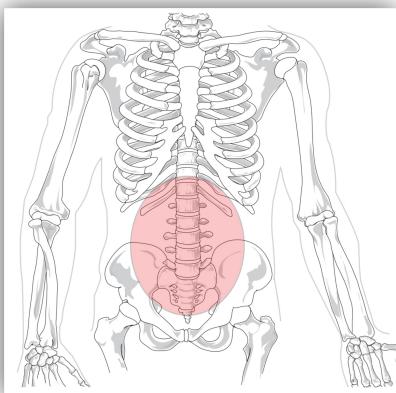


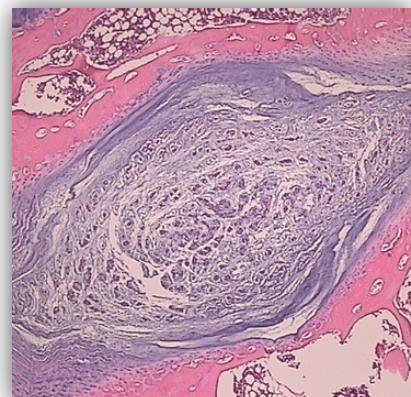


Discogenic Low Back Pain

An Overview on the Disease and its Treatments



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Abstract

Low back pain (LBP) is a major medical and socio-economic burden to the society, which can fluctuate over time and lead to high costs of healthcare, regular work absence and disablement. A vast majority of people will experience LBP some time in their life, which is especially apparent in advanced economies. Studies have shown around 20% of overall LBP cases correlate with intervertebral disc problems occurring in lumbar spine, which contributes to over a half of severe LBP cases. Various clinical guidelines have been established on LBP management, but treatments are rather conservative or ineffectual, and can hardly deal with underlying causes (e.g. lumbar disc degeneration). Surgeries or other forms of disc intervention have received positive feedback, but such may change the physical supporting structure of lumbar spine, exacerbating the situation in the long run. Bearing in mind the goal of reconstruction of properties and functions of the lumbar discs, this report, through an overview on discogenic LBP and its existing therapies, is going to introduce a prospective solution by reviewing cutting-edge research in the field of Tissue Engineering and discussing the challenges ahead. Finally, it is going to suggest a possible approach which may overcome these issues and lead to progress in research and development.

1. Introduction

1.1 Low Back Pain: Epidemiology, Symptoms, and Consequences

Low back pain (LBP) is a musculoskeletal disorder involving the back. While approximately two thirds of people will experience LBP some time in their life, 85% will suffer from it by the age of 50.¹⁻³ Being a major medical problem to western countries, LBP is the one of the most common symptom-related reasons for doctor visits.^{2,4}

To summarize LBP's epidemiological data based on incidence and prevalence has been difficult, mainly because of agreement shortage on classification.^{2,5} Not only a variety of standards have been used to classify LBP, but the situation was also worsened by numerous terms used to define one concept.² Research in LBP's epidemiology is further restricted by 'recall bias' (i.e. people tend to forget their experience of pain) and heavily affected the way epidemiological survey questions are asked.² Nevertheless, studies have conducted towards incidence and prevalence of LBP. Studies in Netherlands and United Kingdom have shown the incidence of LBP was

approximately 4%, with the highest incidence occurring between 45 and 64 years of age.²

Lifetime prevalence of LBP was reported to be over 50% in Netherlands, with about half of the respondents reporting to have LBP in the previous year.^{2,5} Generally speaking, LBP is a common, long-term disorder, especially among the middle-aged group and in western societies, probably due to intensive daily work.

The most significant symptoms of LBP are pain and disability. The description of pain varies from diffuse pain to point tenderness, and pain may be worsen with specific positions or movements.⁴ Disability and work absenteeism thereafter are often reported, lasting a variety of periods from several days to even some months.² Sleep problems are also reported to correlate with chronic LBP, which leaves patients with more difficulty in falling sleep as well as less satisfaction towards sleep quality.⁶ Other problems, e.g. anxiety or depression, may also occur in chronic LBP patients.^{7,8} Although the symptoms usually do not last long, it has been suggested that LBP may fluctuate over time, with recurrence and exacerbation (Fig.1). The suggestion is of significance, since a large proportion of LBP patients have experienced

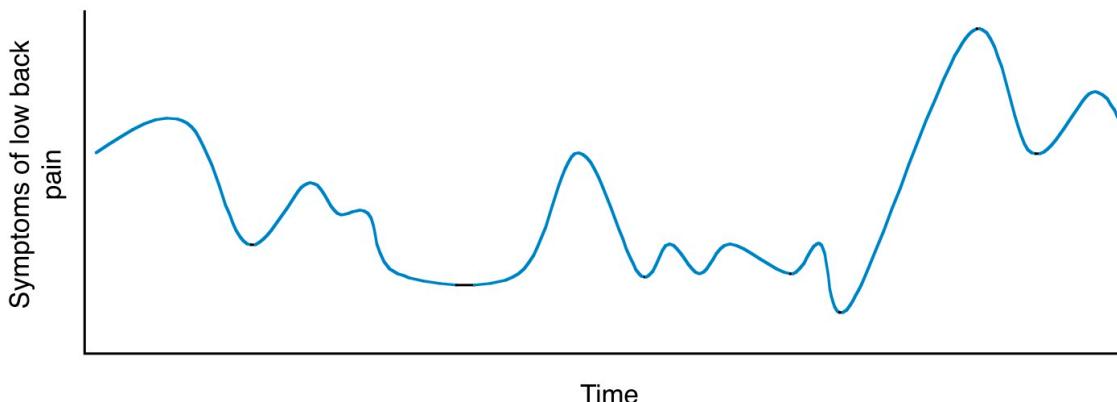


Figure 1. The proposed course of low back pain, showing significant recurrence. (Tulder et al., 2002)

| | United Kingdom | | Sweden | | Netherlands | |
|----------------|-------------------------------------|--------------|-------------------------------------|--------------|-------------------------------------|--------------|
| Costs | Costs in US \$ million (% of total) | Costs/capita | Costs in US \$ million (% of total) | Costs/capita | Costs in US \$ million (% of total) | Costs/capita |
| Direct costs | 385 (11.5) | 7 | 213 (8) | 24 | 368 (7.4) | 24 |
| Indirect costs | 2948 (88.5) | 113 | 2262 (92) | 266 | 4600 (92.6) | 299 |
| Total costs | 3333 (100) | 120 | 2475 (100) | 290 | 4968 (100) | 323 |

Figure 2. Costs of LBP in the UK, Sweden and the Netherlands (in US \$. Tulder et al., 2002).

previous attacks which are often sudden and acute.^{2,9} Thus, it is important to find out the underlying pathological cause of LBP so as to prevent future recurrence and deterioration.

Although far from complete, data from a number of studies has shown that LBP can lead to high socio-economic consequences (Fig.2). If evaluated only through production loss, the total costs of LBP in 1970s and 1980s were both over US\$10 billion,^{10,11} while the total costs in some European countries were around US\$3-5 billion in social perspective.² The majority of the costs are indirect as a result of work absenteeism and disablement, while medical expenses contribute to a significant proportion of burden for some chronic LBP patients.² As a whole, LBP can be regarded as a major social burden.

1.2 Intervertebral Disc (IVD): Anatomy and Physiology

Lying between two vertebrae, an intervertebral disc can be mainly divided into three parts: annulus fibrosus (AF), a thick cartilage structure as outer ring; nucleus pulposus (NP), a jelly-like

core embedded in AF; and two vertebral endplates (VE) lying inferiorly and superiorly, between which NP is sandwiched (Fig.3). IVD is highly hydrated in a healthy adult, containing 70-80% of water¹² (Fig.4). Hydration level in IVD is of utter significance not only in biomechanical perspectives but also in nutrition supply.

The central part of NP is made up of randomly positioned collagen fibres as well as long, radially-arranged elastin fibres. Such composition gives a solidified character in the centre.¹² On the other hand, this small centre is surrounded by a gel rich in proteoglycan (especially aggrecan and versican), whose side chains account for high hydration rate as a whole (Fig.4). Only a low density of chondrocyte-like cells are found in the NP. It may be difficult to purify these cells from surrounding matrix, making in-depth analysis towards their physiological properties hard to progress.

On the contrary, AF contains more collagen than proteoglycan, giving it slightly more stiffness compared with NP (Fig.4). AF comprises 15 to 25 collagen rings, or lamellae, with collagen fibres in

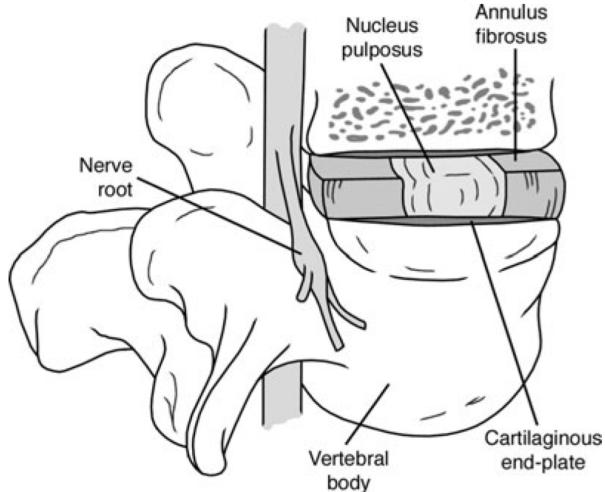


Figure 3. Anatomy of a healthy spinal segment. (Raj, 2008)

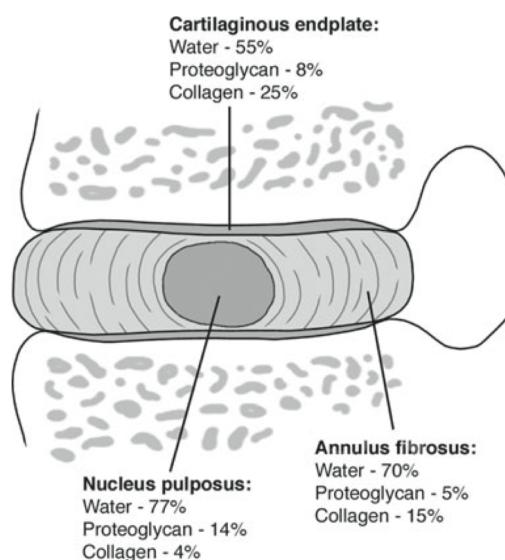


Figure 4. Chemical components of an IVD. (Raj, 2008)

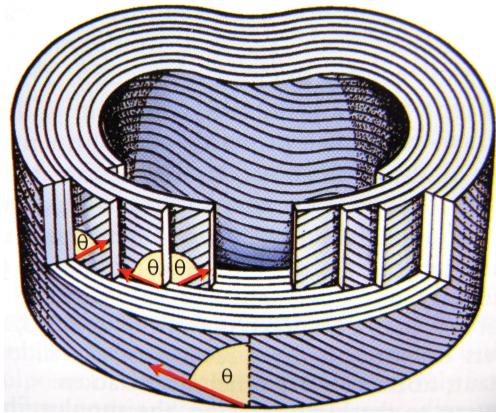


Figure 5. Lamellae of AF. Collagen fibres are arranged at $\theta=65^\circ$ approx. (Neumann, 2010)

each lamellae lying parallel against each other.¹³ The fibres between adjacent lamellae pointing alternately upwards or downwards, but at almost the same angle to the longitudinal axis (Fig.5). Elastin fibres may contribute to the restoration of its original arrangement after bending as well as to the linking of lamellae. Elongated fibroblast-like cells are more likely to be found in the outer range of AF, whose function in disc is still not well-understood.^{12,14}

The VE is a layer of hyaline cartilage which acts as interface between IVD and vertebral body. Collagen fibres therein continues to the disc as well as to the cleft of perforated compact bone, joining the two together (Fig.6). It has been found that VE is critical in NP cells' viability, probably because of the mere path of nutrition delivery through VE to NP.¹⁵ Blood vessels and nerves can be found in VE and sometimes in the outer ring of AF, while most parts of the IVD become avascular and non-neural with growth.

When loaded from above, NP attempts to expand out against AF, stretching AF's lamellae while diffusing the force. Pressure exerted and height reduced in NP can therefore be quickly balanced by tensile strength and strain respectively in AF fibres. In this way, pressure applied vertically to NP through vertebrae is passed on to its stiff surroundings, which acts as a shock absorber. The force can thus be instantly diverted into AF, easing the transmitting speed down the spine. With the load removed, the elastic potential stored in AF's lamellae causes it to recoil and therefore restore the original arrangement of IVD as a whole.^{12,13}

Overall speaking, IVD can be viewed as an extensive extracellular matrix where only few cells reside in. There has been a dynamic yet unclear balance between synthesis, decomposition,

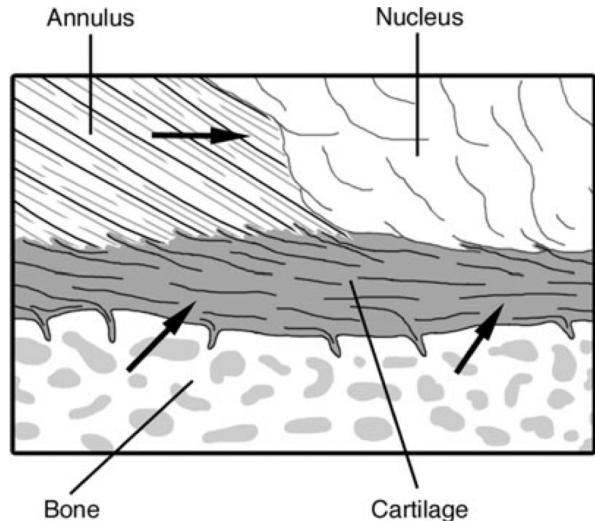


Figure 6. Interface between AF, NP, VE and vertebral body. Arrows indicate nutrition flow. (Raj, 2008)

and accumulation of matrix components, which decides the chemical and mechanical characteristics of the matrix. Such properties are also of significance in maintaining the avascular and non-neural features of the disc.¹²

1.3 Pathophysiology of Discogenic Low Back Pain

A number of pathological signs can indicate the degeneration of IVDs. With the occurrence of trauma or increasing age, NP generally becomes more fibrotic and less hydrated and gel-like, which leads to weakened signals in MRI. With disorganized collagen and elastin networks, lamellae in AF become irregular. Fissures can often be found within the disc, sometimes even deep into NP from AF, through which not only nerves can grow into IVD but also NP can protrude and exert pressure on the outlying nerves thereafter.

Pathology can also be analyzed from cellular and molecular perspectives. Although little is known of its physiological basis, a significant loss of proteoglycan can be identified, especially in NP, causing a decrease in the amount of glycosaminoglycan. Such decrease is found accountable for the loss in disc's hydration level. In cellular level, disc cells are very sensitive to oxygen level and pH *in vitro*, therefore failure in nutrition supply either because of aging or of calcified VEs can result in cell necrosis. Reports have shown over 50% of disc cells are found necrotic in a degenerating disc, losing the ability to maintain the healthy balance in extracellular matrix.

Nevertheless, groups of vascular granulation tissue can be found in the AFs of some discogenic LBP patients. The presence of these tissues may indicate the transmission of some growth factors or even pain regulators through the blood, which is a symbol of the occurrence of inflammatory reaction. Nerves are also found in some areas in IVD that should have been non-neural, increasing the likelihood of LBP occurrence.

Generally speaking, the aetiology of discogenic LBP remains unclear in many aspects although a general outline can be figured out. A large proportion of disc cells necrotize due to changes in extracellular environment, losing the ability to maintain dynamic balance in matrix. Loss in proteoglycan, in particular, is of significance, causing a loss of hydration in the disc and thus making it more fibrotic as well as limiting the nutrition supply towards disc cells. Nerves and blood vessels grow into the previously avascular and non-neural parts of the disc following the occurrence of fissures in AF, thus making inflammatory reaction and pain generation possible. Disc herniation can also exert pressure on peripheral nerve roots.

2. Existing Solutions and Respective Limitations

Treatments towards discogenic LBP need to be adjusted according to the level of the development of pain and disc degeneration. Thus, we can analyze the existing solutions towards the issue from two aspects: conservative early (and middle) stage solutions, as well as more invasive late stage treatments.

2.1 Early and Middle Stages Solutions

Conservative modalities are always the first line of treatment because it is non-invasive to the patients and most of the modalities have nearly no adverse side effects.

2.1.1 Analgesics

One of the most commonly used treatments in an early stage is analgesic. It aims at relieving the patients from pain by the use of simple pain medications.

The typically preferred first medication is acetaminophen, which is usually called paracetamol. It is classified as a mild analgesic because it is less toxic when compared with other

pain relievers, such as NSAIDs when used chronically at standard doses. However, it is significantly more toxic when used overdose. In addition, high doses of it will cause liver damage because it is metabolized by the liver and is hepatotoxic. According to the US Food and Drug Administration, “Acetaminophen can cause serious liver damage if more than directed is used.”¹⁶

The second choice of medication is NSAIDs. They treat pain by blocking cyclooxygenase-2 (COX-2) in the central nervous system. Although they are more effective than acetaminophen, they carry more side effects. For example, since they not only inhibit the activity of COX-2, but also cyclooxygenase-1 (COX-1), they may cause gastrointestinal bleeding and ulcers. Besides, they will also cause cardiovascular problems as they increase the risk of myocardial infarction and stroke.⁸

If the pain is still not managed well after the use of the above two medications, then opioids, such as morphine may need to be used. Opioids work by binding to opioid receptors and the analgesic effects of it are because of the decreased perception and reaction to pain, as well as increase the tolerance of pain. Even though it has a strong analgesic effects, it is not advised to use in long term for chronic low back pain because it will bring the patients a series of severe side effects, including sedation, respiratory depression, cough suppression and constipation. In addition, opioid dependence will be developed with continuous use and it will lead to a withdrawal syndrome with sudden discontinuation.¹⁷

2.1.2 Physiotherapy

Chiropractic is a form of alternative medicine, which holds the belief that mechanical disorders of the musculoskeletal system, such as low back pain affect health through the nervous system.¹⁸

Chiropractors will use a multi-modal approach to cure the patients. Firstly, they will provide reassurance to the patient that there is nothing severe causing the pain, and then help them to relieve pain by heat or cold treatment and over-the-counter medication combined with gentle exercises. They will also have some self-management suggestions on the daily activities, such as sitting, standing, lifting and sleeping position for the patients. After a few days or weeks, the patients will receive spinal

mobilization and manipulation, and soft tissue therapy to the surrounding musculature. All in all, chiropractic seems to be a comprehensive measure due to the combined use of multiple approaches and most importantly, it is a treatment with low risk of severe adverse side effects.¹⁹

However, the current evidence shows that most of the chiropractic therapies, for instance, spinal manipulative therapy and superficial heat application, demonstrate only small effects.²⁰ Most importantly, most of the therapies, for example, Activator used by the chiropractors have not been subjected to strict scientific scrutiny.

Another well-known physical treatment for low back pain is called Alexander Technique, which is an educational discipline to avoid the physical decline leaded by habituated mannerisms. This approach emphasizes on the mindful actions and it is applied dynamically to daily movements, such as sitting and walking. The practitioners will jointly use gentle hands-on guidance and verbal instructions to help the patients to realize and prevent the everyday movements that bring them low back pain. In addition, the patients will also be taught a proper lying down procedure so that the low back pain can be alleviated. After learning all these techniques, the patients can practice it at home every day by themselves. As a result, it is cost-effective in the management of chronic low back pain.²¹

However, the road of learning will be rocky because it is very difficult for the patients to alter their daily habits, for example, the sitting position. Besides, the effects of Alexander technique are typically small and there is no good scientific evidence to support that it is useful in curing low back pain.

2.2 Late Stage Treatments

Surgical disc intervention will then be applied on the patients who have failed conservative means or who demonstrate significant neurological compromise.

2.2.1 Spinal Fusion

Spinal fusion refers to a surgical procedure that joins two or more adjacent vertebrae. Autograft (from the patient) or allograft (from the donor) supplementary bone chips need to be used in the conjunction with the natural bone growth

processes of the bodies in order to fuse the vertebrae. This can help eliminate the low back pain of the patients by immobilizing the degenerated vertebrae themselves.²²

The main disadvantage of spinal fusion is that it will reduce the flexibility of movement of the patients. Since there will be loss of movement in the fusion segment, it will probably limit the range of motion of the patients. Another important consequence is that it will hasten pathological progress in other unaffected sites. Apart from that, there are also some other adverse effects associated with spinal fusion, they include permanent or transient lumbar or sacral root injury, abdominal wall hematoma, deep venous thrombosis and so on.²³

2.2.2 Total Disc Replacement

Total disc replacement, also known as disc arthroplasty, refers to a surgical procedure that a painful intervertebral disc is removed by decompression surgery and replaced with a prosthetic (Fig.7) or donated disc. The artificial one usually consists of two metal plates and in between of them, there will be a polyethylene core glides. It aims at mimicking the movement of a normal disc.^{22,24}

When compared with spinal fusion, disc arthroplasty may probably be better because the mobility in the motion segment can be retained while the movement of the fusion segment will lose after fusion operations. In addition, the effects of total disc replacement seem to be as good as that of fusion surgery, but with fewer complications.²⁵



Figure 7. One of the IVD prostheses used in disc arthroplasty. (Wai et al., 2012)

However, there will be some adverse effects and limitations regarding total disc replacement. For prostheses, the anti-fatigue and anti-corrosion ability of metal components are still in doubt. As for donated ones, availability is extremely limited, and there may be rejection towards disc cells so the disc may degenerate soon after transplantation. Another limitation concerns low availability of donor discs. Symptomatically, side effects include isolated axial neck pain, vertebral body fracture, rheumatoid arthritis and so on.

2.2.3 Discectomy

Discectomy refers to a surgical treatment that removes a herniated disc from the spinal canal. When a disc is herniated, the patients will suffer low back pain since the herniated disc will press on the surrounding nerve root or spinal cord. As a result, the removal of the herniated disc can alleviate the pain of the patients. However, the main common problem of discectomy is recurrent herniation, which means that there will be a chance (about 10-15%) that another fragment of disc will be herniated and lead to similar symptoms in the future.

There are actually two kinds of discectomies: the more traditional open discectomy and the newer endoscopic micro-discectomy.

Open discectomy is the surgical procedure that the surgeon makes an incision over the center of the back of the patients and removes the herniated disc by looking at the actual disc. After that, the pressure applying on the nerves of the patients can then be relieved. However, the surrounding muscles have to be cut in order to give the surgeon to access to the herniated disc, the patients may be more painful and take a longer time to be recovered. In addition, the whole surgery requires general anesthesia.

Endoscopic micro-discectomy is a similar surgical procedure to open discectomy, but with a much smaller incisions made on the back of the patients because the surgeon only need to make a small incision and insert the tiny-shaped implements down to the disc. The whole surgery can then be carried out through the implements and hence the muscles only need to be moved out of the way instead of cutting away. Next, the surgeon will use a very small camera to find out the fragment of the herniated disc and then remove it by special instruments instead of having direct visualization

of the fragment of the disc and remove it. Besides, the procedure may not require general anesthesia. As a result, endoscopic micro-discectomy can allow the patients to have faster recovery and is much less invasive than open discectomy.

2.2.4 Nucleoplasty

Nucleoplasty is a novel technique for the treatment of discogenic low back pain.²⁶ The procedure of it is to first insert a special probe into the faulty intervertebral disc and a small portion of nucleus material from the disc nucleus will be eliminated by emitting Coblation®, which is a form of radiofrequency. Then, the pressure in the nucleus will be reduced. After that, the nerve root tension can be reduced and also the disc will be allowed to protrude to implode inward so that the contact pressure between the spinal nerve root and the protruding disc can be reduced. As a result, the radicular low back pain of the patients can be alleviated.²⁷

This procedure is regarded as minimally invasive because it does not require the surgeon to look at the targeted disc directly and it can be delivered through a very small incision on the back of the patients.^{26,27}

However, nucleoplasty cannot be applied to the injured disc, which is very narrow or if the spine is misaligned. Otherwise, the spine will be unstable. In addition, there is an array of adverse effects resulting from nucleoplasty, including end-plate damage, nerve injury and disc injury.²⁶

3. Tissue Engineering as a Prospective Solution

Having reviewed the current methods dealing with symptomatic IVD degeneration, we come to a consensus that these strategies are hardly effective in tackling the root cause. Realizing the social-economic burden that LBP has brought us, there has been a growing demand recently for brand new treatments.²⁸ Impressive outcomes of stem cell research have provided possibilities of using cell-based therapies. Therefore, we would like to suggest a tissue engineering (regenerative medicine) approach which is widely regarded as a promising solution.^{15,28}

The goal of tissue engineering is clear: to restore or improve physiological and biomechanical properties and functions of IVD. Such can be achieved from various perspectives, e.g. by

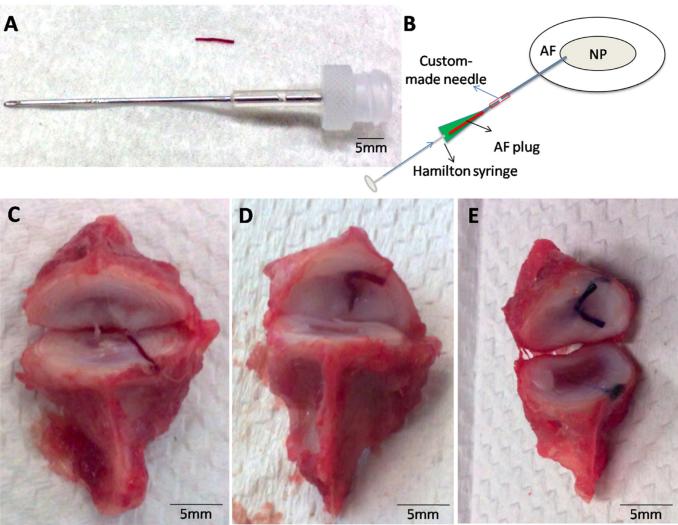


Figure 9. Schematic drawing and successful injection of rabbit MSCs using annulus plug. (Chik et al., 2015)

repopulating the degenerated discs with disc cells, by repair or reconstruction of either a specific tissue or the entire organ, and so on.

Several ways have been proposed under the broad terms of tissue engineering, and they can generally be categorized into injection, insertion and transplant. Injection involves either stem cells (e.g. mesenchymal stem cells, or MSCs) or isolated disc cells, and they will be transmitted into designated IVD parts through a needle. Insertion uses the same method for transmission, but involves a combination of tissues, extracellular matrix (ECM) and sometimes scaffolds. Transplant can best be described as replacement of the entire disc by a structured complex generated *in vitro*.

Cutting-edge research has shown success in animal models as well as confirmed the concept and feasibility of tissue engineering approach in human. Injection of MSCs to human IVD has resulted in improvement in its functions²⁹; a 50:50 mixture of human disc cells and MSCs *in vitro* has yielded ECM rich in proteoglycan²⁹; IVD complex transplant in animals has also performed successfully¹⁵. However, there are a number of doubts and challenges in this field that need further research (Fig.8).

Cell is one of the central components of tissue engineering, and there have been series of obstacles in this aspect. Firstly, it remains controversial whether tissue engineering should use stem cells or autologous disc cells.¹⁵ If we are to use disc cells, there is currently no benign site for harvesting, and puncturing a healthy disc may lead to its degeneration or other detrimental effect. Moreover, cells in different parts of the IVD are largely distinct, which means we have to harvest

at least three types of cells from the body and culture them *in vitro*. On the other hand, if we choose stem cells, there is great difficulty in differentiating them exactly towards disc cells as we do not even know the determining characteristics of different IVD cells, and they may differentiate into a variety of cell types or even fall into oncogenesis after implantation. Another challenge concerns *in vitro* cell culture, especially that of disc cells. As disc cells live in an avascular environment *in vivo* and generate ATP mainly through glycolysis, they seem to be highly sensitive towards extracellular oxygen level and pH, which increases the difficulty in *in vitro* culture.

There are also challenges regarding different categories of tissue engineering approach. Injection or insertion involves puncturing into the disc, which may cause both leakage of engineered materials and damage to the target disc. In fact, studies have shown a considerable proportion of leakage when injecting MSCs as well as giving mechanical loading thereafter^{30,31}, and leaked MSCs will form osteophytes around the vertebrae, which exacerbates the situation. Although there has been improved injection methods where MSCs wrapped in collagen microspheres³⁰, cross-linked collagen annulus plug³¹ (Fig.9) or atelocollagen gel³² are delivered into the IVD, leakage still remains an obstacle that requires better solution and careful consideration. As for transplant, the interface between an engineered IVD and adjacent vertebrae remains a notable barrier, although inspiring efforts have been made in constructing a Spinal Motion Segment which comprises both a disc complex and two vertebra-like subunits³³.

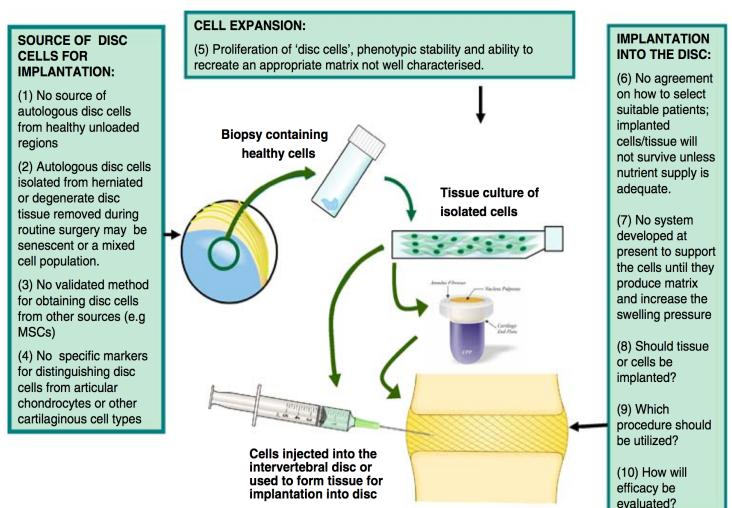


Figure 8. Challenges of Tissue Engineering at a glance. (Kandel et al., 2008)

Even the bioengineered complex has been successfully implanted, there may still be great challenges in maintaining the complex as well as restoring biomechanical functions. Because of the limiting nutrition conditions in the extracellular environment, implanted stem cells may either necrotize or hasten the demise of originally populated disc cells, which ceases the ECM regeneration thereafter.²⁹ Indications may be drawn that authentic disc cells might be the only solution capable of survival. Another limiting factor is the vertebral endplate, whose calcification can terminate the nutrition flow towards the implanted complex, making all previous efforts in vain¹⁵. Furthermore, it has been estimated that the restoration of biomechanical property *in vivo* takes as long as several years, which implies that mature structure may need to be engineered before we can perform any transplantation.¹⁵ Other challenges include but not limited to, the difficulty of structuring scaffolds due to complexity of IVD's biological and biomechanical environment³⁴, the unknown capability of pain relief, as well as the questioned feasibility of detailed assessment for both pre-treatment curability and post-treatment efficacy.¹⁵

Bearing in mind the challenges as well as the goal, we would like to suggest another possible solution consisting of xenogeneic IVD decellularization and recellularization. After harvesting xenogeneic IVD with a case-by-case optimal size, scaffold can be obtained by washing away immunotargeted xenogeneic cells in the selected IVD using chemical solutions, while most parts of the ECM are well-preserved. This decellularized scaffold is then re-populated with autologous MSCs, where these stem cells may be able to settle, migrate, and interact with this well-preserved extracellular environment³⁵, increasing the possibility of a controlled differentiation towards the disc cells we want. Finally, a mature recellularized IVD may be obtained after a period of time if cultured in an optimal environment *in vitro*. Transplantation of this complex into the body can thus be performed after a series of biomechanical and biochemical tests. In fact, there has been research in rabbits using NP-cell derived acellular ECM combined with MSC recellularization, where support towards MSCs' survival and matrix production was identified.³⁵ Nevertheless, we are still clearly aware of the obstacles ahead: important signal molecules in the ECM may be washed away during decellularization process; the decellularization may not be thorough;

reintroduced cells may not survive long; and so on. Further research thereto is urged in light of its delightful outcome as well as its promising potential to be applied in clinical setting.

4. Conclusion

Low back pain has been an increasingly notable musculoskeletal disorder with a high socio-economic burden for the society as consequence. Intervertebral disc degeneration and its associated low back pain has aroused global attention, but pathophysiology of discogenic low back pain still remains ambiguous. Although, over years of clinical practice, conventional approaches have yielded an overall satisfying outcome in pain relief, there has been more and more consensus recently indicating such methods are either ineffectual or potentially detrimental. Limitations of current practice, the goal of restoration, as well as the rise of stem cells have inspired research in tissue engineering as a prospective solution. Notwithstanding the impressive outcomes, a large number of challenges are still lying in front of further progress. In this report, we have proposed a decellularization-recellularization method using scaffold obtained xenogeneically, which, in spite of possible obstacles, may overcome the challenges and lead to delightful progress in research and development. Further analysis towards pathogenesis of the disease and disc cell properties is urgently demanded before we are able to carry on in-depth research in tissue engineering, while popularization of low back pain prevention in daily life also remains important.

5. Acknowledgement

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Jacky Zhao is responsible for outline, introduction, Tissue Engineering and overall editing. Gwinky Yip contributes to research into existing solutions as well as its presentation in this report. Cheston Cheng has made contributions to the project's proposal and presentation.

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