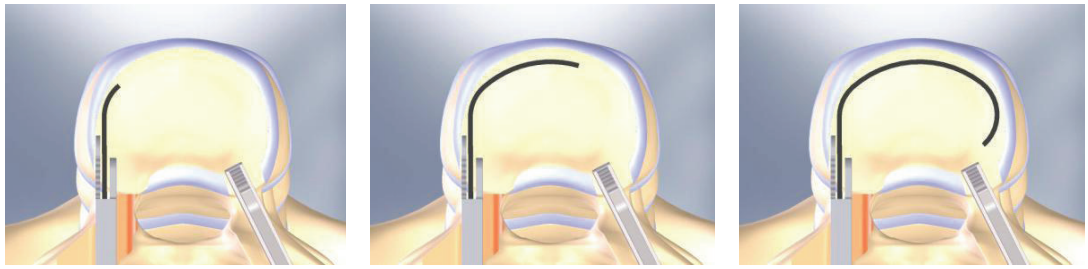

Figure 2: Implantation technique.

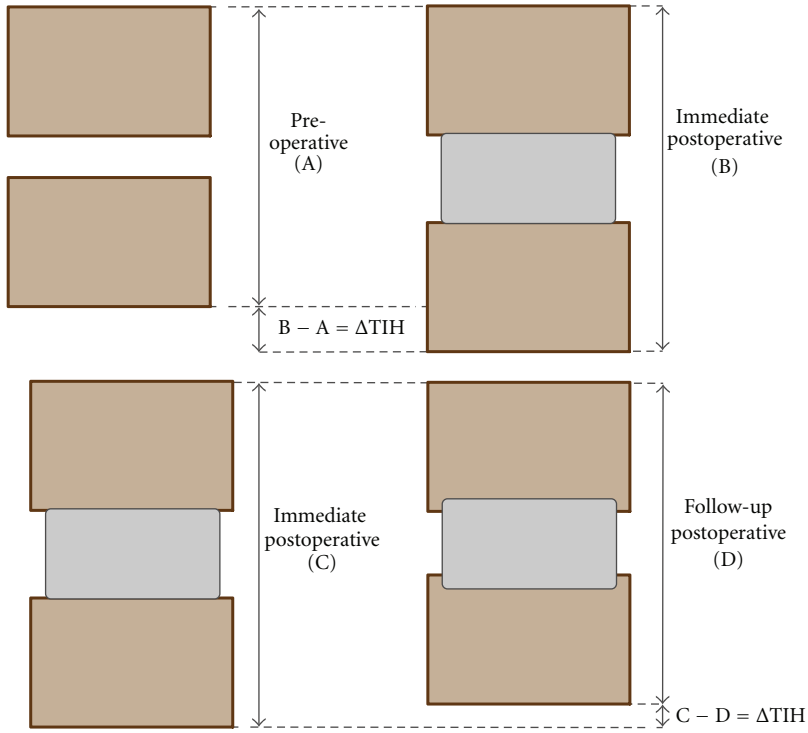

Figure 3: Measurement of the subsidence and total intervertebral height.

Routine lateral and AP radiographs were obtained at each timer interval. Routine radiographs were used to evaluate the total intervertebral height and subsidence. The CT scan at two years followup was used to establish fusion. The total intervertebral height (TIH) of two fused vertebral bodies was measured as distance between the mid-point of upper end plate of cranial vertebral body and the mid-point of lower end plate of caudal vertebral body on digital radiographs with built-in software (PACS viewer). The degree of subsidence (ΔTIH) was reflected by the difference between the immediate postoperative and follow-up TIH (Figure 3). With the same method, change of postoperative disc space height was reflected by the difference between TIH of the postoperative lateral plain radiograph and that of the preoperative lateral plain radiograph (Figure 3). Interbody fusion was defined as complete bridging at any one or more points within the central area of the vertebral body as determined by CT. Intervertebral fusion assessments were determined by one independent radiologist who was not otherwise involved in the study. Fusion was recorded as Yes/No/Can't Assess.

Complications were divided into device-related and non-device-related complications. Non-device-related complications were listed as major and minor.

2.4. Statistics. For statistical analysis, comparisons between pre- and postoperative scores were made using paired t tests.

3. Results

3.1. Radiological Assessment. The primary radiological objective was fusion rate. Fusion success was achieved in 25 (100%) of 25 patients. There was a solid bony fusion on CT at 2 years postoperative. The disc space height was restored to normal as part of the operative procedure. Disc height in the cage levels was increased from an average of 7.6 mm

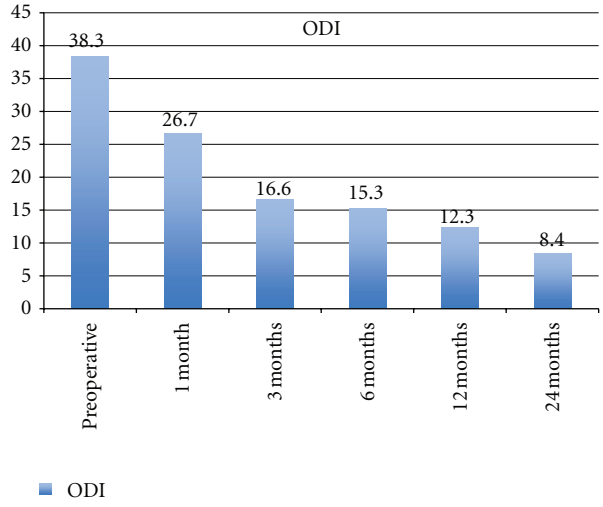

Figure 4: Oswestry Disability Index at baseline and 1, 3, 6, 12, and 24 months after operation.

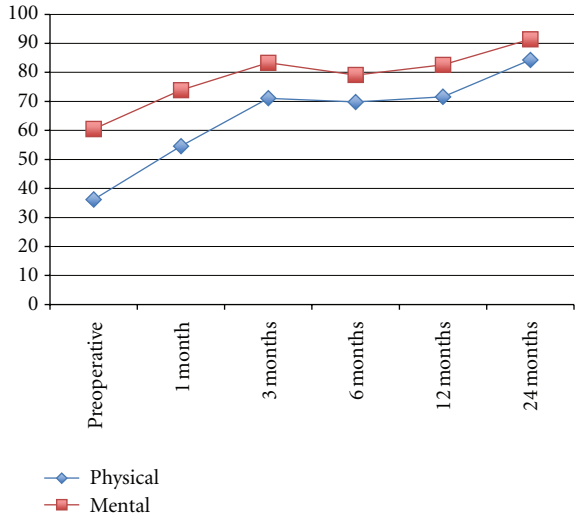

Figure 5: Short Form 36 (SF-36) Health Questionnaire (Physical and Mental) at baseline and 1, 3, 6, 12, and 24 months after operation.

before surgery to an average of 12.4 mm after surgery losing 0.0 mm during healing in 2 years of followup.

3.2. Clinical Data. All 25 patients completed the 24 months of follow-up without any major adverse event. The clinical parameters are summarized Figures 4, 5, and 6.

The clinical outcome was the ODI score at 24 months posttreatment compared to baseline. The mean ODI score preoperative was 38.32 ± 10.64. This significantly improved to 8.4 ± 9.49 at 24 months postoperative ($P < .0001$).

The Short-Form 36 health questionnaire (SF-36) data assessed both physical and mental components. Physical (PCM) 36.15 ± 18.93 improved to 84.25 ± 22.29 ($P < .0001$) and mental (MCM) 60.54 ± 24.22 improved to 91.36 ± 12.76 ($P < .0001$). Pain assessment (both leg and back) by Visual

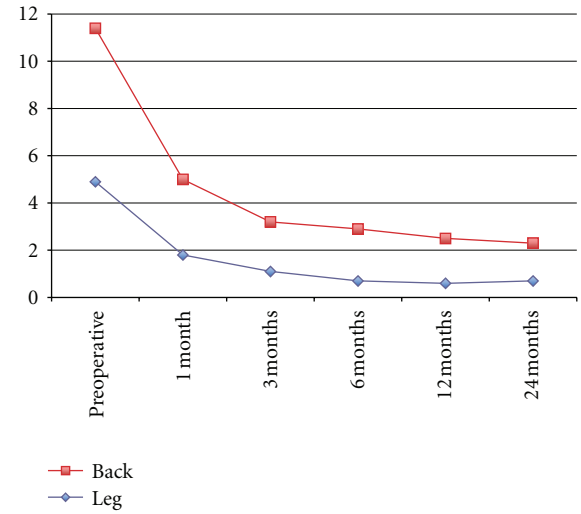

Figure 6: Pain Visual Analogue Scale (VAS) (Leg and Back) at Baseline and 1, 3, 6, 12, and 24 months after operation.

Analogue Scale (VAS) was also performed. Both leg and back pain improved significantly ($P < .0001$).

Bivariate analysis indicated that gender, previous nonsurgical treatment, smoking history, and obesity had no statistical effect on clinical or fusion success.

3.3. Safety. In two patients, an undersized implant was used, resulting in migration of the MAC cage, 1 day postoperatively, which required reoperation.

One patient had a myocardial infarction several days after surgery. There were no deaths or deep infections. There were 4 intraoperative dural penetrations in patients who had previous lumbar operations.

4. Discussion

In this study, a prospective followup on clinical and radiographic parameters was performed in patients with a single level spondylodesis using a new interbody cage design.

4.1. Radiological Assessment. Radiological assessment indicated that there was a 100 percent interbody fusion with the MAC device at 2 years on CT with no subsidence.

Previous studies [2, 4, 24, 33–38] report of PLIF fusion success with fusion in 85% of the cases. The difficulty in determining fusion success by standard roentgenographic methods was emphasized by Hibbs and Swift in 1929 [39], Cleveland et al. in 1948 [40], Prothero et al. in 1966 [41], Stauffer and Coventry in 1972 [42], Chow et al. in 1980 [43], Zinreich et al. in 1990 [44], and Brodsky et al. in 1991 [45]. The recent use of pedicle screw fixation has added to the problem, because overlying shadows of the implants impaired radiographic visualization of posterolateral fusion mass [13, 46]. Santos et al. in 2003 [47] emphasized that there is an overestimation of fusion on plain radiograph compared to CT.

In order to make a good estimation on interbody fusion, we used CT in this study. Previous studies on interbody

fusion, reported significant loss of disc space height during healing of interbody grafts [2, 5, 22, 48–51]. In past reports, even pedicle screw stabilization has not prevented this loss of disc space height during the healing of interbody fusion. [4, 5, 48] Loss of disc space height creates foraminal narrowing and the potential for nerve root compression. The fact that we recorded 100 percent fusion on CT and no subsidence is an advantage over other interbody fusion devices.

4.2. Clinical Data. Numerous studies have provided subjective descriptions of criteria for excellent, good, fair, and poor results [36, 46, 52–57]. We use the ODI as our primary clinical objective because the ODI is valid and vigorous measure and has been a worthwhile outcome measure [58, 59].

The Oswestry Disability Index mean score preoperatively was 38.32 ± 10.64. This significantly improved to 8.4 ± 9.49 at 24 months postoperative. Significant improvement in both physical and emotional components in the SF-36 questionnaires mean scores was also observed, with increases from baseline results of 36.15 ± 18.93 and 60.54 ± 24.22 to 84.25 ± 22.29 and 91.36 ± 12.76 at 24 months, respectively ($P < .0001$). The average level of leg pain was reduced by more than 50% after operation (VAS values reduced from 4.88 ± 2.96 to 1.78 ± 1.97 at 1 month after operation). This reduction further improved over the 24 months after operation (0.73 ± 1.31 at 24 month after operation). A similar reduction in back pain was also revealed. With both ODI and SF-36 results, improvement in condition continued throughout the 24 months after operation. Pain results indicated a rapid improvement after operation, which was maintained during the 24 months after operation.

A study of 60 patients with posterior lumbar interbody fusion combined with instrumented posterolateral fusion reported by Freeman et al. [60] indicated stable circumferential fixation as shown by radiographs and tomograms confirming the presence of a bridging fusion mass. Of the 48 ODI questionnaires completed after 5 years, 79% had an ODI <30. In the present study, 96% (24/25) of the patients indicated an ODI < 30. McKenna et al. reported a prospective, randomized controlled trial of femoral ring allograft (FRA) versus a titanium cage (TC) in circumferential lumbar spinal fusion with minimum 2 years clinical results [61]. Comparison of change in ODI results indicated a significantly larger improvement in the FRA group (reduced from 57 to 42) when compared to the TC group (54 reduced to 48). The corresponding change in ODI results from baseline over 2 years in the current study was larger than that of either the FRA or TC groups (35 versus 15 and 6). SF-36 results for the FRA patients showed a significant improvement in the Physical Function Component but not in the Mental Component (change in SF-36 results of 17 and 2 resp.). In the TC patients, the reverse was found (change in SF-36 results of 5 and 9 for Physical Function and Mental Components, resp.). The MAC in comparison gave a much greater improvement in both SF-36 results (change in SF-36 results of 63.1 and 27 for Physical and Mental Components, resp.). Both FRA and TC patients showed a significant improvement in VAS for back pain (change in VAS 1.9 and 1.1, resp.). However, with leg pain VAS scores only FRA patients demonstrated a significant improvement (change in VAS of 1.3), whereas the TC group had more leg pain increasing the VAS scores postoperatively by 0.4 points. In our study, we found a significant reduction in both back and leg pain. With the MAC, the back and VAS results were reduced by 6.4 and 5.8 points, respectively. This indicates a significant improvement compared to the McKenna study. Cassinelli et al. published a prospective clinical study of revision fusion surgery in 19 patients with pseudoarthrosis who had received posterior lumber interbody fusion using stand-alone metallic cages [62]. SF-36 and ODI data were collected prior to surgery and two years postoperatively. Significant improvement was only noted in two of the eight SF-36 subcategories (Physical Functional and Role Mental). There was no significant difference in ODI scores. A study with two different patient groups of 30 subjects having spondylolisthesis which were subjected to different surgeries: posterior lumbar fusion with pedicle screws (Group I) and posterior lumbar interbody fusion with pedicle screws (Group II) has also been reported [63]. The ODI mean scores preoperatively and 2 years postoperatively were 28.5 and 18.6, respectively for, Group I and 31.3 and 13.3, respectively, for Group II. The ODI scores in the current study show a greater improvement. Glassman et al. reviewed the ODI and SF-36 outcomes in a multicentre lumbar fusion study with followup after 2 years [64]. The minimal clinically important difference (MCID) seeks to differentiate a magnitude of change, which is not only statistically valid but also of real clinical value. Figures for MCID for ODI results have been reported as low as a 4-point decrease [65] and also a 10-point decrease [65]. The Food and Drug Administration (FDA) standards suggest a 15-point decrease in ODI and either maintenance of or any improvement in SF-36 Physical Composite Score (PCS) [66]. Ware et al. [67] reported that an increase of 5.42 points in the SF-36 PCS is clinically important. A more recent study [68] has reported the following MCID values: 12.8 points for ODI, 4.9 points for SF-36 PCS, 1.2 points for back pain, and 1.6 points for leg pain. The improvement in ODI values for the various fusion treatments in the multicentre review ranged from 9.9 to 22.2 points, whereas the improvement in SF-36 data ranged from 13.8 to 6.3 points. The improvement in the corresponding ODI and SF-36 values in the current MAC study were 29.92 and 39.46. The improvement in back and leg pain were 4.88 and 4.15, respectively. In general, the ODI and VAS improved in all PLIF-procedures, according to the literature. The results obtained for the MAC have, therefore, satisfied the MCID reported in the literature.

4.3. Safety. The device-related adverse event recorded in this study was two undersized cages, resulting in migration.

The migration problem lies within the operation technique.

The dural penetrations all developed during decompression in patients who were previously operated on, not during cage insertion, and were repaired at surgery, not requiring reoperation, not causing neurologic injury, and not affecting the hospital course.

5. Conclusion

The Memory Metal Minimal Access Cage performed very well radiographically and clinically. There was a 100 percent interbody fusion at 2 years on CT, no subsidence and significant improvement of clinically important outcomes, although two patients required revision surgery in order to achieve solid fusion.

Key Points

(i) The Memory Metal Minimal Access Cage (MAC) was implanted in humans for the first time and showed 100 percent fusion after two years, confirmed by CT.

(ii) The MAC is safe for implantation into humans with disabling back and/or refractory radicular pain with moderate-to-severe degenerative change in one or two lumbar disc levels based on MRI.

(iii) The MAC performed very well by improving clinically important outcomes. The Oswestry Disability Index significantly improved from 38.32 ± 10.64 preoperatively to 8.4 ± 9.49 at 24 months postoperatively.

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Review Article

Minimal Invasive Decompression for Lumbar Spinal Stenosis

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Lumbar spinal stenosis is a common condition in elderly patients and may lead to progressive back and leg pain, muscular weakness, sensory disturbance, and/or problems with ambulation. Multiple studies suggest that surgical decompression is an effective therapy for patients with symptomatic lumbar stenosis. Although traditional lumbar decompression is a time-honored procedure, minimally invasive procedures are now available which can achieve the goals of decompression with less bleeding, smaller incisions, and quicker patient recovery. This paper will review the technique of performing ipsilateral and bilateral decompressions using a tubular retractor system and microscope.

1. Introduction

Lumbar spinal stenosis remains the most common indication for spinal surgery in elderly patients [1–8]. Lumbar spinal stenosis is a pathologic state where the dural sac and nerve roots are compressed by a combination of degenerative features including bulging of the intervertebral discs, hypertrophy of the facet joints, and thickening/buckling of the ligamentum flavum. The clinical symptoms of this condition include back and leg pain, muscular weakness, sensory disturbance, and/or problems with ambulation [9]. Although the severity of clinical symptoms varies widely, some patients may experience disabling symptoms which required medical intervention [1–5, 10, 11]. The traditional surgical approach for lumbar stenosis has been to perform a wide, bilateral decompressive laminectomy along with resection of the medial portion of the facet joints to decompress the affected neural elements [7, 8, 12, 13]. Although this approach can successfully alleviate nerve compression symptoms, there are drawbacks of the open approach, including amount of soft tissue dissection, blood loss, postoperative pain, and the potential for iatrogenic instability of the spinal segment [14]. These concerns are magnified when treating an elderly fragile patient.

The use of a tubular retractor system for lumbar surgery was popularized by Foley and Smith [15]. As experience has grown with this surgical approach, surgeons are routinely treating patients with lumbar stenosis using a combination of a tubular retractor system and an operative microscope. This approach requires less soft tissue destruction compared to an open lumbar decompression [9, 16, 17]. As a result, the surgeon can expect less bleeding, less postoperative pain, and a reduced risk of iatrogenic instability. Surgery with a tubular retractor system is especially beneficial in elderly patients where there are concerns regarding the physiologic stress and risks of a traditional open surgical approach [2].

This paper will review the operative techniques for treating lumbar stenosis with a tubular retractor system and operative microscope.

2. Surgical Setup

The procedure is typically performed under general anesthesia, although epidural or spinal anesthesia can be used according to surgeon preference. Prophylactic antibiotics and lower extremity compression stockings are provided at the initiation of the procedure. The patient is positioned prone

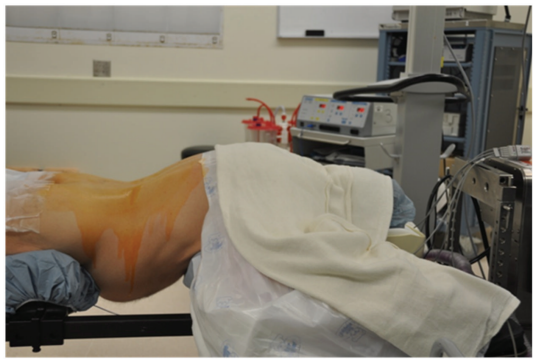

Figure 1: Positioning of the patient in the prone position on a radiolucent operative table.

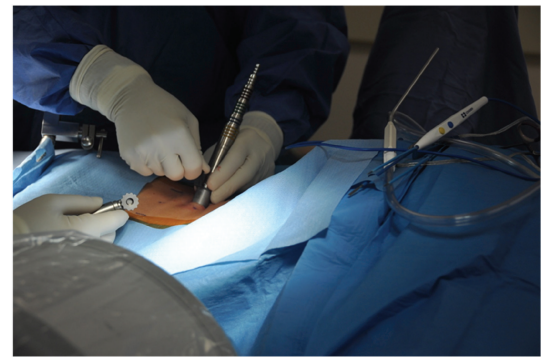

Figure 3: Serial dilation of the soft tissue corridor and placement of the correct length tubular retractor.

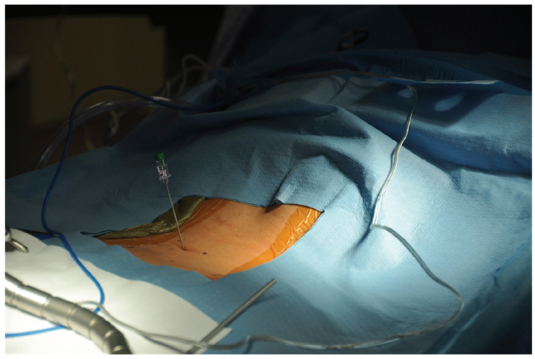

Figure 2: demonstrates a spinal needle introduced at the proposed location of the surgical incision.

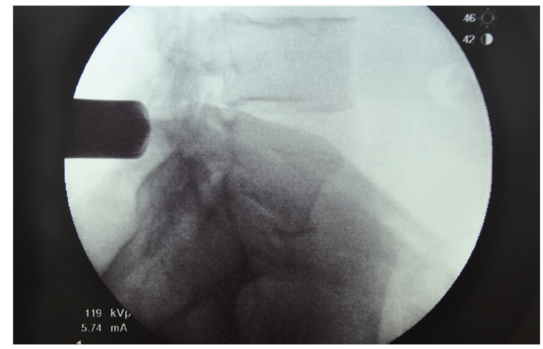

Figure 4: shows the position of the tubular retractor using lateral fluoroscopy.

on a radiolucent spinal frame which allows decompression of the abdomen and access for fluoroscopic imaging (Figure 1).

3. Surgical Approach

After a sterile prep and drape, the location of the spinous processes and iliac crests are marked out on the skin as a guide when localizing the surgical incision. A spinal needle is introduced at the proposed location of the surgical incision, and lateral C-arm fluoroscopy is used to check the position of the needle relative to the site of the neural compression (Figure 2). After confirming correct localization of the needle, the surgical incision is made lateral to the spinous processes. For ipsilateral decompression, the skin incision should be placed about 2 cm lateral to the midline, while bilateral decompression requires an incision about 3 cm lateral to the midline to allow angulation of the tubular retractor to reach the contralateral side of the spinal canal. The length of the incision should be equal to the diameter of the tubular retractor to be used. The authors prefer to use an 18–20 mm outer diameter tubular retractor when performing a decompressive procedure for lumbar stenosis. The thoracolumbar fascia should be sharply incised in line with the skin incision. Next, a small Cobb elevator is placed through the incision down to the spinal lamina, and subperiosteal elevation of muscle tissues away from the lamina is performed. Serial dilation of the soft tissue corridor is carried out followed by placement of the correct length tubular retractor (Figure 3). It is important to be sure that the tubular retractor is firmly seated against the bone of the lamina before securing the tube with a table-mounted retractor holder. Next, a lateral fluoroscopic image is used to confirm correct localization of the tubular retractor (Figure 4).

The operative microscope is then used to visualize the operative field at the base of the tubular retractor (Figure 5). Any residual soft tissues are removed with electrocautery to expose the lamina and medial edge of the facet joint prior to proceeding (Figure 6).

4. Ipsilateral Decompression

A curved curette is used to separate the ligamentum flavum from the undersurface of the lamina (Figure 7). Then, the ipsilateral lamina is removed with a Kerrison rongeur or high-speed drill/burr. The laminotomy should progress to the cranial edge of the ligamentum flavum. If only the ipsilateral side requires decompress, the ligamentum flavum is then removed. However, if bilateral decompression is required (see below), the ligamentum flavum is left intact until after the drilling maneuver has been completed across to the contralateral side. After removal of the ligamentum

Figure 5: shows operative microscope used to visualize the operative field.

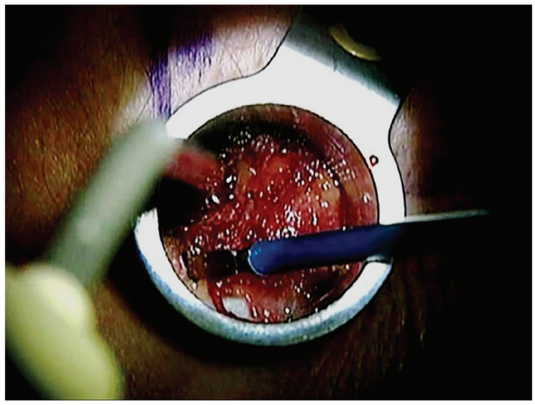

Figure 6: Residual soft tissues are removed with electrocautery to expose the lamina and medial edge of the facet joint.

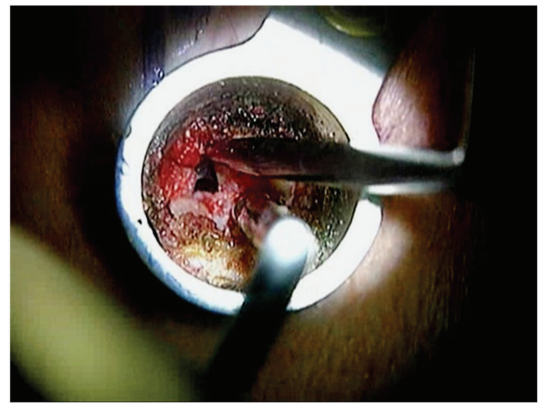

Figure 7: A curved curette is used to separate the ligamentum flavum from the undersurface of the lamina.

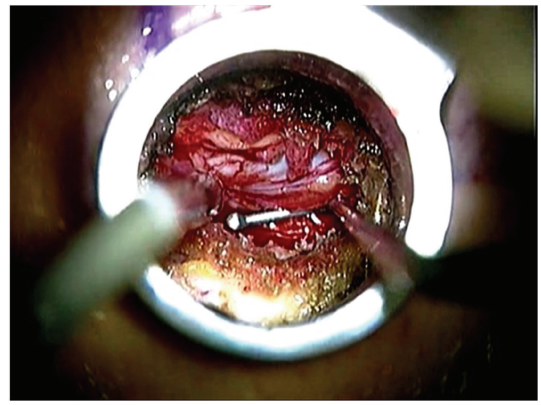

Figure 8: A ball-tipped probe is used for the palpation during and at the end of the decompression procedure.

flavum, the pedicle (as a landmark) is examined by palpation with a ball-tipped probe for identification of the spinal pathology, the medial portion of the facet joint is trimmed as needed to achieve decompression of the lateral recess. The overlying inferior articular process may need to be thinned with a high-speed drill/burr, but care should be taken to preserve adequate bone stock in this region so as to reduce the risk of an iatrogenic fracture. A curved tip kerrison rongeur is used to undercut the lateral recess while preserving the overlying bone stock of the facet complex. The ipsilateral foramen is decompressed by resecting the superior tip of the superior articular process as needed to decompress the exiting nerve root. The disc space is examined, and any herniated disc fragments are removed. Finally, the adequacy of decompression is confirmed with the use of a ball-tipped probe (Figure 8). Hemostasis of the wound is then achieved prior to removal of the tubular retractor system.

5. Contralateral Decompression

When a bilateral decompression is required, the tube is angled (wanded) to the contralateral side after the ipsilateral lamina has been opened (but prior to resection of the ligamentum flavum). The operative table can be angled away from the surgeon and the operative microscope repositioned to provide visualization at the base of the spinous process. Next, a high-speed drill/burr is used to drill away the ipsilateral base of the spinous process dorsal to the ligamentum flavum. Bone bleeding in this region is controlled with bone wax. A small currette is used to separate the ligamentum flavum from the contralateral lamina, and the drilling is continued through the contralateral lamina until the contralateral facet joint is reached. It is important to note that a bone bridge is left connecting the contralateral base of the spinous process and dorsal surface of the contralateral lamina. The "internal laminectomy" is continued along the contralateral lamina until the contralateral facet joint is reached. The medial portion of the contralateral facet is thinned until it can be successfully undercut with a Kerrison Rongeur to adequately decompress the lateral recess and foraminal area. After the drilling maneuver is completed, the ligament flavum is separated from its bony attachments and removed. Under direct visualization of the neural elements, any remaining bony or ligamentous compression is alleviated. The adequacy of the decompression is confirmed with a ball-tipped probe. After completion of the contralateral decompression, the tubular retractor is adjusted (wanded) back to the ipsilateral side, and the decompression of the ipsilateral side is completed as described above.

6. Wound Closure and Aftercare

The fascia, subcutaneous tissues, and skin are closed in a routine fashion. A skin sealant is placed along the skin edges to allow early showering. The subcutaneous tissues are injected with a long-acting local anesthetic to reduce incisional pain, followed by placement of a small dressing.

Patients are mobilized after recovery from anesthesia and discharged on the same day as surgery (in most cases). Early return to ambulation and normal activities of daily living is encouraged. Pain management is generally provided by either a mild oral narcotic or an over-the-counter analgesic depending on the preferences of the patient. Rehabilitation with core muscle stabilization and aerobic activities are encouraged in the early postoperative period.

7. Complications

Although the list of potential complications with tubular decompression is no different from traditional open surgery, the rate of certain complications is significantly reduced. For instance, blood loss, wound infection, iatrogenic instability, and medical deterioration following lumbar decompression using a tubular retractor system are lower compared to open laminectomy [9, 16, 17].

Dural laceration (incidental durotomy) may be managed with either suture repair or dural sealants depending on the location, size, and severity of the durotomy. One report found the incidence of durotomy to be 16%, although no long-term sequelae were noted [9]. Because exposure with the tubular retractor systems produces minimal "dead space," the risk of postoperative dura-cutaneous fistula is reduced with tubular retractor-based surgery in comparison to traditional laminectomy. Small, stable tears may be successfully managed with a small pledget of a hemostatic agent followed by a dural sealant (e.g., fibrin glue). Larger tears or tears with exposed nerve root should be treated with direct suture repair. Although technically demanding, this can be achieved using a small needle and micropituitary instrument as the needle driver and an arthroscopic knot pusher to assist with knot typing. In most cases, prolonged bed rest is not required for patients after a satisfactory dural repair [18].

Infection rates following tubular access surgery are low [19]. In the rare event of a wound infection, treatment with debridement and antibiotic therapy should be instituted. Due to the lack of prolonged anesthesia, heavy blood loss and prolonged bed rest, medical complications after tubular access decompression, are uncommon even in the elderly population [2].

8. Conclusion

With the use of a tubular retractor system and microscope, lumbar stenosis can be successfully treated in the majority of patients. This approach has significant advantages when compared to traditional laminectomy including reduced blood loss, reduced hospitalization, reduced infection, and quicker postoperative recovery. As with all new surgical techniques, an operative learning curve should be anticipated. The learning curve may be successfully managed by supervised cadaver training, surgical visitations and/or formal surgical mentorship. Additionally, it is recommended that the surgeon proceed in a slow, deliberate fashion from simple to more complex cases. Outcome studies have consistently documented favorable results with tubular-based decompression surgery, making this technique worth adding to a surgeon's repertoire.

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Clinical Study

Lateral Interbody Fusion for Treatment of Discogenic Low Back Pain: Minimally Invasive Surgical Techniques

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Low back pain is one of the most common ailments in the general population, which tends to increase in severity along with aging. While few patients have severe enough symptoms or underlying pathology to warrant surgical intervention, in those select cases treatment choices remain controversial and reimbursement is a substancial barrier to surgery. The object of this study was to examine outcomes of discogenic back pain without radiculopathy following minimally-invasive lateral interbody fusion. Twenty-two patients were treated at either one or two levels (28 total) between L2 and 5. Discectomy and interbody fusion were performed using a minimallyinvasive retroperitoneal lateral transpsoas approach. Clinical and radiographic parameters were analyzed at standard pre- and postoperative intervals up to 24 months. Mean surgical duration was 72.1 minutes. Three patients underwent supplemental percutaneous pedicle screw instrumentation. Four (14.3%) stand-alone levels experienced cage subsidence. Pain (VAS) and disability (ODI) improved markedly postoperatively and were maintained through 24 months. Segmental lordosis increased significantly and fusion was achieved in 93% of levels. In this series, isolated axial low back pain arising from degenerative disc disease was treated with minimally-invasive lateral interbody fusion in significant radiographic and clinical improvements, which were maintained through 24 months.

1. Introduction (Succinct)

Intervertebral disc degeneration in the spine is natural process of aging and in many cases is asymptomatic [1]. However, low back pain (LBP) is strongly associated with lumbar disc degeneration [2]. LBP is one of the most common reasons for physician visits and loss of workplace productivity worldwide, thus the issue encompasses important clinic and socioeconomic consequences.

Conservative (nonoperative) care for LBP, while covering many different modalities, generally includes treatment with NSAIDs, weak opioids, and exercise therapy [3]. When extensive conservative therapies fail to adequately manage LBP, lumbar fusion is on possible surgical option, though its use remains controversial, as reported in the literature [4–8].

The objective of this work was to evaluate minimally invasive lateral interbody fusion in the surgical treatment of lumbar discogenic pain, and to perform a literature review of degenerative disc disease and its treatment in the literature.

2. Methods

Data were collected through retrospective review of prospectively collected clinical and radiographic registry at a single institution. Inclusion in the current study included consecutively treated patients with degenerative disc disease presenting with discogenic low back pain without radicular symptoms, after failing at least 6 months of conservative care. Discogenic pain was assessed by clinical examination [9], such as centralization phenomenon and pain during standing, and radiological signs of degeneration [10], such as black discs and endplate modifications. Provocative discography was not routinely used in making diagnostic conclusions. Patients with idiopathic/degenerative scoliosis

or grade II/III/IV spondylolisthesis were excluded from the study. A psychological screening [11] was performed preoperatively, to assess psychosocial features, patient understanding and to adapt patient expectations according to the surgical objective.

Patients were treated via the minimally invasive, lateral retroperitoneal transpsoas approach [12]. The surgical procedure was performed with patients in a true 90° lateral decubitus position and the table was flexed to increase the distance between the iliac crest and the rib cage. Retroperitoneal blunt was used to dissect through the psoas muscle, using progressive dilators and an expandable retractor to expose the lateral surface of the spine. Real-time directional electromyography (EMG) with discrete-threshold responses was used in all cases (NeuroVision JJB System, NuVasive Inc, San Diego, CA). Wide discectomies were performed with release of the contralateral annulus while preserving the anterior and posterior longitudinal ligaments. Interbody spacers were placed on the lateral and posterolateral borders of the apophyseal ring to increase contact with strong cortical bone [13, 14], to restore disc height, sagittal and coronal plane alignment [15–18], and to indirectly decompress the neural structures [19]. The interbody grafts were made from polyetheretherketone and filled with recombinant human BMP-2 (Infuse, Medtronic Sofamor Danek, Memphis, TN), silicate substituted calcium phosphate (Actifuse ABX, Apatech, Hertfordshire, England), calcium sodium phosphate cement (Graftys HBS, Graftys, Aix-en-Provence, France), or hydroxyapatite (HAP-91, Implamed, Sao Paulo, Brazil).

Clinical evaluations were performed by a clinical and included a physical exam for lower extremity motor and sensory function and self-assessed questionnaires using the Oswestry disability index (ODI) and visual analogue scale (VAS) for back and leg pain. Evaluations were performed preoperatively and at 1 and 6 weeks, 3, 6, 12, and 24 months postoperative. Minimum follow-up for inclusion in the current analysis was 24 months postoperatively.

Bony fusion was assessed by two spine surgeons and two spine researchers in CT scans and dynamic X-rays. Fusion was considered complete when translational motion was <3 mm, angular motion was <5°, and >50% of disc space showed complete bony bridging.

Statistical analyses included descriptive statistics to characterize baseline variables and paired t-testing to evaluate differences in mean outcome variables from pre- to postoperative time points. Statistical analyses were performed using SPSS software (SPSS, Version 10, SPSS, Chicago, Ill, USA) and statistical significance was evaluated at $P < 0.05$.

3. Results

From 220 patients that underwent lateral interbody fusion for degenerative disc disease between August 2007 and December 2009, 22 (10%) patients met inclusion-exclusion criteria (mean age 57.6 years, range 32–85; mean BMI 28.9, SD 7.9; 50% female) with 28 spine levels treated. One- and two-level procedures were performed in 16 (73%) and 6 (27%) cases, respectively. Levels treated included L2-3, L3-4, and/or L4-5.

Surgical procedures were performed in an average of 72.1 minutes (range 40–110 min) with an average blood loss of less than 50cc. The average hospital discharge was 21 hours (range 8–44 hours). Intraoperative complications included one instance of anterior longitudinal ligament rupture, which resulted in the placement of posterior pedicle screws. No other intraoperative complications were observed. Three patients (5 spine levels) required supplemental percutaneous pedicle screw instrumentation for grade I spondylolisthesis with instability, while other cases (23 spine levels) were performed as stand-alone interbody constructs.

Four stand-alone levels experienced cage subsidence (14.3%) by 6-week followup. These patients experienced transient axial back pain (persisting several months) and in one (4.5%) case radiculopathy arose, which required a foraminotomy 12 months postoperative.

Clinical outcomes improved postoperatively (Figure 1 and Table 1). LBP, assessed by VAS, showed a 44.2% improvement at the first postoperative visit (1 week) further improving to a 70.1% reduction at final followup. Disability was also significantly lowered as early as one week following surgery (24% improvement in ODI) and was further lowered until last followup, when a 52.5% improvement was observed (Figure 1).

Index level lordosis significantly changed from a mean preoperative value of 12.2° (7.4° SD) to 16.7° (6.5° SD) at final followup ($P = 0.032$). Bony fusion was observed in 92.9% (26/28) of total lumbar levels treated (exemplified in Figures 2 and 3).

4. Discussion

This work examined the treatment of discogenic LBP in patients with degenerative disc disease treated with a discectomy and interbody fusion via lateral access. Isolated axial low back pain rapidly resolved after surgery and disability more gradually improved, as would be expected. Radiolographic analysis revealed improvements in segmental lordosis at treated levels and a high rate of solid fusion. Additionally, few complications occurred, as would be expected using a modern minimally invasive approach, and the patients were generally treated successfully through removal of the pathological intervertebral disc and by stabilizing and fusing the level.

This work represents a retrospective study on prospectively collected data in a small case series with midterm followup, so conclusions are limited to the study design drawbacks. The primary reason for a small sample size was the relative infrequency of surgical candidates for lumbar spine fusion surgery without radicular symptoms (only 10% of all cases in this series). This strengthens the results through sample homogeneity, but greatly limited the sample.

Intervertebral disc morphology continuously changes from birth to late stages of the human life [20]. Disc degeneration is a natural phenomenon, detectable in individuals as early as 11 to 16 years old. By the age of 50, approximately 10% of lumbar intervertebral discs would be classified as degenerated to some extent on MRI and severely degenerated

Table 1: Clinical and radiological results.

	Preop	6 weeks	*P* value	24 months	*P* value
VAS (cm)	7.7 ± 2.4	4.3 ± 2.2	0.001*	2.3 ± 1.9	<0.001*
ODI (%)	46 ± 19	27 ± 14	<0.001*	19.6 ± 13	0.003*
Segmental Lordosis (degrees)	12.2° ± 7.4°	—	—	16.7° ± 6.5°	0.031*
Fusion	—	—	—	92.9% (26/28)	—

P Values are referent to comparison to Preop values. *Statistically significant.

in as many as 60% of 70-year-old discs [21, 22]. Macroscopical changes during this process have been described [23, 24]: the nucleus is the first to change and goes from exhibiting fluid-like to solid-like behavior; the annulus suffers a decrease in the number of layers, decrease in radial permeability, defects in the structure, and microfailure; subchondral bone/nucleus junction calcification, exhibition of focal defects and Modic changes culminate to display the ongoing inflammatory process.

Various phenomena are involved in lumbar disc disease. Genetics, trauma, nutrient pathways, cell death, and matrix synthesis can be primary degeneration inductors [24] and biomechanical matters also greatly contribute to the disease [25, 26]. Impaired neuromuscular control of the paraspinal and abdominal muscles (muscle hypo- or hyperfunctionality) and external forces (e.g., sustained and repetitive loading) can additionally cause disc damage [25, 26], to the point where only a narrow safe window remains between hypermobility (wear and tear) and underuse (immobilization).

Although in normal anatomy, intradiscal nerve terminations have a limited distribution (mostly on the posterolateral annulus), disc degeneration has been shown to have a massive ingrowth of nerves fibers [27–32]. These growths seem to penetrate from outside to inside the annulus, along the edges of annular fissures, dependent of the inflammation process and dependent upon specific markers like substance P and receptor to CGRP-ir nerve growth factor [29–31]. Nociceptive information is transmitted primarily by small neurons associated with inflammatory pain and some specific proinflammatory mediators (NGF; PGE2, IL-1, IL-6; IL-8) [29, 32, 33]. And importantly, these networks tend to resultantly function under peripheral and central sensitization [9, 29–31].

One of the most challenging factors of discogenic low back pain is an accurate differential diagnosis. Morphological and functional statuses of apophyseal joints, ligaments and musculature and spine biomechanics must be analyzed [9, 34–36]. Additionally, external forces and postural behavior also interfere in symptoms onset [25, 26]. Psychosocial factors such as depression, anxiety, and worker's compensation act an positive feedback in pain modulation and may be a drawback in diagnosis and treatment [11, 37–39].

Classically discs are innervated segmentally and discogenic pain pathways flow through the sinuvertebral nerve into the corresponding dorsal root ganglion and into the spinal cord, generating symptoms located at the index level [29, 40, 41]. More recently, an alternative pathway through the grey ramus communications has been described [41, 42]. The signal travels into the upper lumbar dorsal root ganglion (especially at the L2 level), when a L4-5 disc pathology may generate signals in an L2 dermatome, like a groin and anterior tight pain during a L4-5 provocative discography procedure [41, 42].

Identification of signs and symptoms of discogenic back pain includes continuous axial low back pain persistent in extended period deep in the central line of the spine, usually with no irradiation (few times with diffuse or inguinal irradiation), possible relief when lying, no significant worsening with movements, and worsened with axial load and long standing or sitting periods. In radiolographic analysis, low signal intensity of the disc on sagittal T2W, high-intensity zones, annular damages, and especially Modic changes corroborate clinical findings [9, 28, 36, 43].

Provocative discography is one of the possible tests to contribute in the diagnosis of discogenic pain, but a few studies have shown equivocal results for discography [44–46] and the procedure can also accelerate progression of degeneration changes in the lumbar disc [47]. False-positive rates were once reported to reach up to 40% [46], and the presence of many confounding factors can limit its potential: speed and pressure control; low/high pressure provocation; quiescent phase of the illness; somatization disorder; regular medications; abnormal psychometric scores; worker's compensation.

When a degenerated intervertebral disc is determined to be the primary pain generator, surgical removal must be considered. Nucleus replacement was one attempt to treat discogenic pain and maintain movement and function, but the ideal indication window is too narrow and several unwanted complications have occurred [48–52]. Lumbar fusion has been widely used for different pathological conditions resulting from idiopathic changes, degeneration, trauma, infection, or neoplasia. As reviewed elsewhere [53], lumbar fusion has more high-quality studies testifying favorable comparative outcomes [54–56] than with nonoperative care [57].

For a painful disc, discectomy and interbody fusion intend to remove the pathologic tissue, which presents itself as nonfunctional fibrotic structure, soaked with inflammatory mediators and nerve ingrowth, and to fuse the segment. Additionally, index motion is related to pain occurrence and can be treated with lumbar level stabilization, and the addition of interbody fusion has show the favorable results in lumbar fusion [56, 58, 59], especially for discogenic pain.

Lateral interbody fusion has been shown to significantly increase foramen and disc height [19], impact sagittal [60–62] and coronal plane reconstruction [15, 16, 18, 63, 64], and provide indirect decompression and relief of low back and irradiated symptoms [65, 66]. With true 90° lateral access, satisfactory results have also been shown in thoracic access for the treatment of tumor [67, 68], trauma [68], spondylolisthesis [61, 64], and disc herniation [69]. Moreover, artificial discs placed laterally have been an advance in lumbar arthroplasty due to anterior and posterior longitudinal ligament preservation [70].

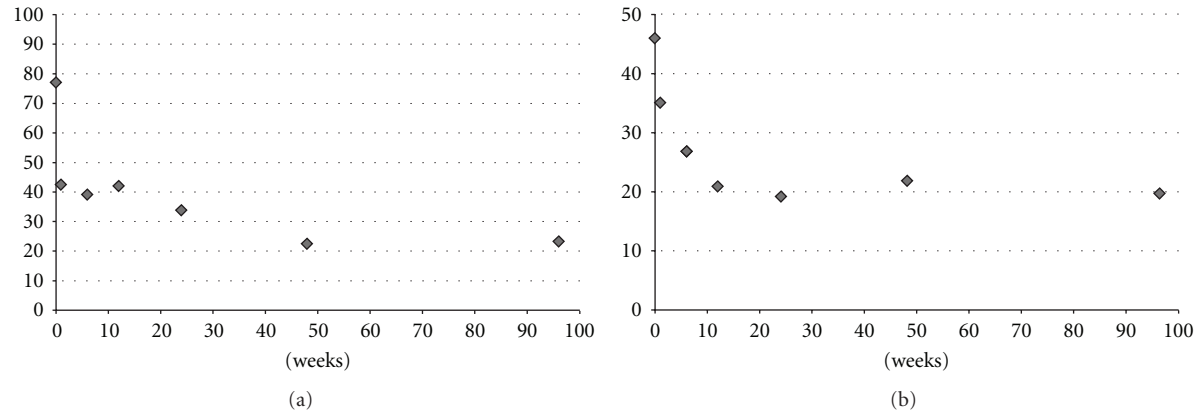

Figure 1: Clinical outcomes. (a) VAS back pain scores, all postoperative results are statistically significant compared to baseline ($P < 0.003$). (b) ODI scores, results are statistically significant since 1-week followup ($P < 0.04$) and in other postoperative visits ($P < 0.001$) compared to baseline.

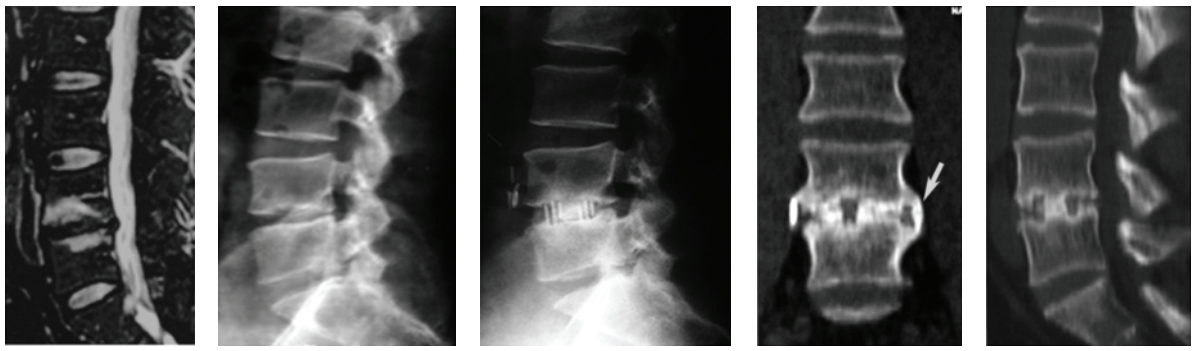

Figure 2: Case example number 1. Male, 54 years old, 7-year pain history which used to get worst by end of the day, refractory to physiotherapy and chiropractic. VAS scores-preoperative 8; 1-week 2; 24-month 1. Patient underwent an L4L5 stand-alone lateral interbody fusion. (a) Preoperative sagittal MRI. (b) Preoperative lateral orthostatic X-ray. (c) 24-month lateral orthostatic X-ray. (d) 24-month computed tomography coronal reconstruction, arrow shows fusion sentinel sign. (e) 24-month computed tomography sagittal reconstruction.

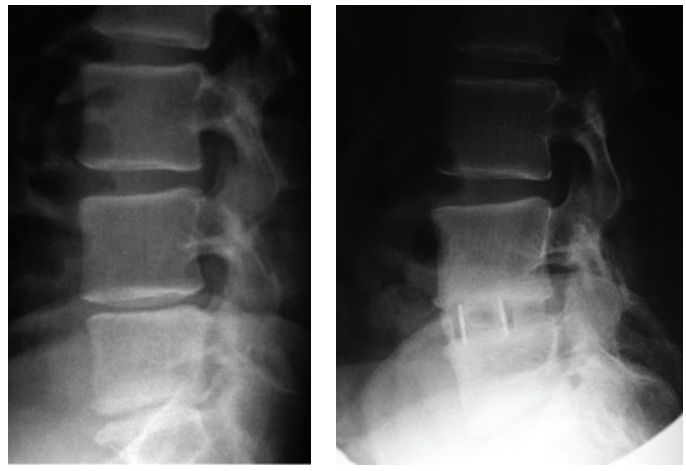

Figure 3: Case example number 2. Male, 58 years old, long history of lumbar axial pain and recurrent crisis event. VAS scores-preoperative 6; 1-week 3; 24-month 1. Patient underwent an L4L5 stand-alone lateral interbody fusion using rh-BMP. (a) Preoperative lateral orthostatic X-ray (b) 12-month lateral orthostatic X-ray.

If the affected lumbar level does not present with gross instability, a stand-alone interbody construction may be considered. In this instance, posterior muscle damage is prevented as well as posterior instrumentation complications. Biomechanical studies [71] have shown lateral interbody implants provide the largest reduction in range of motion in a stand-alone construct, with this stability increasing when moving from 18 mm cages (anteroposterior dimension), to wider ones (22 and 26 mm) [72].

Payment and reimbursement for lumbar fusion, especially for degenerative disc disease, are being rigorously reviewed by North American and worldwide institutions with the premise that it is ineffective. In this study, however, at 2 years postoperatively over 70% improvement in VAS and patient outcomes was demonstrated, much higher than previous studies on treatment for degenerative spine condition [55, 73–76]. This study, while somewhat limited, has shown that, in carefully selected patients, MIS lumbar fusion can be effective in treating isolated axial discogenic low back pain. The spine community must continue to debate the benefits and drawbacks of lumbar fusion for degenerative disc disease.

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Review Article

Lumbar Degenerative Disc Disease: Current and Future Concepts of Diagnosis and Management

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Low back pain as a result of degenerative disc disease imparts a large socioeconomic impact on the health care system. Traditional concepts for treatment of lumbar disc degeneration have aimed at symptomatic relief by limiting motion in the lumbar spine, but novel treatment strategies involving stem cells, growth factors, and gene therapy have the theoretical potential to prevent, slow, or even reverse disc degeneration. Understanding the pathophysiological basis of disc degeneration is essential for the development of treatment strategies that target the underlying mechanisms of disc degeneration rather than the downstream symptom of pain. Such strategies ideally aim to induce disc regeneration or to replace the degenerated disc. However, at present, treatment options for degenerative disc disease remain suboptimal, and development and outcomes of novel treatment options currently have to be considered unpredictable.

1. Introduction

Low back pain (LBP) is the single most common cause for disability in individuals aged 45 years or younger and as a result carries tremendous weight in socioeconomic considerations. National economic losses resulting from LBP are estimated to exceed $100 billion per year and are mainly indirect due to reduced productivity [1]. Even though radiographic signs of degenerative disc disease (DDD) have been shown in asymptomatic individuals [2] and the degree of degeneration is by no means a marker for duration or severity of symptoms associated to DDD, ways of limiting disc degeneration or even inducing disc regeneration are still desirable goals in its treatment.

Strategies for stopping or reversing disc degeneration in the lumbar spine range from mechanical treatment options, that rely on the traditional concept of removing the pain generator, the disc, and eliminating pain by stopping motion, to more recently emerging and developing treatment options involving gene therapy, growth factors, and cell transplantations. The traditional approach of motion-eliminating fusion surgery, which may be effective for the treatment of pain in some cases, may also increase the rate of degeneration at adjacent spinal motion segments. Furthermore, this strategy does not halt the progression of the degenerative cascade of events that leads to pain and disability. So despite its undeniable significance, lumbar fusion surgery as a treatment of LBP has to be regarded suboptimal, as it targets the symptom of pain rather than its causes. The modern molecular biology era has brought revolutionary advances in fields such as genomics, nanotechnology, stem cell biology, gene therapy, and tissue engineering, which together hold tremendous therapeutic potential for clinical applications in degenerative disorders such as DDD.

2. Pathophysiology of Disc Degeneration

2.1. Anatomy and Innervation of the Intervertebral Disc. The intervertebral disc (IVD) is composed of the nucleus pulposus (NP) centrally, the annulus fibrosus (AF) peripherally, and the cartilaginous endplates cranially and caudally at the junction to the vertebral bodies. Within the NP, an abundance of proteoglycans allows for absorption of water. This property of the NP is essential for the IVD's handling of axial loads. In the healthy disc, the most common type of

collagen within the NP is type II collagen. The AF surrounds the NP and consists primarily of type I collagen.

Descriptions of the innervation of the IVD have been published more than 20 years ago [3]. Branches of the sinuvertebral nerve, the spinal nerves, and gray rami communicantes [4] are believed to be part of the neurologic basis for discogenic back pain. An increase of nerve fibers and blood vessels in the painful disc, reaching regions of the annulus fibrosus and nucleus pulposus that are usually aneural in the healthy disc, has been reported, and a correlation between these findings and the expression levels of neurotrophins has been suggested [5].

2.2. Aging and Degeneration. The process of degeneration compares to the process of aging in many ways. However, disc degeneration often occurs at a faster rate, making DDD a condition often encountered in patients of working age. Quantitative gene expression analysis in a rabbit model suggests age to contribute uniquely to the degeneration process when compared to an injury-induced degeneration model [6]. With increasing age, the water content of the IVD decreases and fissures in the NP, potentially extending into the AF, can occur, and the start of this process, termed chondrosis intervertebralis, can mark the beginning of degenerative destruction of the IVD, the endplates, and the vertebral bodies [7]. DDD is a complex degenerative process due to age-related changes in molecular composition of the disc. This cascade has biomechanical and often times clinical sequelae that can result in substantial impairment in the afflicted individual.

2.3. Genetic Component of Degeneration. An undeniable genetic component to degenerative disc disease becomes evident when looking at results from twin studies and studies involving mice with a knockout for genes suspected to play a role in disc degeneration [8, 9]. Among the genes suggested to be involved in DDD, are genes that code for collagens I, IX, and XI, interleukin 1 (IL-1), aggrecan, the vitamin D receptor, matrix metalloproteinase 3 (MMP-3), and other proteins [10]. It is well recognized that DDD is regulated by these and many other genes. Interactions among those genes, which in concert contribute substantially to DDD despite presumably small individual contributions, as well as gene-environment interactions, are very likely [11].

2.4. Environmental Factors. Many practitioners believe environmental factors to be a secondary consideration to the genetic component of DDD. Nevertheless, the influence of environmental factors on DDD is far from negligible and has been defined in a comprehensive manner by Williams and Sambrook in 2011 [12]. In a meta-analysis, odds ratios for manual materials handling, frequent bending or twisting, and whole-body vibration were calculated to be 1.51, 1.68, and 1.39 in regard to DDD, respectively [13]. A modest association between smoking and disc degeneration has been shown, suggesting possible influences of chemical exposures [14]. Twin [15] as well as animal studies [16] have postulated an involvement of nicotine in disc degeneration, which might be due to impaired blood flow to the disc [17]. Furthermore, an association of atherosclerotic lesions in the aorta and LBP, reflecting a possible link between atherosclerosis and DDD, has been reported [18].

3. Clinical Presentation

Patients with lumbar disc disease often present with a myriad of symptoms including pain, radicular symptoms, and weakness. LBP may be exacerbated by position and movement. Flexion often worsens the symptoms, while extension will relieve them. An increase in pain with extension may indicate facet arthropathy.

When examining patients with presumed lumbar DDD, it is important to exclude other potential known etiologies for their pain. Abdominal pathology including aortic aneurysms, pancreatic disease, and renal calculi must be excluded. Furthermore, it is imperative that patients be questioned regarding other symptoms such as fevers, chills, fatigue, and weight loss, which may be indicative of other pathology.

4. Diagnosis

Upright plain radiographs in two planes are the initial imaging study of choice. They aid in ruling out pathologies such as deformity, fractures, or metastatic cancer as underlying causes of back pain and, often supplemented by other imaging modalities, are evaluated for signs of degeneration. Findings in degenerative discs include disc space narrowing, endplate sclerosis, "vacuum" phenomenon within the disc, and osteophytes. Flexion and extension views may be helpful if instability is suspected.

Magnetic Resonance Imaging (MRI) is a more sensitive imaging study for the evaluation of degenerative disc disease. Findings on MRI scan include disc space narrowing, loss of T2 signal within the nucleus pulposus, endplate changes, and signs of internal disc derangement or tears (Figure 1). High Intensity Zones (HIZ) have been found in close to one third of patients undergoing MRIs for low back pain and have been used as a marker for internal disc derangement. However, the accuracy and reliability of these HIZs has been questioned [19, 20].

Modic et al. were among the first to radiologically characterize vertebral endplate changes that are associated with degenerative disc disease [21, 22]. The Modic classification system includes three types of changes, and grading has been shown to be reliable and reproducible [23]. In Type I, there is increased signal on the T2-weighted sequence and decreased signal intensity on the T1 sequences indicative of marrow edema. Type II is characterized by fatty infiltration of the marrow as demonstrated by hyperintense T1 and T2 images. Finally, Type III demonstrates hypointense signals on T1 and T2 sequences, which corresponds to endplate sclerosis. The Modic types are summarized by Table 1.

Pfirrmann et al. further examined and characterized intervertebral disc pathology using MRI [24]. The degree of disc degeneration were graded I through V. Grade I

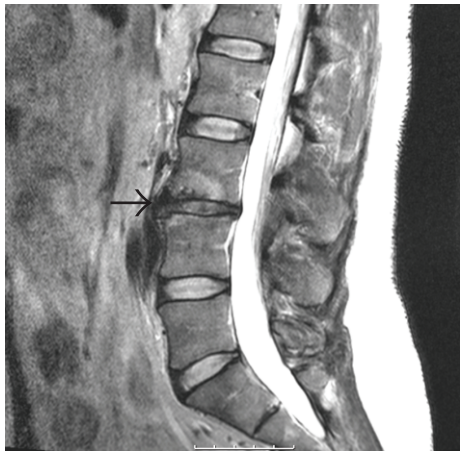

Figure 1: Disc space narrowing and degenerative changes at the L3-L4 level (arrow) on sagittal T2-weighted MRI.

Table 1: Modic changes as illustrated by Jones et al. [23].

Type	T1 MRI signal intensity	T2 MRI signal intensity
I	hypointense	hyperintense
II	hyperintense	iso- or hyperintense
III	hypointense	hypointense

Table 2: Pfirrmann grades as illustrated by Pfirrmann et al. [24].

Grade	Structure	Distinction (nucleus and annulus)	T2 MRI signal intensity	Disc space height
I	white, homogenous	clear	isointense to cerebrospinal fluid (hyperintense)	normal
II	inhomogeneous, with banding	clear	isointense to cerebrospinal fluid (hyperintense)	normal
III	gray, inhomogeneous	unclear	intermediate	normal to decreased
IV	gray to black, inhomogenous	no distinction	intermediate to hypointense	normal to decreased
V	black, inhomogenous	no distinction	hypointense	collapsed

discs are white, and homogenous on T2 sequences. Grade II discs are white, but somewhat inhomogenous with banding. Grade III discs are grey with unclear distinction between the nucleus and annulus. Grade IV discs are inhomogenous and dark without distinction between the nucleus and annulus. Finally, Grade V discs demonstrate a collapsed disc space. The Pfirrmann grading system is depicted by Table 2.

While plain radiographs and MRI provide information regarding the health of the intervertebral segment, they do not provide any information regarding the segments impact on clinical symptoms. The use of discography has attempted to identify specific degenerated discs as pain generators [25]. Provocative discography involves the injection of contrast dye into the nucleus. Computed tomography is used to evaluate for extravasation of dye indicating annular tears. The patient's symptoms and intradiscal pressure during the injection are also recorded. If the pain on injection is similar to their back pain, then the discogram is considered concordant. Also, if pain is produced at low pressures, it is felt that there is symptomatic annular disruption or internal derangement. However, if the pain is different or produced at high pressures of injection, the test is often considered discordant. Still, low-pressure discography has been found to have false positive rates of up to 25% in asymptomatic individuals and may accelerate disc degeneration [26, 27].

5. Treatment Strategies for Lumbar Degenerative Disc Disease

5.1. Mechanical Concepts of Lumbar Disc Regeneration. Spinal fusion surgery is a recognized treatment option of LBP but its efficacy and success remain controversial. It can be achieved by a variety of approaches and techniques, including posterolateral fusion, anterior lumbar interbody fusion, and posterior lumbar interbody fusion. Minimally invasive approaches to the lumbar spine for interbody fusion, such as lateral lumbar interbody fusion, have been gaining popularity within the last 5 years [28].

While fusion procedures offer a way of eliminating motion between spinal segments, and thus alleviate discogenic pain associated to degenerative changes, they address only a symptom and not the cause of DDD. Furthermore, there are significant concerns regarding alterations in adjacent segment motion, which may lead to the introduction of adjacent segment degeneration [29–31]. As a result, motion preserving procedures have been introduced to assist in preventing adjacent segment changes. Disc arthroplasty has the purported advantage of removing the degenerated intervertebral disc and replacing it with a prosthesis that will allow motion between the segments. Clinical trials have shown equivalent results compared with circumferential fusion for the treatment of discogenic pain [32]. In a two-year follow-up study, total disc replacement patients compared favorably to an arthrodesis control group in terms of pain relief and recovery, but a potential early time point patient bias in favor of the arthroplasty group necessitates a longer followup and concern was expressed in regard to long-term polyethylene wear in total disc replacements with a polyethylene component [33]. Furthermore, the purported advantages of preventing adjacent segment disease are unclear and require additional long-term results [34].

Another potential motion-preserving surgery involves posterior dynamic stabilization. These systems involve placement of pedicle screws across a motion segment connected by a flexible graft. These devices are designed to restrict motion across the interspace to limit discogenic pain [35]. Early followup of this technique has demonstrated some

promising result in the treatment of discogenic back pain with regard to improved VAS and ODI scores [36, 37]. However, longer-term studies have demonstrated adjacent segment disease in 29–47% of patients [38–40].

5.2. Cell-Based Therapies and Growth Factors in Lumbar Disc Degeneration. While there are a variety of invasive, surgical options for the treatment of lumbar degenerative disc disease, recent emphasis has been directed at the reversal of disc degeneration or the replacement of the affected disc. Various therapies have been investigated including biologic growth factors, stem cells, and gene transplant. While these novel therapeutic modalities have shown some early promising results with regards to reversal of the degenerative cascade, their clinical effects and long-term results are uncertain [41]. It is also unclear, whether differentiation of stem cells into mature tissues may cause them to express immunogenic markers, which ultimately may result in stem cell rejections.

In 2002, Bone Morphogenetic Protein (BMP) was approved as a bone graft substitute for anterior lumbar interbody fusion (ALIF), but in addition to its osteoinductive properties, BMP also demonstrated some potential for the treatment of disc disease [42]. Current human and animal studies have shown upregulation of BMP-2 and -7 in aging discs. This upregulation has been found to have an antiapoptotic effect on the cells of the nucleus pulposus [43]. Also, the introduction of BMP-2 into intervertebral discs has resulted in increased extracellular matrix production [44]. However, the direct introduction of BMP into the intervertebral disc may lead to potential undesired osteogenic effects. In recent years, concerns about the safety of BMP-2 have arisen following reports of adverse reactions attributable to its use in ALIF and its off-label use in other spinal fusions [45–47]. In 2008, the FDA published a public health notification about potentially life-threatening complications associated with use of BMP in cervical spine fusion [48]. To date, the safety of recombinant BMP-2 as a bone graft substitute remains controversial. Recent studies have shown the potential for the drug simvastatin to induce chondrogenesis and the production of Type II collagen and aggrecan through BMP-mediated pathways [49].

Transplantation of stem cells has emerged as another promising treatment strategy for DDD [40, 50–52]. Recent animal studies have shown increased extracellular matrix when autologous disc-derived chondrocytes were introduced into a canine disc degeneration model. Furthermore, recent human trial involving the introduction of autologous chondrocytes into postdiscectomy patients has resulted in decreased pain at 2 years compared with controls. Also, there was increased disc hydration at the treated levels and adjacent levels as evidenced by MRI evaluation [53].

An alternative technique to chrondrocyte transplantation has been the use of adipocyte progenitor cells. The advantage to this technique is the relative abundance of adipose-derived stem cell when compared to chondrocytic stem cells. In a rat degenerative disc disease model, transplanted adipose-derived stem cells resulted in increased extracellular matrix production, minimally decreased disc height, and improved discal hydration when compared to controls [54].

Finally, another promising type of stem cells for future investigation are bone-marrow-derived stem cells. *In vitro* studies have demonstrated that these cells have similar chondrogenic capacity when compared to nucleu-pulposus-derived cells [55]. However, *in vivo* studies are needed to confirm their potential efficacy, and any strategy involving the introduction of new cells into the human intervertebral disc to induce regeneration would have to account for the increased demand of nutritional supply by the increasing number of cells or the increased activity of previously present cells [56].

5.3. Gene Therapy in Lumbar Disc Degeneration. Transduction of genes that have the potential to interfere with disc degeneration or even induce disc regeneration is a concept recently applied to DDD by researchers. This strategy requires identification of relevant genes that play a role in the disc degeneration cascade, as well as ways of delivering those potentially therapeutic genes into disc cells. This can be obtained by so-called gene vector systems, which include a variety of viral and, more recently, nonviral vectors [57]. Safety issues are imminent to the use of vectors, and absence of adverse effects is imperative to any vector system.

Early studies used viral vectors to deliver marker genes into discs *in vitro* and *in vivo* [51, 58]. The first gene with potentially beneficial effects on disc degeneration to be experimentally delivered to the IVD in an animal model was TGF-β1 [59]. A similar approach of initial transduction of a marker gene was taken by Moon et al. to deliver genes into human IVD cells [60].

Additionally, other growth factors [61], inhibitors of metalloproteinases [62], and also a transcription factor, Sox-9 [63], have received consideration as possible targets for gene therapy for DDD. Following identification of ADAMTS5 as a contributor to cartilage degradation in a mouse model [64], ADAMTS5 small interference RNA was successfully used in a rabbit model to suppress degradation of NP tissue [65]. A similar approach was used to target caspase 3, a main executor of apoptosis, in a rabbit model [66]. Future *in vivo* studies linking theoretical benefits of any of these gene therapy approaches to situations possibly encountered in clinical practice are desirable [67] and comprise the long-term perspective of applying gene therapy as a strategy to treat the underlying mechanism of disc degeneration.

5.4. Summary. Degenerative lumbar disc disease and resulting low back pain impart a large socioeconomic impact on the health care system. Disc degeneration is a multifactorial occurrence with a strong genetic component. Age and environmental factors contribute to the degenerative process. While current strategies aim to remove the pain generator through surgery, future, emerging modalities aim to reverse the degenerative cascade through the use of biologics and

gene modification. Advances in fields such as genomics, nanotechnology, stem cell biology, gene therapy, and tissue engineering have tremendous therapeutic potential for clinical applications in degenerative disorders such as DDD, but novel treatment strategies for lumbar disc degeneration require further evaluation in preclinical and clinical trials.

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Clinical Study

Usefulness of the Core Outcome Measures Index in Daily Clinical Practice for Assessing Patients with Degenerative Lumbar Disease

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Introduction. Outcome evaluation is an important aspect of the treatment of patients with degenerative lumbar disease. We evaluated the usefulness of the Core Outcome Measures Index (COMI) in assessing people affected by degenerative lumbar disease in daily clinical practice. *Methods*. We evaluated 221 patients who had completed preoperatively and 2 years after surgery VAS pain, Short Form-36 (SF-36), Oswestry Disability Index (ODI) and COMI. We calculated the change of scores and its sensitivity to change. The internal consistency of the COMI items and the correlation between the COMI scores and the scores of the other measurements were assessed. *Results*. Statistically significant differences were observed between the mean scores of the preoperative and 2 years questionnaires for nearly all measurements. COMI showed a good internal consistency, except for the preoperative pain subscale. The sensitivity to change was high for the total COMI and its pain and well-being subscales and moderate for the rest. The COMI demonstrated strong correlation with the other measurements. *Conclusions*. The COMI is a useful tool for assessing the patient-based outcome in the studied population. Given its simplicity, good correlation with the SF-36 and ODI and its good sensitivity to change, it could replace more cumbersome instruments in daily clinical practice.

1. Introduction

Degenerative lumbar disease (DLD) and chronic low back pain (CLBP) are orthopaedic problems of the highest incidence in the Spanish population [1]. In the United States, the lifetime prevalence of low back pain has been reported to be as high as 84% and the prevalence of CLBP to be about 23%, with 11-12% of the population being disabled by low back pain [2]. Often, DLD and CLBP require surgical intervention so that DLD has become the leading cause of arthrodesis in the spine [1]. In the USA, the annual number of lumbar fusions for degenerative lumbar disease has increased from 174,223 in 1998 to 413,171 in 2008 [3].

Patient-based outcomes may be the most important tool clinicians, patients, and policymakers can use to identify the effectiveness of different low back pain treatments. In 1998, a multinational group of back pain investigators designed the Core Outcome Measures Index (COMI) to evaluate pain, function, generic health status or well-being, disability, and satisfaction [4]. The COMI ultimate goal was to provide a standardized outcome assessment without an excessive burden of instruments or questions that make it difficult for patients to complete the instruments of evaluation. The COMI was validated against well-validated instruments such as the Roland-Morris or the Oswestry Disability Index (ODI) for back specific function and the Medical Outcomes Study Short Form-36 (SF-36), its Short Form SF-12, or the EuroQol for general health status. In 2006, a Spanish group validated the Spanish version of the COMI [5]. The authors designed a prospective study that aimed to evaluate the reliability, validity, and responsiveness of this instrument. They evaluated this instrument in patients with subacute osteoporotic fracture (quick improvement of the pain after treatment) and chronic low back pain (slow improvement of the pain) and related the COMI scores to the scores of the Spanish-validated ODI, SF-36, and SF-12. They concluded

that the COMI was a useful tool to evaluate patient-based outcomes when the respondent burden is an important problem. Still, subscale scores needed to be further tested in other populations.

The objective of our study is to evaluate the usefulness of the COMI as an outcome measurement in daily clinical practice for patient suffering from DLD.

2. Material and Methods

2.1. Patient Sample. We reviewed the outcomes from 263 patients operated between 2005 and 2008 for degenerative lumbar disease. Of those 263 patients who had completed the preoperative questionnaires, 221 also completed the questionnaires 2 years after surgery. Thirty-five of the 42 patients without postoperative outcomes could not be found, and 7 had died.

Patients were excluded if they were younger than 18 years old, had surgeries for infectious disease, tumours, or rheumatic origin, or had a language barrier that prevented them from properly understanding the questionnaires. We included all patients older than 18 years old who were operated for the following diagnoses: degenerative disc disease, stenosis, disc herniation, spondylolisthesis, and pseudarthrosis. Epidemiological data collected during the study were age, sex, employment status, diagnosis, surgical procedure, and degree of comorbidity on the American Society of Anaesthesiologists (ASA) scale [6, 7].

2.2. Questionnaires. All patients were clinically evaluated and then self-completed the validated Spanish version of the SF-36 version 2 [8, 9] to evaluate their general health, the validated Spanish version of the ODI [10, 11] to assess their disability, visual analogue scales (VAS) [12, 13] to evaluate lumbar and sciatic pain, and the validated Spanish version of the COMI [4, 5] used to comprehensively evaluate patients. All questionnaires were filled out before surgery and 2 years after surgery.

The COMI [4, 14] is a questionnaire composed of 8 questions that evaluates pain (2 items), function (1 item), well-being (1 item), disability (2 items) and satisfaction (2 items). The scores of the questionnaire range from 1 to 5, with 1 being the best possible result. The total COMI score is the average of the 5 dimensions. It was designed for a simpler but effective standardized evaluation of outcome in patients with low back pain and would replace more cumbersome health-related questionnaires in daily practice.

2.3. Data Analysis. Statistical analyses were performed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Student's t-tests were used to compare the pre-operative and post-operative scores; a P value below 0.05 was considered statistically significant. The change in scores from pre-operative to 2-year follow-up was calculated as the preoperative scores minus the post-operative scores. A negative change score indicates improvement for ODI, COMI, and VAS, while a positive change score indicates improvement for the SF-36. The magnitude of change (sensitivity to change) was assessed by the standardized mean response (SMR). SMR is one of the possible calculations of effect size; specifically it is obtained by dividing the mean difference by the standard deviation of the change scores [15]. The use of effect size allows for comparisons between different outcome measures because it translates score differences into a standard unit of measurement. Applying Cohen's threshold values of effect size to SMR, sensitivity is considered trivial for SMR values lower than 0.20, small for SMR values between 0.20 and 0.50, moderate for SMR values between 0.50 and 0.80, and large for SMR values greater than 0.80 [16].

The internal consistency of the various questionnaires was evaluated with Cronbach's alpha test. Cronbach's alpha was not applicable for the function and well-being subscales of the COMI because they are composed of a single item. Alpha values between 0.8 and 0.9 indicate a good consistency, and values between 0.7 and 0.8 indicate an acceptable level of consistency [17].

Construct validity was assessed through Pearson's correlation. Items measuring similar concepts were expected to have high correlation coefficients (>0.6), and items measuring different concepts were expected to have low correlation coefficients (<0.4) [5].

Table 1: Epidemiological data (221 patients).

Age years	(range)
55.1	(22–86)
Sex	*n* (%)
Female	112 (50,7)
Male	109 (49,3)
Employment situation	*n* (%)
Employed	119 (53,8)
Permanent disability	27 (12,2)
Temporary disability	28 (12.7)
Retired	40 (18,1)
Unemployed	7 (3,2)
ASA score	(range)
2	(1–4)
Diagnostics	*n* (%)
DDD	86 (38,9)
Lumbar stenosis	76 (34,3)
Disc herniation	28 (12,7)
Spondylolisthesis	16 (7,2)
Pseudarthrosis	15 (6,7)
Treatment	*n* (%)
TLIF	80 (36,2)
Posterolateral fusion	71 (32,1)
PLIF	31 (14,03)
Discectomy	28 (12,7)
Laminectomy	11 (4,97)

3. Results

The mean patient age was 55.1 years (22 to 86 years), and 112 patients (50.7%) were women. At the time of surgery, 53.8%

Table 2: Preoperative and 2-year postoperative scores and magnitude of change.

Health status measures	Preoperative		Postoperative		Difference		SMR
	Mean	SD	Mean	SD	Mean	SD	
ODI	45.60	17.85	36.60	22.24	−8.76*	19.43	−0.451
COMI	3,77	0.76	2.60	0.53	−1.07*	1.19	−0.899
Pain	3.88	0.89	2.79	1.27	−1.13*	1.28	−0.883
Function	3.99	1.12	2.90	1.53	−1.01*	1.68	−0.601
Well-being	4.83	0.47	3.19	1.49	−1.60*	1.48	−1.081
Disability	3.35	1.67	1.89	1.29	−1.01*	1.85	−0.546
Satisfaction	2.81	1.09	2.21	1.34	−0.61*	1.15	−0.530
SF36v2							
Physical Function (PF)	29.29	9.48	36.68	12.79	7.18*	12.05	0.596
Role physical (RP)	30.66	8.76	21.17	4.37	−9.79*	9.46	−1.035
Bodily pain (BP)	30.25	6.99	39.10	12.56	8.87*	12.54	0.707
General health (GH)	42.16	9.01	39.83	11.98	−1.90**	11.13	−0.171
Vitality (VT)	35.35	9.36	44.17	12.01	8.82*	11.69	0.755
Social function (SF)	30.45	13.71	39.68	13.89	8.56*	15.71	0.545
Role emotional (RE)	36.26	14.82	16.10	5.39	−20.38*	13.91	−1.465
Mental health (MH)	39.40	10.64	37.90	11.92	−1.09	1.77	−0.085
PCS	30.90	7.41	36.66	10.89	6.38*	10.9	0.585
MCS	39.91	12.28	32.78	9.76	−6.10*	12.50	−0.488
VAS							
Back	7.55	2.15	5.40	3.41	2.01*	3.34	0.601
Sciatica	7.62	2.62	4.18	3.47	2.39*	3.81	−0.627

* $P < 0.001$, ** $P < 0.05$.
Sensitivity to change (SMR): low ≈ 0.2; moderate ≈ 0.5. High > 0.8.

of the patients were employed, 24.9% were on disability, 18.1% were retired, and 3.2% were unemployed (Table 1).

The most frequent causes of surgical intervention were degenerative disc disease (DDD, 38.9% of cases) and lumbar spinal stenosis (34.3%). The most common surgical treatments were transforaminal lumbar interbody fusion (TLIF, 36.2%) and posterolateral fusion (32.1%). The average degree of comorbidity measured by ASA scale was 2 with a range from 1 to 4 (Table 1).

3.1. Magnitude of Change and Responsiveness. There was an overall improvement in the average scores of the different questionnaires from the preoperative visit to the visit at 2 years, and this difference was statistically significant in all measures except for the mental health subscale of the SF-36 (Table 2). The SMR indicated a high sensitivity to change for the total COMI and its pain and well-being subscales. The sensitivity to change was moderate for the COMI function, disability, and satisfaction subscales (Table 2).

3.2. Internal Consistency. Cronbach's alpha indicated a good internal consistency of the COMI both in the preoperative phase (alpha = 0.807) and the 2-year evaluation (alpha = 0.91), except for the preoperative pain subscale (Table 3). The low internal consistency of the pain subscale may be due to the fact that it is a combination of back pain and leg pain while the patients in our sample were not likely to evenly suffer from back and leg pain.

Table 3: Internal Consistency (cronbach's alpha coefficient).

	α	
	Preoperative	Postoperative
ODI	0.854	0.915
COMI (Total)	0.807	0.910
Pain	0.446	0.776
Function	—	—
Well-being	—	—
Disability	0.911	0.749
Satisfaction	0.827	0.858
SF-36v2		
PF	0.888	0.938
GH	0.750	0.839
RP	0.889	0.938
RE	0.879	0.932
SF	0.662	0.856
BP	0.768	0.887
VT	0.828	0.811
MH	0.862	0.763

α > 0.7-0.8 (max value = 1) → good reliability.

Table 4: Pearson's correlation coefficients.

		ODI	SF-36v2									VAS	
			PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS	Lumbar	Sciatica
Total	Before	**0.706**	**−0.549**	**−0.672**	**−0.728**	**−0.333**	**−0.568**	**−0.582**	**−0.397**	**−0.573**	**−0.610**	**−0.497**	**0.522**	**0.421**
	After	**0.340**	**−0.814**	**−0.714**	**−0.886**	**−0.678**	**−0.695**	**−0.759**	**−0.573**	**−0.577**	**−0.849**	**−0.538**	**0.823**	**0.642**
	Change	**0.728**	**−0.669**	**−0.486**	**−0.842**	**−0.466**	**−0.491**	**−0.760**	−0.074	**−0.492**	**−0.724**	**−0.410**	**0.760**	**0.643**
Pain	Before	**0.460**	**−0.364**	**−0.375**	**−0.533**	**−0.230**	**−0.393**	**−0.238**	*−0.171*	**−0.336**	**−0.432**	**−0.234**	**0.521**	**0.675**
	After	**0.740**	**−0.726**	**−0.695**	**−0.821**	**−0.549**	**−0.600**	**−0.630**	**−0.468**	**−0.467**	**−0.789**	**−0.438**	**0.755**	**0.740**
	Change	**0.483**	**−0.573**	**−0.481**	**−0.644**	*−0.246*	**−0.377**	**−0.482**	−0.112	**−0.319**	**−0.552**	−0.193	**0.758**	**0.751**
Fuction	Before	**0.583**	**−0.448**	**−0.537**	**−0.644**	**−0.275**	**−0.453**	**−0.429**	**−0.216**	**−0.377**	**−0.580**	**−0.301**	**0.476**	**0.425**
	After	**0.750**	**−0.739**	**−0.638**	**−0.788**	**−0.682**	**−0.629**	**−0.702**	**−0.560**	**−0.502**	**−0.753**	**−0.491**	**0.647**	**0.538**
	Change	**0.575**	**−0.470**	**−0.499**	**−0.693**	**−0.405**	**−0.422**	**−0.461**	−0.124	*−0.208*	**−0.563**	−0.159	**0.655**	**0.624**
Well-being	Before	**0.235**	*−0.167*	**−0.215**	**−0.223**	**−0.212**	**−0.174**	*−0.145*	−0.126	**−0.233**	**−0.210**	*−0.163*	*0.205*	0.094
	After	**0.675**	**−0.667**	**−0.566**	**−0.729**	**−0.644**	**−0.598**	**−0.573**	**−0.490**	**−0.497**	**−0.707**	**−0.465**	**0.615**	**0.407**
	Change	**0.464**	**−0.470**	**−0.230**	**−0.605**	**−0.462**	**−0.370**	**−0.215**	−0.109	*−0.190*	**−0.568**	−0.039	**0.396**	*0.374*
Disability	Before	**0.627**	**−0.443**	**−0.607**	**−0.529**	**−0.237**	**−0.470**	**−0.618**	**−0.342**	**−0.493**	**−0.472**	**−0.471**	**0.369**	0.219
	After	**0.707**	**−0.613**	**−0.567**	**−0.710**	**−0.517**	**−0.536**	**−0.631**	**−0.527**	**−0.364**	**−0.682**	**−0.399**	**0.627**	**0.556**
	Change	**0.531**	**−0.452**	**−0.593**	**−0.585**	*−0.359*	*−0.348*	**−0.515**	−0.093	**−0.364**	**−0.522**	−0.277	0.458	*0.560*
Satisfaction	Before	**0.228**	*−0.174*	**−0.252**	**−0.300**	**−0.217**	**−0.269**	**−0.260**	*−0.163*	**−0.276**	**−0.229**	**−0.246**	*0.256*	*0.274*
	After	**0.566**	**−0.549**	**−0.509**	**−0.620**	**−0.522**	**−0.469**	**−0.610**	**−0.450**	**−0.435**	**−0.553**	**−0.405**	**0.570**	**0.402**
	Change	**0.326**	**−0.452**	−0.205	**−0.413**	−0.161	−0.175	**−0.502**	−0.088	−0.203	**−0.522**	−0.277	**0.535**	*0.367*

Statistical significance (P): $P < 0.05$ (italics). $P < 0.01$ (bold).

3.3. Construct Validity. Pearson's correlation coefficients indicated that the COMI total score and its subscales had a statistically significant correlation with almost all values of the ODI, SF-36, and VAS before surgery and after surgery and the score difference (Table 4). In general, items measuring similar concepts had a high (>0.6) correlation coefficient, for instance, the total COMI and ODI ($r = 0.7$) or the disability scale of the COMI and ODI ($r = 0.6$). Items measuring different concepts had low (<0.4) correlation coefficients, for example, the COMI satisfaction scale and the PCS of the SF-36 ($r = -0.2$) or the COMI well-being scale and the PCS ($r = -0.2$). However, this trend was not consistent for all measures of similar/dissimilar concepts (e.g., $r = 0.5$ between COMI pain scale and lumbar VAS) and for measurements times (e.g., $r = 0.5$ between preoperative COMI pain scale and lumbar VAS while $r = 0.8$ between postoperative COMI pain scale and lumbar VAS).

4. Discussion

In this study, the COMI demonstrated good internal consistency, validity, and responsiveness to change in our patient population. Its brevity makes it easier for patients to answer. Its simple scoring and free availability simplifies its administration. For all these reasons, the COMI appears a useful measurement tool of patients' outcomes in daily practice.

The COMI was originally designed by a multinational group as a standardized core of questions that assess briefly but globally patients based outcomes [5]. The design took into account factors such as breadth of coverage, demonstrated validity and reproducibility, and demonstrated responsiveness, practicality (brevity and low cost), compatibility with widely promoted instruments or batteries, and importance to patients and society. The resulting COMI is comprised of 5 scales already validated and in use in some form in other instruments such as EuroQol, National Health Interview Survey, the North American Spine Society, and American Academy of Orthopedic Surgeons instruments.

The psychometric characteristics of the COMI were established with a study of the COMI prospectively administered to 277 patients with low back pain. It demonstrated good reliability, reproducibility, validity, and sensitivity of the COMI composite score and subscales [18]. The German [14], French [19], and Italian [20] versions as well as a neck [21] version of the COMI have been validated. It is recommended as "*a suitable instrument for implementation in the Spine Tango Registry or in any other multi-language databases of outcomes in LBP patients*" ... "*the systematic and widespread use of this version in similar settings might enhance the quality of the follow-up of patients with chronic LBP*" [20]. This instrument is considered in both versions as a practical, reliable, and valid tool and will be of value for international studies and surgical registries.

In 2006, Spanish groups of the *Hospital Universitari Vall d'Hebron* (Barcelona) and *Fundación Jiménez Díaz* (Madrid) published the validation study of the Spanish COMI [5]. Their sample included two groups of patients (osteoporotic vertebral fracture and chronic low back pain), and outcomes were evaluated with the Spanish version of COMI and Spanish well-validated versions of SF-36, SF-12, and Oswestry Disability Index. The COMI showed good reproducibility, internal consistency, construct validity,

and responsiveness, comparable to the more generally used outcome measurements.

The present study examined the use of the COMI in patients with various spine pathologies as typically encountered in daily clinical practice. An important methodological limitation of our study is the lack of test-retest study to confirm the reproducibility of the COMI in our population. Our retrospective analysis did not allow for a test-retest study. Otherwise, just as in the Spanish, German, Italian, and French validation studies, the results of our studies showed similarly good internal consistency, construct validity, and sensitivity to change.

5. Conclusion

The COMI is a valid and sensitive questionnaire for the evaluation of patients with degenerative lumbar disease before and after treatment. The results of this study confirm that the COMI is a short, time-saving, easily scored, and multidimensional instrument that can be widely used in daily clinical practice for assessment and monitoring of patients with degenerative lumbar disease.

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