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APPLICATION OF MESENCHYMAL STEM CELL FOR DEGENERATIVE DISC DISEASE

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ABSTRACT
During a person's life, the spine will experience continuous changes in response to physiological axial loads. Increasing age is also a cause of pathological degenerative changes. Degenerative disease of the spine is a condition that many people complain about and requires appropriate and effective treatment. Degenerative disc disease is the most common cause of low back pain and disability worldwide, involving people of all ages and socioeconomic statuses. This study aims to explain and analyze the effectiveness of Mesenchymal Stem Cell therapy in treating Degenerative Disc Disease. The research method used is a case study where Mesenchymal Stem Cell therapy offers the potential to modify the natural recovery of Degenerative Disc Disease using stem cell-based technology. Case studies were carried out at the Vinski Regenerative Center clinic, on several patients. And the results are that stem cells have the potential to be an ideal non-surgical treatment for low back pain and degenerative disc disease, because of their ability to differentiate into various connective tissue cells and their ability to restore damaged tissue and the results of case studies have proven to tend to improve the condition. However, long-term clinical studies are still needed, specifically focusing on the safety and efficacy of stem cell therapy in degenerative disc disease.

Keyword: Aplication, Degenerative Disc Disease, Mesenchymal Stem Cell.

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INTRODUCTION

DDD, or Degenerative Disc Disease, is an age-related medical condition that is diagnosed when one or more intervertebral discs are damaged, or their condition worsens (Beall et al., 2020); (Kirnaz et al., 2021). This condition occurs due to erosion of the discs or pads between the vertebrae, causing the vertebrae to rub against each other. DDD usually occurs due to a decrease in spinal disc function due to aging. Lower lumbar disc disease is often painful and can significantly impact a patient's quality of life (Beall et al., 2020).

Disc degeneration is part of the aging process and often occurs in older people; DDD may not cause problems, but degenerated discs can cause severe pain and chronic discomfort affecting the knee joints, back, hip joints, shoulders, and neck area (Wangler et al., 2021). Apart from increasing age, injuries such as tears or cracks in the disc structure. This condition can cause the discs to bulge out (nucleus pulposus hernia), which causes excessive pressure on the spinal nerves (Kirnaz et al., 2021).

Causes of Spinal Disc Damage

The nucleus pulposus in a healthy disc of the spinal column has a jelly-like core. On the other hand, the annulus fibrosus is made of concentric lamellae of collagen fibers (Bogduk, 2022). The central nucleus pulposus is a soft, gooey, and well-hydrated structure. The center of the disc (NP) loses its ability to act as the shock absorber over time, and continuous damage and gets stiff and dehydrated. The accompanying dehydration decreases the disc height and the cup diameter, thus perverting normal stress transfer and further annoying the annulus fibrosus. Disc displacement, protrusion or herniation, instability, and back pain result from annular damage. This condition, intervertebral disc degeneration, or degenerative disc disease (DDD) for short, is known as degenerative disc disease (DDD).

Multiple causes of spinal disc degeneration can be detected. Obesity, spinal cord injury, excessive physical activities, and smoking are risk factors that increase the chances of developing degenerative disc disease (Zielinska et al., 2021); (Kirnaz et al., 2021); (Rajesh et al., 2022). The spine gets some micro-injuries while doing everyday chores such as walking, carrying loads, and hard exercise (Li et al., 2021). This damage over time causes asymmetric joint space narrowing, osteophytes, subchondral sclerosis, and cyst formation (Regeneration Center of Thailand, 2024).

Symptoms of Degenerative Disc Disease

Minor degeneration in Degenerative disc disease can cause few or no symptoms. The symptoms caused vary depending on the part that is experiencing erosion and the extent of the erosion that occurs (Kirnaz et al., 2021); (Scarcia et al., 2022). In relatively mild cases, this condition may not show symptoms. However, in more severe cases, degenerative disc disease can cause a number of symptoms, such as:

a. Neck pain
b. Lower back pain, radiating pain, tingling, burning sensation in lower extremities
c. Loss of spinal movement
d. Tingling or numbness around the arms and legs
e. Weakness or numbness in the lower back, buttocks, groin, legs, or feet. Low back pain: a major cause of disability affecting people of all ages and socioeconomic status.
f. Decreased muscle strength, impaired bowel and bladder function, paralysis
g. Pain that gets worse when changing positions, such as sitting, bending, or standing from a sitting position, including lifting, standing, or walking for long periods.

Symptoms tend to subside when doing activities that bend the spine or reduce stress, such as sitting or lying down (Lyu et al., 2021); (Xin et al., 2022). Moreover, according to the National Institute of Neurological Disorders and Stroke (NINDS, 2024), low back pain is the most common cause of work-related disability. LBP incurs large health costs each year, even greater in lost earnings and revenue due to reduced productivity (NINDS, 2024).

Etiology

Establishing the causes of low back pain and disc degeneration is very complicated because of the different elements involved. Mechanical loading is a causative factor that may contribute to the onset of the condition from common occupational exposure like heavy lifting or vibration, obesity, or trauma (Kirnaz et al., 2022); (Zielinska et al., 2021). Other proofs for genetic detriments are also given, especially the existing various gene mutations that include a greater predilection of disc degeneration (Xie et al., 2021); (Zielinska et al., 2021). Sometimes, herniation of the disc

accompanied by neuropathy may occur due to pathological factors such as infection, inflammation, hematoma, or neoplastic etiologies (Wong et al., 2017). Nevertheless, in many cases of chronic non-specific low back pain, factors that cause this problem are ambiguous, so it is improbable that these are single factors.

Low back pain is a complex alignment between the structural joint lesion, the central nervous system sensitization, mechanical stress, pro-inflammatory state, visceral referred pain, psychosocial factors, and illness cognitions. Given the vast differential diagnoses and often non-specific symptomology, clinical determination of the precise etiology proves challenging. Imaging frequently reveals concurrent degenerative pathologies that may cloud the definitive identification of the pain generator (Chou et al., 2018). Thus, in most cases of chronic low back pain, the source is best categorized as non-specific, with contributions across biopsychosocial domains (Foster et al., 2018).

Pathophysiology

Progressive changes to the intervertebral discs are an inherent part of spinal aging. Calcification and thinning of the cartilaginous end plates reduce the diffusion of nutrients into the avascular disc (Scarcia et al., 2022); (Zehra et al., 2022). This leads to cell senescence, microfractures in the subchondral bone, sclerosis, and significantly diminished vascular supply to the end plates. Reduced circulation impedes waste removal, resulting in hypoxia, lactic acid buildup, inflammation, and disrupted cell metabolism (Kim et al., 2021); (Kirnaz et al., 2022).

The sparse vascularization and impaired diffusion set up an imbalance between anabolic and catabolic activity (Cannata et al., 2020). Matrix synthesis declines while matrix-degrading enzymes increase. This imbalance, combined with repeated mechanical stress, results in extracellular matrix degradation and structural failure. Concentric fissures expand through the annulus fibrosus, provoking a pro-inflammatory state, ingrowth of nociceptive nerve fibers and vessels, and painful signal transmission. Reactive cytokines stimulate further matrix breakdown while impairing regenerative cellular responses—changes that propagate and accelerate age-related disc degeneration (Kirnaz et al., 2021); (Kirnaz et al., 2022).

Stages of Degenerative Disc Disease

According to (Thailand, 2024), here are the four stages of DDD:

a. Stage 1 is the first indicator of spine damage, the way discs get involved. Stage 1 could destroy spine checks so that your posture will be tampered with. The nerves and joints nearby frequently get inflammation, which is due to stress, and grow up by age very fast. Although the disc height reduces just a little, some patients experience either no pain or even the mildest discomforts.
b. Stage 2 entails the degradation of the condition, the reduction of the disc space, and the formation of bone spurs (bone deformities). The patient's spinal condition continues to evolve; the worsening posture and the drying and narrowing of the discs have become more noticeable. Stage two patients most frequently experience shortcomings and pain.
c. Stage 3 is the level when the condition has reached its advanced stages with multilevel posterior disc desiccation and clear/heavily changed posture, vacuum forming of discs, compressing the nearby nerves, and formation of bone spurs and scar tissues due to inflammation. Moreover, it is often the case that this stage involves body deterioration that is very intense and, consequently, more physical pain due to the additional mental stress.
d. Stage 4 is the most serious type of subluxation degeneration and diffuse disc bulge, which is not treatable, even with stem cells in some cases. During this advanced stage, the disc height may be

almost zero, and this can lead to either bone-to-bone damage, reduced movement, constant pain, nerve damage, bone fusion, and additional scar tissues, and there may be no possibility of healing.

Pain Level

Numerical Pain Intensity Scale (Numerical rating scales): This scale is used as a substitute for word description tools. Patients rate pain on a scale of 0-10. The number 0 means no pain, while the number 10 means the most severe pain. The Numerical Rating Scale (NRS) is almost the same as the Visual Analog Scale but has numbers along the lines.

Figure 1 : Pain Level

The numbers are 0-10 or 0-100, and the child is asked to indicate the pain they feel. This Numerical Scale can be used on younger children, such as those aged 3-4 years or older. Pain levels can be classified as follows:

a. Scale 1: no pain
b. Scale 2-4: mild pain, where the client has not complained of pain, or it can still be tolerated because it is still below the arousal threshold.
c. Scale 5-6: moderate pain, where the client begins to groan and complain that someone is pressing on the painful part
d. Scale 7-9: including severe pain, the client may complain of extreme pain, and the client is unable to carry out normal activities
e. Scale 10: including extreme pain; at this level, the client can no longer recognize himself.

Complications of Degenerative Disc Disease

In the long term, spinal disc damage that is not treated properly can trigger various medical conditions, such as:

a. Scoliosis.
b. Herniated nucleus pulposus.
c. Spondylolisthesis.
d. Spinal stenosis.

Diagnosis of Degenerative Disc Disease

The first step to diagnose DDD and cervical degenerative disc disease is a medical interview with the patient (anamnesis), where the orthopedic doctor needs to know the patient's symptoms and medical history. The doctor can also perform a physical examination to evaluate the patient's nerve function, muscle strength, and pain. After that, a number of supporting examinations that are commonly carried out to help confirm the diagnosis of degenerative disc disease are X-rays, CT scans, MRIs, and discograms (discography). In patients who cannot undergo an MRI scan, “a computerized tomography (CT) scan can be used to identify vacuum phenomena, slipped discs, cracks/defects in bone structures, or damage to soft tissue structures within the spine. Our functional medicine team can also use Radiology scans, which can also help identify spondylolisthesis (slippage) around the

discs so that the patient can be assessed and offered treatment depending on the scale and severity of the spinal degeneration" (Thailand, 2024).

Prevention of Degenerative Disc Disease

While genetic factors play a role, there are lifestyle measures that may slow the progression of degenerative disc changes (Kirnaz et al., 2021); (Lyu et al., 2021); (Kirnaz et al., 2022); (Cao et al., 2022). Maintaining a healthy body mass index through caloric restriction aids in reducing mechanical stress on spinal structures. Improving posture and body mechanics protects against injury and asymmetric loading. Smoking cessation can mitigate matrix degradation and inflammation underlying disc degeneration. Limiting alcohol consumption prevents associated B vitamin deficiencies that precipitate nerve damage. Frequent low-impact cardio exercise augments disc nutrition and hydration through passive diffusion effects. Therapeutic yoga, Pilates, and focused spinal flexibility training help preserve a range of motion as discs desiccate. Minimizing repetitive vertebral compression and adopting spine-sparing habits offer the best defense against the progression of degenerative disease.

Therapy

Conservative

1. Drugs: Common pharmacological treatments like NSAIDs, opioid and neuropathic pain medications, muscle relaxants, and epidural steroid injections may provide temporary analgesia but do not address underlying degeneration or stimulate healing (Chou et al., 2018). These medication classes also carry substantial side effect risks, including gastrointestinal bleeding, kidney dysfunction, falls, hypertension, stroke, and addiction.
2. Physiotherapy: Manual therapy, acupuncture, therapeutic exercise, mindfulness training, and psychological interventions represent first-line conservative therapy to improve mobility and strength while modulating pain perception. Evidence demonstrates short-term benefits, but effects beyond one year are less certain. None have proven to reverse pathological disc changes (Chou et al., 2018).

Surgery

Another treatment option in the case of mild to severe degenerative disc disease is surgical intervention, but this measure is recommended if none of the non-surgical therapies work (Thailand, 2024). Surgery for Degenerative Disc Disease can be unsuccessful or even lead to severe and permanent damage, and it may take a long time for a person to recover. Moreover, rehabilitation for surgery should be compared periodically with daily life.

Mesenchymal Stem Cell for Degenerative Disc Disease

Mesenchymal stem cells (MSCs) have proven very attractive for regenerative cell therapy for degenerative disc disease, where the combination of stem cell therapy and conservative treatment can maintain normal physiological function and disc structure, reversing the cascade. The long-term implications, safety, and efficacy of stem cell therapy as a standard treatment for degenerative disc disease require future research.

The application of Stem Cells is distinctive from other applications because it employs therapeutic levels of Mesenchymal stem cells that have been enhanced (Lee & Kang, 2020); (Samadi et al., 2021). These MSCs can be further differentiated into stem cells that originate from the chondrogenic lineage. This lineage of cells would provide the best possible candidates for cartilage regeneration therapy for patients with DDD (Thailand, 2024). Isolated and enhanced MSCs can

differentiate into chondrocytes and provide an ideal microenvironment that accommodates regeneration and repairs, suppresses inflammation, reduces the number of pro-inflammatory cytokines, and strengthens the immunomodulatory function of the body. The game of harvest for back pain and disc regeneration therapy offers a safe alternative to back surgery, which brings about disc regeneration with a new technique leveraging enhanced stem cells for managing pain (Thailand, 2024). This process helps to heal and restore the loss of nerve sensation.

Celltech Stem Cell Centre with Vinski Regenerative Center provides high-level treatment of sports-related injuries, osteoporosis, and chronic degenerative disc disease. Our cell injections for back pain can be administered much more safely in contrast to invasive surgical procedures and aim at the exact cause of the disease in an attempt to restore the initial proper condition by the use of a multi-step non-invasive treatment directed to regenerate the damaged disc.

Source of Stem Cell Therapy

Cell types	Source	Advantages	Disadvantages
MSCs			
BMSCs	Bone marrow	Strong self-renewal ability, multiple differentiation potential, with homing ability, and technology for solation and expansion is mature	The way obtaining BMSCs is invasive
ADMSCs	Adipose	Abundance, ease to harvest, low immunogenicity	Poor ability to differentiate into chondrocytes
UCMSCs (WJMSCs)	Umbilical cord	Pluripotent, with no ethical barriers, strong proliferation ability, extensive differentiation ability, low immunogenicity and no tumorigenicity	Almost impossible to obtain autologous cord cells, and the experimental cost of WJMSCs is high
IVDSCs	IVD	Can be stimulated to proliferate and differentiate in situ	Low yield in number, decreased viability, and expression of proteoglycan and COL II in IDD, and the curative effect is not obvious
PSCs			
IPSCs	Artificially derived from somatic cells by reprogramming with transcription factors	High capacities of self-renewal, proliferation, and differentiation	Safety problems, especially potential tumorigenicity
ESCs	Early-stage embryo	High capacities of self-renewal, proliferation, and differentiation	Ethical barriers

ADMSCs adipose mesenchymal stem cells, *BMSCs* bone marrow mesenchymal stem cells, *COL II* collagen type II, *ESCs* embryonic stem cells, *IDD* intervertebral disc degeneration, *IPSCs* induced pluripotent stem cells, *IVD* intervertebral disc, *IVDSCs* intervertebral-derived stem cells, *MSCs* mesenchymal stem cells, *PSCs* pluripotent stem cells, *UCMSCs* umbilical cord mesenchymal stem cells, *WJMSCs* Wharton's Jelly mesenchymal stem cells

Figure 2 : Source of Stem Cell Therapy

METHOD

Research Design

This research uses a qualitative descriptive method with a case study where the Application of Mesenchymal Stem Cells for Degenerative Disc Disease offers the potential to modify the natural recovery of degeneration using stem cell-based technology.

The reason the Qualitative Method was chosen is because this research aims to explain and analyze the effectiveness of combination stem cell therapy and PR Application of Mesenchymal Stem Cells for Degenerative Disc Disease in the treatment of Degenerative Disc Disease.

Research Settings

This research was carried out at the Celltech Stem Cell Center Laboratory and Banking with the Vinski Regenrative Center which is the main stem cell therapy clinic from the Celltech Stem Cell Center laboratory located at Vinski Tower, Jl. Ciputat Raya No. 22 A Pondok Pinang, South Jakarta, Indonesia 12310.

Participants

This study involved 2 female patients and 4 male patients aged between 36 and 70 years who experienced DDD with various complaints such as neck pain that spread from the back to the waist accompanied by a burning sensation. Decreased muscle strength, back weakness, and pain that gets worse when changing positions such as sitting, bending, or standing from a sitting position, including

lifting, standing, or walking for long periods. Each patient was studied using comparative literature studies and based on each patient's MRI results. Then, each patient undergoes a combination of stem cell therapy which is injected repeatedly over a certain period of time, which can be 3 to 4 repetitions in 12 months. Patient data is collected periodically and recorded in a notation book containing personal data and health history.

Techniques of Data Collection

Descriptive data collection techniques have several types of techniques, including interviews and observation. All participants provided baseline data, including demographic information and disease characteristics.

Dose

Patients are treated with live stem cells maintained at CELLTECH's Stem Cell and Banking Laboratory, and therapy is performed at the Vinski Regenerative Center clinic. Stem cells are stored in cryo tanks at -1900 Celsius (190 degrees below freezing), which is done in a “closed system” or “open system.” Closed systems run independently of human operations and are fully automated, whereas open systems use human operators to adjust the process as necessary. Closed systems are also referred to as quantum processes. This system is considered more efficient and sterile than an open system because it operates automatically in an isolated system and is separated from human intervention. The main concentration of stem cells comes from the umbilical cord and umbilical cord blood. Stem cells are stored in vials containing 20 million cells or more. The administration of stem cells for therapeutic purposes depends on the type and severity of the disease, as this determines the number of stem cells required.

The stem cell dose is calculated by measuring the patient's body weight (in kilograms) and multiplying it by a factor of one million. For example, the dose for a person weighing 70 kg is 70 million stem cells (70 x 1,000,000). The allogeneic nature of stem cells allows the replacement and restoration of damaged cells at the target site of recovery (Soufi et al., 2023); (Zhang et al., 2022). The dosage is also influenced by the number of cells damaged and needing to be restored. The quality of recovery depends on the dose. For example, a stem cell pack containing 20 million stem cells may have minimal effects, while a higher dose will be more effective for severe conditions.

Three months after each round of stem cell therapy, patient progress is monitored to determine treatment efficacy. The treatment used for this case study is consistent with the success of stem cell treatment for diseases such as Prader-Willi syndrome, autism, stroke, diabetes, and several other diseases. The theory underlying this case study is that stem cells have regenerative properties that can rejuvenate and replace damaged cell tissue, and because of their allogenic nature, stem cells can be applied to any part of the body (Xia et al., 2022).

RESULTS AND DISCUSSION

There were 6 patients undergoing spinal treatment with stem cells at our clinic, aged between 36 - 70 years, 2 women and 4 men. They have neck pain, lower back pain, tingling, burning sensation in the lower extremities, loss of movement of the spine, and tingling or numbness around the arms and legs. There are also those who feel weakness or numbness in the lower back, buttocks, groin, legs, or feet. Decreased muscle strength so that pain will get worse when changing positions such as sitting, bending, or standing from a sitting position, including lifting, standing, or walking for a long time.

Stem cell therapy is commonly used in Degenerative Disc Disease (Xie et al., 2021); (Li et al., 2021); (Zhang et al., 2022); (Soufi et al., 2023). This treatment method offers the benefits of stem cells in shortening recovery time and reducing pain associated with the procedure. Here, we will review the main benefits that stem cells can provide in Degenerative Disc Disease.

Patient A, Male, 45 years old, had a motorcycle accident. Paint Level: 8

Tetraplegia, incontinent bladder, and bowel. Refuse for surgery. Underwent physiotherapy and Intrathecal stemcell therapy 3 weeks prior to injury.

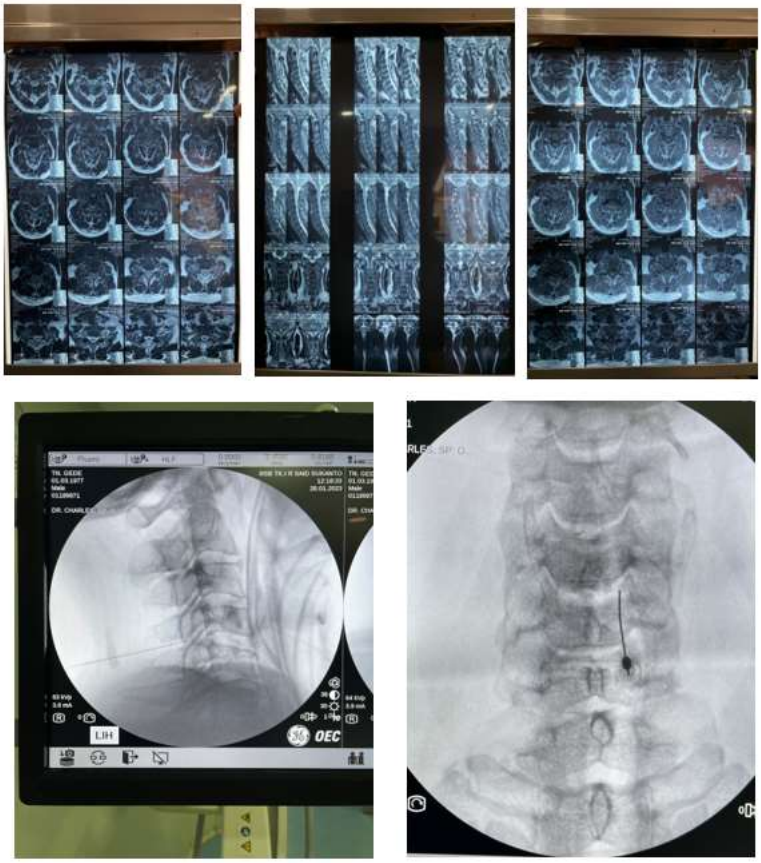

Figure 3. Patient MRI Result

Other patients indicated as follows:

1. Patient B, male, 70 years old. Symptoms: Neck pain, Lower back pain, radiating pain, tingling, burning sensation in lower extremities. Paint Level: 8. Therapy schedule: 15-9-21 & 29-9-21
2. Patient C, male, 52 years old. Symptoms: Lower back pain
3. Paint Level: 7 . Therapy schedule: 16-2-22 & 4-3-22
4. Patient D, female, 63 years old. Symptoms: Decreased muscle strength, Lower back pain. Paint Level: 7. Therapy schedule: 17-12-22 & 18-4-23
5. Patient E, female, 58 years old. Symptoms: Weakness or numbness in the lower back, buttocks, groin, legs, or feet. Paint Level: 8 Therapy schedule: 19/01/2023 & 31/01/2023
6. Patient F, male, 34 years old. Symptoms: Neck pain, Lower back pain. Paint Level: 7 Therapy schedule: 8-2-23

Based on research on Degenerative Disc Disease patients at our clinic, almost all of them experience pain in the spine. There are also those who have previously experienced injuries, then there are also those whose joint bearings are thinning due to age and various other symptoms. Then,

each patient is injected with stem cells. After 3 months, patient monitoring and evaluation is carried out. The spinal repair process varies. There are patients who feel the effects immediately after one injection, and there are also those who only feel the effects of stem cell therapy after 1 month.

Symptoms that patients felt before therapy, such as neck pain, back pain that radiated to the waist, a burning sensation in the waist and leg area, and decreased muscle strength gradually recovered after the stem cell injection. The patient was able to carry out activities again, and the pain he complained of gradually disappeared. Stem cells taken from the patient's own body will replace damaged cells, especially in the spine area, and the effect of treatment with stem cells depends on the patient's condition.

CONCLUSION

The use of stem cells for regenerative therapy has provided insight into potential therapeutic options for degenerative disc disease. Long-term clinical studies are required to establish the full potential of stem cell regenerative therapy. The long-term implications of stem cell transplantation with respect to safety and efficacy need to be better defined prior to making this tissue regenerative approach a standard of care. MSC therapy for disc repair has experienced significant progress over the last few years with respect to further understanding of stem cell biology and various applications of MSCs for the treatment of low back pain. MSCs have been reported to be effective for the differentiation of disc-shaped cells. Additionally, MSCs have been shown to have regenerative potential in several patients at the Vinski Regenerative Center. Overall, recent advances in MSC therapy suggest a promising future for disc repair therapy.

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