Frontiers in Degenerative Disc Disease

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Abstract
Degenerative Disc Disease continues to have a global impact on the physical health of the aging population. The current gaps in the advancement of preventative and interventional treatment options and diagnostics have created an enormous opportunity for researchers and device/pharmaceutical companies to help bring solutions to patients with lower back pain. The pathomechanics of a degenerated disc are reviewed to lay the framework for further discussion regarding the progress and potential of cell-based and injectable technologies for treatment of DDD. However, challenges within this space must be understood and taken into consideration during clinical studies and product development. Aside from the clinical advantages, the value proposition and cost effectiveness for early and interventional treatment of DDD are reviewed.

ABBREVIATIONS
DDD: Degenerative Disc Disease; MPCs: Mesenchymal Precursor Cells; IVD: Intervertebral Disc

INTRODUCTION
Degenerative disc disease accounts for the greatest burden of disability globally. The disc is of great interest for the future of spine care, as it is the most common link underlying neurologic disease and axial back pain. The clinical features of many cases of low back pain with DDD are inadequately explained by anatomic abnormalities alone. Overall, the standard of care includes interbody fusion or total disc replacement which addresses the end-stage of the disease. There is little application of prevention or early intervention of the underlying pathophysiology of DDD which creates enormous opportunity to make an impact in healthcare across large populations and markets globally [1-3].

PATHOMECHANICS AND POTENTIAL THERAPIES FOR DISC DEGENERATION

The spine is composed of both active and passive elements that interact simultaneously to provide stability, flexibility and protection of the neural elements. The disc is a non-synovial joint and the largest avascular structure in the human body. It accounts for approximately 50% of the torsional load and approximately 80% of the axial load seen in the spinal column, as seen in Figure (1).

The disc has a low stiffness nucleus (>0.01 MPa) which facilitates minimal resistance to flexion/extension [4]. The disc has a semi-fluid nucleus, floating center of rotation and facilitates uniform load distribution. Pathophysiology of the disc can be explained by the loss of cells; examples include a decrease in proteoglycans, H2O and Type II collagen accompanied by an increase in Type I, III collagen. Other pathophysiological causes include the development of annular fissures, loss of mechanical competence, and endplate changes/osteophyte formations.

With degenerative changes to the disc, the chemical and morphological changes result in decreased disc height and osteophytes. These changes can lead to axial pain, radiculopathy, stenosis and myelopathy [5]. To achieve neurological recovery, physicians have historically utilized mechanical solutions...
to maintain decompression and/or eliminate abnormal intervertebral motion and deformations. However, mechanical solutions, such as fusion or motion preservation devices, can alter the biomechanics of the operative and adjacent functional spinal units. In addition, there is a strong theoretic basis to support the concept that the clinical features of many lumbar disc patients cannot be explained by mechanical factors alone. Rather, it may be explained by inflammation of neural elements caused by biochemical factors alone, or combined chemical/mechanical factors. There have been advancements in both cell based and injectable technologies to address this.

For a biologic solution to gain traction, it must target a well-established cellular response of molecular mechanism. For example, the company Mesoblast [11] is addressing DDD through the use of MPCs to increase the water content of diseased disc to reduce pain and inflammation while also improving stability at the diseased level. The use of MPCs stems from its anti-inflammatory effects and ability to secrete paracrine factors for the stimulation of proteoglycan and collagen synthesis. Mesoblast is currently undergoing a randomized, double-blinded study to clinically evaluate the safety and efficacy of MPCs in patients with lower back pain. Other companies, such as ISTO [12] and SpinalCyte [13] summarized in Figure (2), are also undergoing clinical trials with cell based therapies to reverse, stop or slow the progression of DDD. The exploration of injectable technologies, as seen by Orthopeutics [14] and Yuhan Corporation [15], are intended to cure DDD in situ. The intention of injectable technologies includes the ability to restore the disc height by supplementing the dehydrated and degenerated nucleus pulposus. The goals of these devices are to restore physiologic intervertebral ligamentous stress and annular tension in order to reestablish spinal kinematics. One incentive for developing such technologies is to lower the chance for extrusion, as they are implanted via a smaller needle-stick annulotomy. In addition, insertion is potentially less invasive than with nucleus replacement. Challenges related to injectable technologies include the ability to maintain disc space height long-term, achieving adhesion to the host tissue, and creep. As a minimally invasive procedure, its future role may be to delay or mitigate the need for open surgical treatment of discogenic low back pain.

CHALLENGES

Disc regeneration and repair are attractive concepts, as the opportunity to address unmet clinical needs for impactful, global change is possible. However, the disc has proven to be a harsh and complex environment. One of the greatest challenges in regenerative attempts includes the lack of understanding pain generators of early disc degeneration, or “black disc.” Our growing understanding of the molecular mechanisms behind IVD homeostasis and the molecular events leading to disc degeneration is one example of how basic research may lead to potential new biologic therapies for this difficult clinical problem.

In addition, the lack of good discogenic pain in large animal models that mimic the human situation poses challenges. Most of the animal degenerative disc models are induced by acute sharp trauma to achieve herniation which is not the common cause of the “black disc” degeneration or herniation. Furthermore, establishing pain measurements in these animal models is still a considerable challenge. The unique biomechanical environment of the human spine resulting from our upright posture often leads researchers to pilot human clinical trials to explore the effects of proposed treatments [16-19]. However, without double blinded randomized clinical studies, or other high quality data, the results of such pilot studies should be cautiously interpreted.

The need for double blinded studies for clinical studies investigating biologic or cell-based injection treatment is critical to overcome the challenge of advancements in this area. Bae et al., recently conducted a randomized, double-blinded and prospective clinical study of the effect of biologic or cell-based injections on lumbar IVD repairs. One particularly interesting finding was the “saline effect” in which there was statistically significant difference (p<0.05) between the investigation and control groups; findings showed a 36.6% decrease in VAS pain for patients treated with the investigational treatment and 58.5% less VAS pain for saline injected patients by 12 months[19] as depicted below in Figure (3).

Figure 2 Examples of recent technologies addressing DDD.
Whether the "saline effect" was clinically relevant or simply a placebo effect needs to be further investigated, but there were a few key takeaways from this study. Future clinical studies in this space may benefit from investigating 1) carrier of the therapy alone, 2) saline injection 3) discograms or sham control with needle injections. Post intervention follow-up needs to be with an independent physician, different than whom initially provided treatment.

There are also challenges treating DDD related to diagnostics, including both sensitivity and specificity [20-22]. Therefore, it would be ideal for tissue engineering solutions to be developed simultaneously with new early stage diagnostic tools that enable better understanding of the pain source associated with DDD. Areas of interest include diagnostics that might elucidate pathophysiology, mechanical integrity, pain markers such as cytokines, and genetic analysis to enable optimal patient selection and dosing strategy. This will allow optimization of potential clinical benefit and reduction of potential patient harm.

VALUE IN ADDRESSING CHALLENGES OF DDD

New technologies in biologics and injectable drugs/molecules will have to demonstrate its value from a clinical and cost perspective. In the U.S, this value is known as the Institute for Healthcare Improvement (IHI) Triple Aim [23,24] and, we believe, it is the ultimate goal for Spine companies, high-performing hospitals and health systems of the future. The pursuit of better health, better health care, and lower per capita costs has opened doors for health care reformers. Johnson & Johnson was one of the early adopters of the Triple Aim as it resonates with its Credo values. A means of adding value in a cost effective manner is honing in on less invasive intervention of DDD. Some current options include chemonucleolyis, percutaneous endoscopic discectomy, Radiofrequency Lesioning (RF) or laser decompression. The limited expansion of “needle based” procedures can be explained by clinical complications, moderate patient outcomes and a narrow patient selection [25]. However, these types of treatment options are worth further evaluation as more patients are requesting less invasive procedures.

CONCLUSIONS

Patients with DDD are relying on new spine technologies. In order to product cost effective solutions and improve the quality of life for billions of patients, we need to consider less invasive technologies such as regenerative therapies for degenerative disc disease. A meaningful advancement in treating DDD should halt or delay the disease. Double-blinded randomized clinical studies, or other high quality data, is highly important as the scientific community continues to review and interpret results and findings in this space. The advancements addressing DDD will help health care systems, governments and providers: (a) improve clinical outcomes (b) increase patient satisfaction and (c) contain costs.

REFERENCES

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