New Horizons in the Treatment of Lumbar Disc Disease

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Introduction. Lumbar pain secondary to disc degeneration constitutes one of the most formidable challenges currently facing orthopedic surgery. The purpose of this paper is to present a bibliographical review of the techniques used at present for treating disc-related lumbar pain in its different evolutional stages.
Review of the literature. There are several alternatives to conventional lumbar fusion for the treatment of intervertebral disc degeneration. Among the techniques reviewed we should mention the so-called optimized arthrodesis, which incorporates minimally invasive techniques, the use of navigation and biomaterials that promote lumbar fusion; disc prostheses and dynamic lumbar stabilization. For the disc's surgical treatment in the initial stages, the techniques of choice are: intrasdiscal annuloplasty, nucleus pulposus prostheses and several types of cell therapy. We weigh the pros and cons of the different techniques, of the designs and mechanisms of action of the various implants and the clinical results published in the last few years.
Conclusions. Spine surgeons can avail themselves of several possibilities when treating disc degeneration. Nonetheless, most of these are either not sufficiently developed or have not been the subject of high quality comparative clinical studies. In other cases, it is difficult to determine at what point in the evolution of the degeneration they should be used. It is necessary to acquire a higher degree of experience of the use of these techniques and to limit their indications by to stringent patient selection criteria.

Key words: *degenerative disc disease, biomaterials, lumbar fusion, disc prosthesis, cell therapy.*

Nuevas perspectivas en el tratamiento de la enfermedad discal lumbar

Introducción. El dolor lumbar secundario a la degeneración del disco representa uno de los retos más importantes a los que se enfrenta la cirugía ortopédica actual. El objetivo de este trabajo es presentar una revisión bibliográfica de las actuales técnicas quirúrgicas utilizadas para el tratamiento del dolor lumbar de origen discal en sus distintas fases evolutivas.
Revisión de la bibliografía. Se presentan diferentes alternativas quirúrgicas a la fusión lumbar convencional para el tratamiento de la degeneración del disco intervertebral. Entre las técnicas evaluadas cabe destacar la denominada «artrodesis optimizada», que incorpora la cirugía mínimamente invasiva, el uso de navegadores y la utilización de biomateriales que favorezcan la fusión lumbar; la prótesis discal y la estabilización dinámica lumbar. Para el tratamiento quirúrgico del disco degenerado en su fase más inicial se analizan la anuloplastia intradiscal, las prótesis de núcleo pulposo y la terapia celular en sus distintas modalidades. Se revisan las ventajas e inconvenientes de las distintas técnicas, el diseño y mecanismo de acción propuesto para cada implante, y los resultados clínicos publicados durante los últimos años.
Conclusiones. Distintas posibilidades terapéuticas están al alcance de los cirujanos de columna para el tratamiento de la degeneración discal. No obstante, la mayoría de ellas no están suficientemente desarrolladas, se desconoce el momento más adecuado para su ejecución durante la evolución de la enfermedad o carecen de estudios clínicos comparativos de calidad. Debe alcanzarse un mayor nivel de experiencia con estas técnicas y limitar sus indicaciones a estrictos criterios de selección de pacientes.

Palabras clave: *enfermedad degenerativa discal, biomateriales, fusión lumbar, prótesis discal, terapia celular.*

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In the year 1976 professor Alf Nachemson published, in the first issue of the journal Spine, a study with the suggestive title: "The spine, an orthopedic challenge" It is now 30 years since the publication of this article and "lumbar pain" continues, in spite of technical advances, to be one of the

most important problems that orthopedic surgeons must deal with. There are 3 basic aspects involved in this situation: a high incidence within the general population, limited diagnostic capacity to determine the exact source of pain, and current controversy as to appropriate treatment with evident benefit for the patient.

The enormous socioeconomic impact of lumbar pain and sciatica associated to degenerative disc disease (DDD) is well known. Although, according to studies carried out, the prevalence of DDD is very variable, pathological changes such as disc decrease in height affect up to 56% of the population[1]. This, therefore, is of epidemic proportions, especially in industrialized countries and in urban environments. On the other hand, the problem of diagnosis mainly lies in the lack of specific signs that will permit clear identification of the pathological condition responsible for the pain, and in the frequent discordance between the clinical history and the structural findings seen in the images.

The last controversial issue is appropriate treatment for DDD. There is no evidence that many of the treatments used are effective, there is, therefore, little consensus, and a great disparity of criteria, between physicians at the moment of choosing the most appropriate treatment. One of the greatest barriers to the research of appropriate therapies for lumbar pain is that the results of clinical studies are not comparable, or very poor quality methodologies[2] are applied in the studies.

The aim of this study is to present an update of different surgical techniques used for lumbar pain caused by vertebral disc degeneration, during its different phases.

EPIDEMIOLOGY

Many epidemiological studies have tried to identify a concrete cause responsible for lumbar pain in DDD. However, no simple explanation has been found for the development of pain, there seem to be a series of different factors that fit together like parts of a puzzle. Amongst the risk factors it is necessary to mention: aging, trauma, constitutional, individual, psychological and hereditary factors. Studies have shown that some signs of disc degeneration may even be identified in adolescents, and that there is a great variability of these signs in all age groups. Although trauma may contribute to the development of DDD, it is not usual to find a clearly established lesion; therefore this factor is usually overestimated by the patients themselves.

Amongst constitutional factors that have been related to DDD, one is anatomic lack of proportion between a long back and a narrow pelvis, weakness of trunk muscles and a reduced lumbar lordosis. Amongst occupational factors related to DDD we wish to highlight physical strain, exposure to vibration while driving motor vehicles and static work postures. Individual factors that affect DDD are obesity and smoking. Psychological factors such as mental stress or low professional satisfaction have also been related to clinical persistence of pain. There is an ever greater recognition of the influence of hereditary factors, as has been seen in the studies carried out on identical twins[1].

PATHOLOGY OF THIS CONDITION

Neuroanatomical studies have shown that the intervertebral disc is a source of pain since it possesses innervation limited to the most superficial area of the fibrous ring, and this innervation is made up of an extensive network of sinuvertebral nerve free-endings. An increase in the density of nerve-endings has been found in samples of patients with DDD; these nerve-endings reach deep layers of the fibrous ring or *annulus fibrosus* of the intervertebral disc[3]. Furthermore, a great number of neuroactive agents have been discovered during pathological conditions that have the capacity to directly stimulate said nerve-endings and to decrease the threshold for new stimuli, this process has been named "peripheral sensitization". This process is followed by another process of central sensitization. The spinal cord has a certain degree of "plasticity", so that the massive entry of afferent stimuli from peripheral receptors converge on the dorsal horn, where they are capable of producing neuronal changes that could explain chronic pain.

It has been proposed that DDD is the factor that triggers lumbar pain. Degeneration is thought to begin in the so-called "terminal plate". Microfractures have been found in this area as a consequence of compressive forces, since it is the weakest link in the vertebra-disc joint. Vertebral discs are avascular structures that receive nutrients by diffusion through the terminal vertebral plate. Therefore, a lesion of the terminal plate causes mechanical alteration characterized by a decrease in disc hydrostatic pressure, metabolic alteration due to a lower influx of nutrients, which in turn leads to a reduction in the synthesis of proteoglycans and an inflammatory and immunological response, with the local presence of cytokines and proteases. All this causes established structural alteration of the intervertebral disc. Adams and Roughley[4] have proposed that disc degeneration be defined as an aberrant cell response to progressive structural failure.

Subsequently, there is a cascade of events that affect the vertebral segment triarticular complex. This process has been divided into 3 phases: malfunction, instability and stabilization. During the malfunction phase, there is degeneration of the facet cartilage and radial fissures of the fibrous ring, causing disc profusion. During the instability phase,

the joint facets undergo subluxation, as a consequence of the increase in capsule laxity, and simultaneously there are phenomena of internal disruption of the disc that cause a reduction in disc height. All this causes a dynamic foraminal stenosis and degenerative listhesis. Finally, during the stabilization phase there is hypertrophy of the ligamentum flavum and formation of osteophytes that cause central lumbar canal stenosis.

LIMITATIONS OF CONVENTIONAL SURGICAL TREATMENT

During the last decade surgery has been widely used in the treatment of DDD. However, this therapeutic procedure has evident limitations, mainly due to lack of precise indications, scarcity of available surgical options and the disparity of clinical results obtained. Identification of the source of pain in the lumbar area, indispensable for successful surgery, is more by guess than fact-based. Magnetic resonance allows us to clearly assess the changes associated with DDD (Fig. 1). However, these findings are not determinant factors, since it is well known that degeneration is not a synonym of pain. In fact, images of these conditions are frequently found in asymptomatic individuals, especially in elderly ones[5]. Discography, as a provocation test that should make it possible to identify those patients that would benefit from surgery, has also been shown to have a low predictive value, between 50 and 60%, due to the subjectivity of responses[6].

The most widely accepted and assessed standard surgical technique over the last 2 decades for the treatment of DDD, when it proves refractory to conservative treatment, is vertebral fusion. Recent comparative studies favor surgery over conservative management. Fritzell et al[7], showed, with a total of 294 patients, that the clinical results of surgical treatment for lumbar pain are superior to those of medical treatment. Similarly, Möller and Hedlund[8] obtained better results with vertebral surgery in adult patients with spondylolysthesis.

Vertebral fusion may be vertebral body fusion, posterolateral fusion or combined fusion (of the circumference). Medical literature also seems to support the associated use of so-called "vertebral instrumentation". Pedicle screws increase the rate of fusion, favor early mobility of the patient and allow correction of deformities on the sagittal plane, but do not significantly modify clinical results[9]. Other authors support vertebral body fusion, since it is carried out in the supposed painful area and provides better and larger surface contact. The use of vertebral interbody boxes to achieve this purpose furthermore makes it possible to recover disc height and provides an immediate structural support for the graft (Fig. 2). Recent published series describing this technique have shown fusion rates above 90% and satisfactory clinical results in almost 80% of cases (Table 1)[7,10-12].

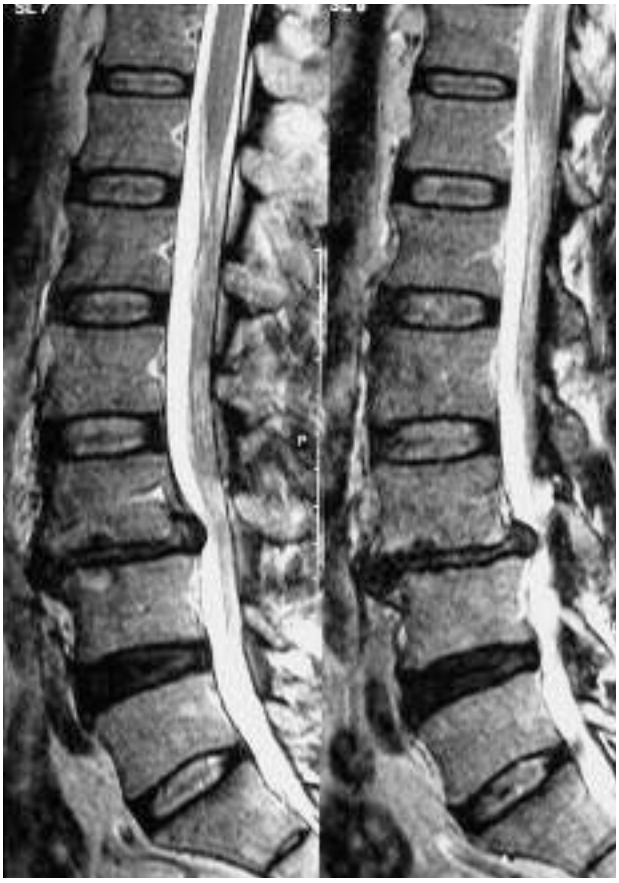

Figure 1. *MRI image weighted in T2 that shows findings compatible with DDD in L3-L4: decrease in height, change of signal and plate irregularity.*

However, all this vertebral instrumentation is not free of complications. Neural problems have been described, due to malposition of pedicle screws, deep infection due to wide dissection of soft tissues and material failures such as fractures, loosening or intolerance[13]. Problems associated with the interbody boxes have also been seen, such as tears in the dura during implantation, dysesthetic syndromes or permanent root deficits and difficulties to carry out rescue operations.

On the other hand, it is clear from the medical literature, that the success of conventional surgery is not capable of guaranteeing optimal clinical results. It is well known that solid fusion does not ensure the disappearance of pain, and malunion condemns the patient to inevitable failure. However, Bono and Lee[2] found, in a recent meta-analysis on vertebral arthrodesis in cases of DDD, with rates of circumferential fusion of 91% and rates of posterolateral fusion with instrumentation of 89%, satisfactory clinical results of conventional arthrodesis in 75% of these patients.

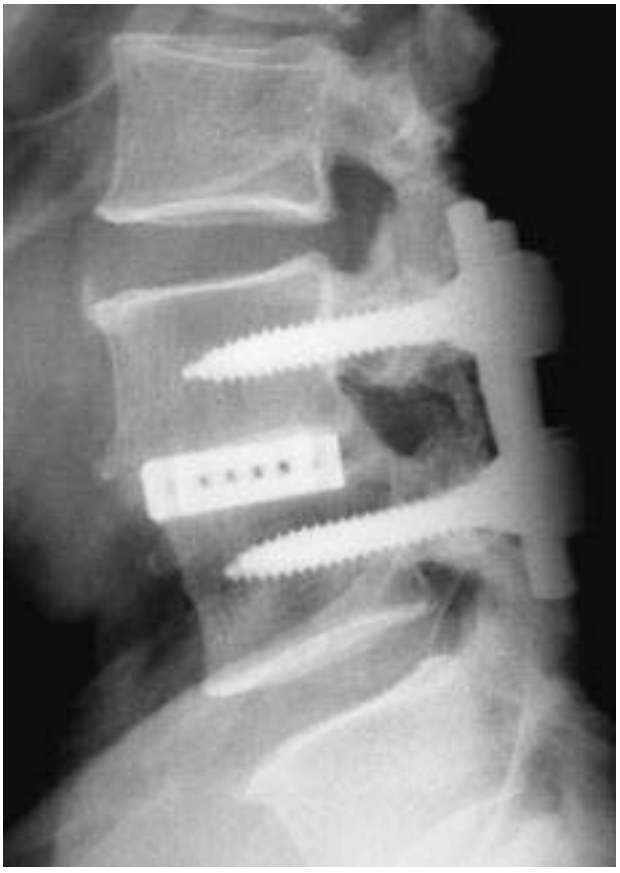

Figure 2. *Circumferential fusion with instrumentation.*

ALTERNATIVE TECHNIQUES TO CONVENTIONAL VERTEBRAL FUSION

Currently, in cases of chronic pain of disc origin, a series of alternative surgical techniques to conventional lumbar fusion are being used that have the aim of improving clinical outcome and patient satisfaction. Amongst these techniques can be mentioned: a) optimized arthrodesis that includes a minimally invasive approach, the use of navigators and biomaterial that favors fusion; b) intervertebral disc prosthesis, and c) posterior dynamic stabilization. To carry out optimized lumbar arthrodesis using a minimally invasive approach means that certain basic surgical equipment must be used, a guided image, an access port, appropriate magnification and illumination and correct manipulation of special surgical instruments[14]. A guided image is necessary to locate the exact area on which to work and is achieved using an image intensifier. The disadvantage of this is that the surgeon is exposed to a significant amount of radiation. The access port to the work area is achieved using tubular retraction systems. These systems are formed by sequential telescopic dilators to separate the muscles and once this is achieved an expandable tubular retractor with halves of appropriate length to reach the desired depth is used. The retractor is attached to the operating table by means of a flexible handle.

Magnification and illumination are essential and are achieved with a surgical microscope, an endoscope with a low profile light source and a magnifying glass with appropriate magnification. Finally, the surgical instruments necessary for the operation must be designed for microsurgery, possess sufficient length and adopt a bayonet shape so that they are easy to manipulate.

The aim of a minimally invasive approach is to limit the extensive muscular and soft tissue dissection that is necessary to achieve adequate exposure during conventional vertebral fusion. The aim is to reduce the rate of local infection and return the patient to activity as soon as possible. However, currently, there are no comparative clinical studies of open fusion procedures and minimally invasive procedures. It seems evident that this type of technique has the disadvantage of requiring a significant learning curve.

The use of navigators must allow exact and safe placement of vertebral instrumentation during surgery. Amongst currently existing navigators we must highlight conventional fluoroscopes (2D), CAT image guided surgery, and three-dimensional fluoroscopes (3D). Conventional fluoroscopes, habitually used in operating theatres, have the drawback of causing high exposure to radiation, requiring constant repositioning for visualization in 2D and poor quality of images in some cases, such as those of obese patients or patients with deformities. CAT image guided procedures have improved vertebral navigation, but possess disadvantages since preparation is a complicated process, it is necessary to have a preoperative CAT image obtained according to a specific protocol, and a preoperative register with markers and wide exposure of each of the vertebrae to minimize anatomical variations. Furthermore, there is the possibility of mistakes during surgery due to small changes in the pa-

Table 1. Rates of fusion and clinical results in circumferential lumbar arthrodesis

Author	Year	No. of patients	Follow-up	Fusion	Satisfaction
Fritzell et al[7]	Spine 2001	71	2 years	91%	79%
Madan et al[10]	Clin Orthop 2003	35	2 years	100%	83%
Lowe et al[11]	Clin Orthop 2002	40	3 years	90%	85%
Brantigan et al[12]	Spine J 2004	37	2 years	96%	86%

tient's position on the operating table due to the force required to introduce the catheter or the pedicle screw. Three-dimensional fluoroscopes have been a major advance in the field of navigators and have recently proved successful in the placement of percutaneous pedicle screws[15]. They possess an isocentric C arm that can automatically revolve in a 180° radius around the patient with an anatomical landmark as reference.

The multiple images obtained are interpreted by specific software that allows a 3D reconstruction, similar to that obtained with CT. This system is the navigation of the future for vertebral surgery[16].

There are a series of biomaterials that can be used to improve vertebral fusion, prevent problems associated with autologous graft implantation and limit malunion rates. These biomaterials can be classified in bone substitutes and osteogenic proteins. Bone substitutes are materials that are osteo-conductive and osteo-inductive.

Amongst the osteo-conductive materials we must mention organic materials, such as collagen, and inorganic materials, such as tricalcium phosphate with hydroxyapatite; this is mainly recommended for interbody fusions, which are easier to achieve because of the greater area of the contact surfaces. Amongst osteoinductive materials are demineralized bone matrix and platelet concentrates that contain autologous growth factors. They are mainly indicated in posterolateral fusions that *a priori*, present a greater challenge. An experimental study in rabbits has shown an increase in fusion rates when demineralized bone matrix is added to autologous bone[18]. However, the addition of a platelet gel to the autologous graft did not increase the rate of posterolateral fusion in humans[19].

The osteogenic proteins that have been most developed for use in lumbar surgery are rhBMP-2 and rhBMP-7 or osteogenic protein 1 (OP-1). Experimental studies in animals have shown, in histological studies, a greater and more rapid formation, consolidation and remodeling of bone when BMP-2 is used in posterolateral fusions. More recently, BMP-2 has also been used in humans. X-ray assessment shows a greater percentage of bone fusion with relation to autologuos graft, both in interbody arthrodesis[20] and in posterolateral fusions.

It is necessary to possess a transporter for the administration of these materials. The most commonly used is collagen, although Boden et al[21] recommend tricalcium phosphate with hydroxyapatite for posterolateral fusions because collagen may have a barrier effect. However, Vaccaro et al[22], in cases of spondilolisthesis in which they have used OP-1, have not been able to demonstrate a greater percentage of posterolateral fusions when using iliac crest grafts. The greatest drawback of these products continues to be their high cost and scarcity.

Over the last decade, disc prosthesis have been used to reestablish the biomechanics of the intervertebral segment and reduce degeneration of adjacent levels (Fig. 3). The main indication is DDD with lumbar pain that does not respond to medical treatment, but when there is still preservation of an acceptable intervertebral disc height. Other indications, such as in upper adjacent disc syndrome after a previous lumbar fusion, are being studied. On the other hand, disc prosthesis is contraindicated in patients with osteoporosis, facet osteoarthritis, non-contained disc hernia and vertebral pathological conditions associated with scoliosis, listhesis or spinal canal stenosis[23]. Using strict inclusion criteria, only 5% of patients with DDD would be appropriate candidates for disc prosthesis[24].

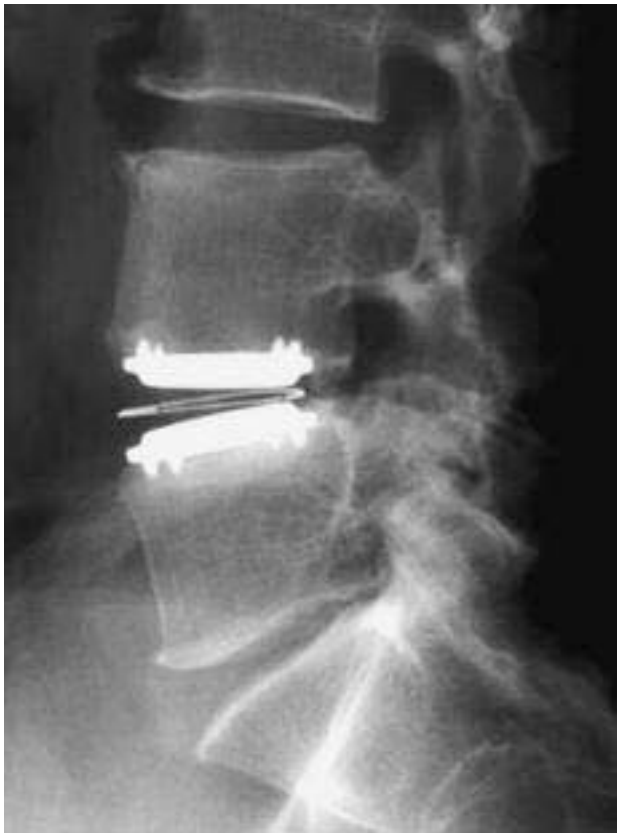

Figure 3. *Intervertebral disc prosthesis type Charité III®.*

Steffee developed an initial design that consisted of a central rubber nucleus between two titanium terminal plates (Acroflex®). The possibility of toxicity related to rubber vulcanization caused these to be withdrawn. Some of the best known prosthesis currently in use, mainly in Europe, are SB Charité III® (De-Puy Spine®) and La ProDisc II® (Synthes Inc). SB Charité III® is a modular prosthesis with 2 terminal chrome-cobalt plates with porous coating that is attached to the bone by means of spicules and a central non-slip polyethylene. On the other hand, ProDisc II® is also formed by 2 metal plates with a plasma coating and attaches to the bone by means of a keel and a central fixed polyeth-

Table 2. Published data on satisfactory results in patients with an intervertebral prosthesis

Author	Year	Prosthesis	Patients	Follow-up	Result
Blumenthal et al[25]	Spine 2005	Charité III	205	24 months	74%
Lemaire et al[26]	Clin Orthop 1997	Charité III	105	51 months	79%
Bertagnoli et al[27]	Eur Spine J 2002	ProDisc II	108	3-24 months	91%
Tropiano et al[28]	J Bone Joint Surg 2005	ProDisc II	55	8.7 years	75%

ylene component. Other prosthesis, such as Maverick ® (Medtronics) and FlexiCore® (Stryker), are designs with a friction pair that is metal-metal, that have come on the market during recent years and are still in the assessment stage.

Clinical studies presented over the last few years with Charité® and ProDisc® prosthesis report satisfactory clinical results in about 80-90% of patients, with variable follow-ups of 1 to 8 years (Table 2)[25-28]. Reports of significant complications rates have been published with these techniques, amongst which are those related to the approach route —severe vascular or neurological lesions in 9% of patients[28]—, others related to the implant itself —mal positioning or loosening in 2 and 6.5% of cases[29]— and a reoperation rate of 3.2 to 19.6%[30]. Furthermore, there are a series of issues pending resolution related to the future use of lumbar disc prosthesis.

The possible influence of the prosthesis on joint facets is unknown: We must keep in mind that the vertebral segment is formed by 3 joints and we are only carrying out a replacement of one of these. Another controversial issue is the problem due to reduced thickness of the polyethylene component in this type of prosthesis, both from the point of view of possible wear as also the pathological condition derived from the particles it may generate locally. We must also think of the future consequences of a disc prosthesis in case of possible osteoporosis which could cause migration or displacement[23].

McAfee et al[31] have shown that disc prosthesis placement is a very "demanding" technique, since the improvement in vertebral range of movement and final clinical results will depend directly on exact surgical positioning. X-ray follow-up in the long term has shown that disc prosthesis placement is not capable of completely eliminating the possibility of degeneration in the upper adjacent disc.

Bertagnoli[27] has found a rate of 4.6% of alteration in the upper adjacent disc in his cases. On the other hand, a systematic review of the literature shows that comparative studies of anterior vertebral fusions do not show significant differences in clinical results between these two surgical techniques[30].

Posterior dynamic stabilization procedures have been carried out for a decade. The aim of these procedures is to achieve an appropriate distribution of the load born by the intervertebral disc while maintaining physiological vertebral movement[32]. They are based on the rationale that postural lumbar pain is generated when the vertebral segment has to support an abnormal load, rather than on the idea of the instability of the segment itself. Load redistribution is achieved with 2 types of implants: pedicle stabilizers and interspinous spacers.

Dynamic stabilizers carry out a limited distraction of the interspinous processes and restrict lumbar extension movements. The proposed mechanism of action would be a reduction in foramen impingement, thus limiting the occupation of space in the spinal canal caused by the invagination of the hypertrophied ligamentum flavum during lumbar extension and unloading of the posterior joint facets due to absorption of part of the axial load, all of which would decrease posterior tension on the disc fibrous ring[33].

Pedicle implants are based on pedicle screws linked by a tension band. The most popular design is Dynesis® (Zimmer Spine), that connects the screws to a central polyester cord surrounded by a polyurethane cylindrical tube that limits lumbar extension (Fig. 4A). Another implant based on similar principles is Modulus C®, formed by polyaxial pedicle screws and a sliding plate made of carbon fiber with a preformed lordosis-shaped curvature.

Grob et al[34] have presented the results seen in 31 patients treated with Dynesis® with a 2 year follow-up. There was clinical improvement in 67% of cases, although 19% required reoperation. More recently, Schnake et al[35] reported failures with this same implant in 17% of cases. Therefore, the degree of fatigue suffered by the material in the long term if there is no fusion is controversial, and, furthermore, the implanted system may suffer breakage or loosening.

Based on the above mentioned mechanism of action, Senegas[36] has proposed the following indications for the implant of an interspinous spacer: a significant loss of disc material during a discectomy, a disc adjacent to a fused segment suffering degeneration, lumbar pain secondary to DDD in the early stages, symptomatic stenosis of the vertebral canal that improves with flexion and non-deforming facet syndrome caused by lumber hyperlordosis.

Amongst the designs currently available on the market we wish to mention: the interspinous U shaped (Fixano®), made of titanium, that is stabilized by adjusting the terminal brackets to the spinous processes; the Diam® (Medtronics),

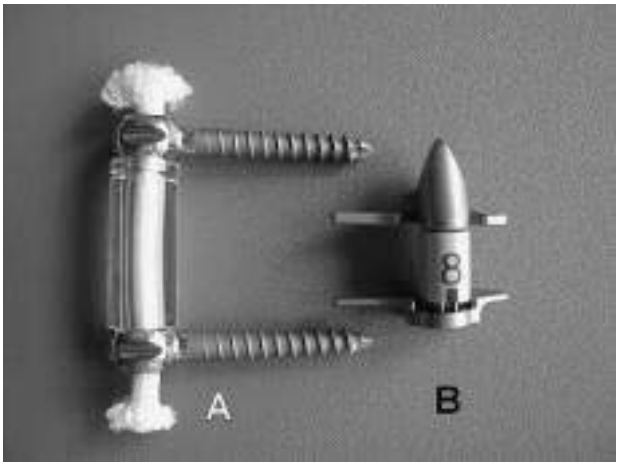

Figure 4. *Dynamic stabilizers: with pedicle screws type Dynesis® (Zimmer Spine®) (A), and interspinous spacer type X-Stop® (Zimmer Spine®) (B).*

a silicone flexible spacer that is attached by crossed ligatures; the Wallis® (Abbott Spine), an H shaped design, made of polyether ether ketones (PEEK), that is attached with Dacron tapes to adjacent spinous processes; and the X-STOP® (Zimmer Spine), an oval spacer, made of titanium, that is kept in place by the attachment of a lateral wing (Fig. 4B), and the ISS® (Biomet), dock shaped, made of titanium, that is attached by miniscrews to the spinous processes.

The surgical technique consists of removal of the interspinous ligament by means of a small posterior approach and the placement of an implant without distraction of the spinous processes. This technique is not advisable for L5/S1. The clinical results reported with the use of X-STOP® are good in 59% of cases with a 1 year followup[37]. Different complications related to the surgical technique have been reported, such as spinous process fracture or implant migration.

OTHER THERAPEUTIC OPTIONS: DISC REPAIR

There is growing interest in developing therapeutic options that are more physiological for DDD, and that could reduce the morbidity related to current more aggressive techniques. Indications for this type of treatment are limited to disc disease in the initial phase with lumbar or sciatic pain refractory to medical treatment, when there is disc protrusion, ring rupture or an MRI signal change, but always preserved acceptable disc height above 50%. The aim of the proposed therapy is to repair or regenerate the damaged disc using physical, chemical or biological means.

Within the physical therapies to be considered is "thermal discoplasty". This is based on the application of heat to the disc by means of a thermal catheter that has the capacity to generate a controlled temperature. The technique consists in placing a catheter tip in the posterior zone of the fibrous ring using a percutaneous approach.

The theoretical biological effect caused by the application of heat is denervation of nerve-endings within the fibrous ring, alteration of the ring collagen structure due to fibril retraction and an increase in subsequent vertebral segment stability. However, in the medical literature there is no clear consensus as to the achievement of these effects[38].

Another therapeutic option on the market is intradiscal electrothermal annuloplasty (IDET), which consists in the direct application of progressive heat to the disc for 4 minutes by means of a flexible thermal electrode. Treatment by radiofrequency is based on the introduction of a fine catheter that transmits the heat generated by a radiofrequency generator. There are 2 types on the market: one consists of a catheter that is introduced into the interior of the disc between the nucleus and the ring (SpineCath®), or the catheter can be placed between the lamina of the fibrous ring (DiscTrode®).The other one, a laser, is based on the use of a catheter that is capable of generating photothermal heat by means of red light emission. The most used is neodym (Nd): YAG laser. It has the drawback of not being able to control the temperature applied, therefore it is necessary to be able to see the disc directly by means of endoscopy.

Saal and Saal[39], in 58 selected patients, with a minimum followup of 2 years, obtained satisfactory results in 71% of cases treated with IDET. However, random and comparative studies with a placebo have not been able to show significant differences in the final clinical results obtained[40]. Furthermore, Cohen et al[41] have found in their series a complication rate of 10% related to the surgical technique: paresthesias and transient nerve root pain, specially in obese patients.

On the other hand, certain controversial aspects still have to be evaluated, such as the distribution of heat in the interior of the disc. Bono et al[42] have shown that the heat applied only penetrates a distance of 9 to 14 mm from the tip of the electrode. It is also necessary to assess the duration of symptomatic improvement in the long term, since it is not known if the disc nerves have the capacity to regenerate, and it is also necessary to take into account possible repercussions of annular collagen change on future disc degeneration.

The chemical alternative used to repair a damaged disc is based on the use of hydrogels as substitutes of the *nucleus pulposus.* These hydrogels are synthetic polymers with a three-dimensional structure and hydrophilic properties, which means they have the capacity to absorb and retain water in their interior[43]. These characteristics provide them with a certain elasticity, so that they are resistant to axial loading and, moreover, they become swollen with water and can therefore fill-in the disc cavity. Due to these properties they have been proposed as prosthesis for the *nucleus pulposus* with the aim of reestablishing and maintaining disc

height, uniformly distributing loads and in this manner generating tension in the fibers of the disc ring and also stabilizing segment movements. Ray has developed a so called a prosthetic disc nucleus or PDN (Raymedica®). It consists of a hydrogel (polyacrylonitrile, PAN) encapsulated in a polyethylene jacket, that increases in thickness and height when hydrated.

Since 2003 the third generation of this implant is used with specific instruments for its placement. It requires a minimum disc height of 5 mm for its placement and an unbroken fibrous ring to prevent its migration. The technique consists in introducing a device mediolaterally in the disc space after conventional discectomy.

Biomechanical studies carried out on cadavers have shown behavior similar to that of an intact intervertebral disc. Tests have also been carried out with a hydrogel based on polyvynylalcohol (PVA). This device is capable of absorbing up to 80% water. It is placed by the percutaneous route with a trocart designed to cause a minimal annulotomy through which the device is introduced. It is known as "Aquarelle Hydrogel®" (Stryker). So far only preclinical studies have been carried out in animals that have demonstrated that this device is biocompatible.

Other designs that have recently come on the market are the Newcleus spiral® (Zimmer Spine) and the NeuDisc® (Replication Medical). The Newcleus is a polycarbonate urethane elastomere (PCU) with a capacity of absorbing water of 35%. It possesses a spiral form and is introduced within the disc by means of conventional discectomy. Preclinical studied have confirmed adequate biocompatibility and optimum biomechanical behavior. NeuDisc is made of a polymer known as "Aquacryl®", reinforced by a Dacron mesh. The material is inserted in a dehydrated state, so that its introduction is minimally invasive. This device is capable of absorbing up to 90% water. Biocompatibility studies have been favorable.

A variant of nucleus prosthesis are so-called "*in situ* polymers". These are not solid implants themselves, but liquid components that harden a few minutes after placement in the disc space. The best known is Dascor® (Disc Dynamics), an injectable polyurethane. Implantation is performed by discectomy and introduction of a catheter that inflates a balloon, which is subsequently filled with the material. Biomechanical studies have been carried out on cadavers that show that the behavior of this component is appropriate. A small trial has also been carried out on humans using injectable silicone material introduced percutaneously, "Sinux Anr®"; *in vivo* results have been satisfactory.

There are still very few clinical studies in humans with these implants. The design that has been most assessed up to date is the PDN®. Klara and Ray[44] have presented results since 1999 in 51 patients, and these have been satisfactory in 90% of the cases. Newcleus® has been implanted in 5 patients, with a follow-up of 23 months, clinical improvement was seen in all of these[45]. Dascor® has been tested in 16 patients, results are still pending publication. The main problem seen with this type of implant is material migration or extrusion, and fracture of the terminal plate, usually seen in about 10% of cases in which PDN was used. With the new design (PDN-SOLO) the rate of reoperations has been reduced to less than 5%. Therefore, an essential requirement for its use is a limited opening of the fibrous ring and absence of alterations in the facet joints.

There is also so-called "cell therapy" as a biological alternative. Within this alternative there are reparation techniques and regeneration techniques. Reparation techniques consist in transplant of the intervertebral disc. There have been attempts made to transplant frozen or cryopreserved discs in experimental animals. Up to date, all these have failed, because during the period of initial incorporation, the first 4-6 months, there has been evident structural degeneration and loss of height of the transplanted disc[46].

There is important work being carried out on the development of techniques of disc regeneration. The rationale for this is the potential for inducing growth and cell differentiation to promote the synthesis of extracellular matrix: proteoglycans in the *nucleus pulposus* and type II collagen in the fibrous ring. There are two possibilities within disc regeneration techniques: the culture of disc cells and tissue engineering of non-disc cells.

There have been trials of disc cell culture in experimental animals (*in vivo*), in which autologous disc cell cultures have been inoculated into the previously damaged disc space. Ganey et al[47] have shown in dogs that both disc structure and height are maintained after 12 months of the transplant of this autologous cell culture. They have also determined that the transplanted cells that participated in the formation of the extracellular matrix survived. In humans, there have been some preliminary phase clinical studies with very promising results and there are certain firms (CoDon) that market this technique.

Tissue engineering with non-disc cells has the theoretical advantage of preventing the morbidity associated with the extraction of disc cells and the uncertainty of using biological material that is already suffering degeneration. Bone marrow mesenchymal stem cells (MSC) have been used. These were cultured in microenvironmental conditions similar to an intact disc and cell proliferation and differentiation with phenotypes similar to the *nucleus pulposus* cells have been obtained; therefore these cells may be of use to repair discs suffering degeneration. Recently this technique has been assessed in experimental animals, with similar results to those seen when MSC are transplanted to discs suffering degeneration[48].

Another important technique used for disc repair are the so-called "coadjuvant techniques" that have the aim of stimulating or increasing cell development in cultures. The following have been studied in recent years: the appropriate

cell support, microenvironmental conditions, the administration of growth factors and gene therapy. The use of synthetic polymers as a cell substrate or support, such as porous calcium polyphosphate, in *nucleus pulposus* cell cultures has increased the synthesis of proteoglycans and type II collagen, but has not achieved the values of native disc tissue. Other substrates used have been hyaluronic acid and collagen[49]. As to appropriate environmental conditions for cell growth, it has been demonstrated that a reduced oxygen tension in cultures of MSCs increases the expression of the hypoxia factor that promotes a phenotype similar to that of *nucleus pulposus* cells.

The administration of growth factors, such as the transformed growth factor (TGF-_1) and OP-1, in *in vitro* studies have shown a promising capacity for increasing the synthesis of proteoglycans on the part of disc cells. Kim et al[50] have administered BMP-2 to cultures of human disc cells and have achieved an increase in the synthesis of proteoglycans of 200%. On the other hand, using gene therapy, coded genes with the capacity to produce growth factors have been transferred to degenerated discs. Using this technique it was seen that there was a significant increase in the production of growth factors and proteoglycan synthesis by the modified cells, in relation to the control group.

In spite of all these promising experimental and preliminary clinical results, there are still a number of important issues that must be resolved in relation to the use of cell therapy in disc disease. It is necessary to know the stage of disc degeneration for optimum treatment, how long the cell response will persist, and finally, if a repaired disc will no longer cause the patient pain.

THE FUTURE OF NON-FUSION TECHNIQUES

The main problems encountered by research of the so-called "non-fusion techniques" are lack of knowledge of intervertebral disc biology, biomechanical complexity of a triple joint and the lack of capacity to identify the specific pain generating entity or site. Therefore, work is mostly being done on mechanical solutions that attempt to imitate the biology of the vertebral segment. Amongst the prototypes under development are prosthesis for facet joints (Archus®) and systems for the reconstruction of the posterior ring wall, that act in a similar way to an "expandable patch" when placed in the subannular space after a discectomy (Anulex®).

CONCLUSIONS

In spite of sophisticated modern methods, in cases of DDD, spine surgeons continue to apply the same procedures they have been performing for the last 50 years: neural decompression and lumbar fusion. Although clinical results support this surgical procedure, possible complications, effects on adjacent segments or the uncertainty of what the final results will be, all stimulate the search for other options that allow the preservation of lumbar segmental movement or are surgically less aggressive.

Currently there are many alternatives to conventional vertebral arthrodesis. However, the most appropriate moment for this procedure during the evolution of disc degeneration is still unknown. Many resources require improvements of their designs and implantation techniques before their use should become generally accepted. Furthermore, some of them are still in the experimental phase or there are only data from preliminary studies.

Therefore, the challenge of the future for all those who work with lumbar pain is the performance of good quality comparative studies that identify the time factors of the different systems, that differentiate DDD from other conditions by means of specific diagnostic tests, and that determine the most effective treatments.

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