



(REVIEW ARTICLE)



## Stem cell therapy for degenerative disc disease: A review

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### Abstract

Degenerative Disc Disease (DDD) is a prevalent musculoskeletal disorder associated with lower back pain that typically occurs with age but can also be precipitated by other factors. At present, the available treatments such as physical therapy, analgesics, anti-inflammatory drugs, and surgical interventions are aimed at addressing the symptoms of the disease but not the degeneration process. Among the various biological disc repair therapies, cell therapy has gained interest as it offers a disc regenerative potential while being minimally invasive. Stem cells have the unique property of differentiating into chondrocytes (specialized cells found in cartilage) that resemble Nucleus Pulposus (NP) cells of the disc. Therefore, stem cells can be used to replace the lost NP cells in the degenerated disc. This reduces inflammation and helps in the regeneration of the degenerated disc. *In vitro* studies, several animal-based studies, and a few human pilot studies have demonstrated safety and efficacy in the treatment of DDD with different types of Mesenchymal Stem Cells (MSCs), Induced Pluripotent Stem Cells (iPSCs), and Intervertebral Disc Stem Cells (iVDSCs). This review aims to address the current status, recent advancements, and different types of stem cells in degenerated disc therapy.

**Keywords:** Degenerative disc disease (DDD); Cell therapy; Nucleus pulposus (NP) cells; Intervertebral disc stem cells (iVDSCs); Degenerated disc therapy

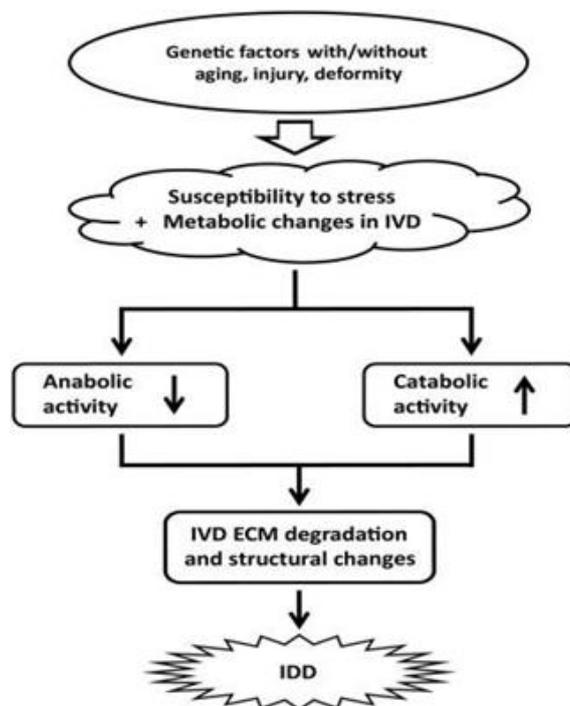
### 1. Introduction

According to the recent analysis of Global Burden of Disease (GBD) by WHO approximately 1.71 billion people globally have musculoskeletal conditions and lower back pain is the main contributor to this overall burden. A common cause of lower back pain is disc degeneration. Degenerative disc disease (DDD) or Intervertebral disc degeneration (IVD) is a prevalent musculoskeletal disorder associated with lower back pain that typically occurs with age. It affects the functional capability of the intervertebral disc, making it unable to bear physiological loads, thus leading to damage to structural integrity, formation of disc herniation, osteophyte, and vertebral micro-fracture [1].

DDD can be attributed to many factors, including genetic factors, injury, spine deformity as well as aging. These biological and environmental risk factors may lead to the spine being susceptible to stress and abnormal gene expression which results in disc degeneration (Fig 1) [2].

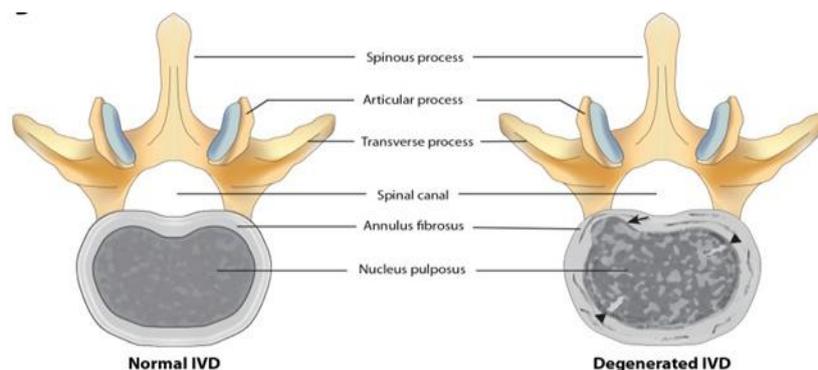
Treatment options for the early stages of the disease are physical therapy, analgesics, administration of anti-inflammatory drugs, and surgical interventions. These treatment methods are aimed at addressing the symptoms but not the cause of the disease [3]. Therefore, it is necessary to understand the molecular and cellular basis of DDD and develop alternative biological treatment modalities to reverse or halt the progression of degenerative changes within the native disc [4].

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**Figure 1** Factors influencing Intervertebral disc degeneration [2]

Among the various biological disc repair therapies, cell therapy has gained interest as it offers a disc regenerative potential while being minimally invasive. A cell therapy approach aims to address disc inflammation by inhibiting aberrant cytokine production; water loss in the disc and height restoration by initiating matrix anabolism, repopulating, and stimulating the native cells [5].



**Figure 2** Illustrations showing the normal and degenerated intervertebral disc [2]

## 2. Morphology of the disc and degeneration

Intervertebral discs are the fibrocartilaginous cushion-like structures that separate the bones of the vertebrae. They allow limited movement of the spine and resist spinal compression [6].

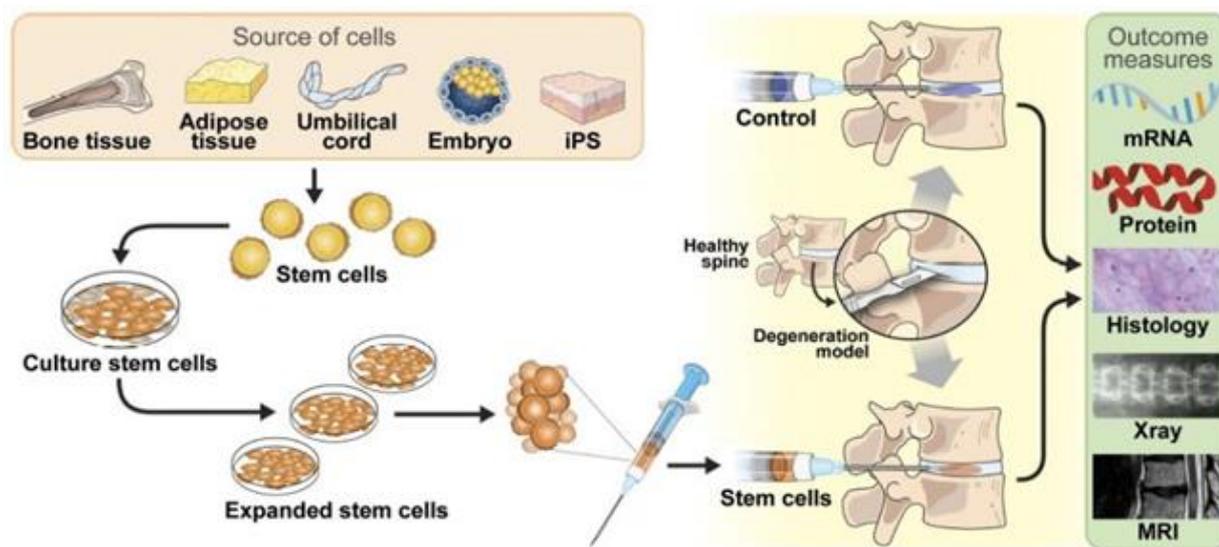
The disc consists of four major parts:

- an extracellular matrix,
- the elastic outer shell called the annulus fibrosus (AF),
- an inner jelly-like structure called nucleus pulposus (NP),
- the cartilaginous endplates (CEP) (Fig 2) [2].

The structural components in the matrix include the collagen of AF and the proteoglycan or aggrecan of NP. The collagenous proteins provide shape and tensile strength to the discs and the proteoglycans impart water holding capacity, tissue viscoelasticity, stiffness, and resistance to compression. To maintain the integrity and mechanical activity of the disc a balance between the matrix synthesis and degradation is necessary. This balance is mediated by the activity of cytokines, enzymes, enzyme inhibitors, and growth factors [1][7]. With aging, there will be structural, molecular, and cellular changes in the disc. The structural changes are dehydration, tearing of AF, NP, and CEP, molecular changes include limited synthesis of collagen, proteoglycans, loss of nutrients and water, which in turn causes cellular changes such as necrosis/apoptosis resulting in the loss of disc cells. All these changes result in the imbalance between the matrix synthesis and degradation resulting in degeneration of the disc [8]. Therefore, the advanced stages of degeneration require biological treatment at the molecular level, stem cell therapy is one such effective treatment method [4].

### 3. Sources and cell types

The different types of stem cells in the human body range from embryonic stem cells to adult stem cells (Fig 3). Even though embryonic stem cells are totipotent, they are usually not preferred in any clinical application due to legal and ethical controversies. Adult stem cells can be used in regenerative medicine without any legal or ethical barrier as they can be isolated from the patient itself. Adult stem cells represent the group of progenitor cells in various regions of the body of an adult organism. These cells are characterized in the tissues of bone marrow, adipose, blood, skin, and skeletal muscle. The cell types are selected based on the abundance, ease of isolation, and capability to survive in the disc microenvironment with minimum or no immune reaction. NP cells of the disc resemble chondrocytes in terms of phenotype and molecular markers, therefore the cells which are capable of differentiating into chondrocytes, have been considered to be a potential source for degenerated disc therapy [9]. Apart from the adult stem cells induced pluripotent stem cells and intervertebral disc stem cells are also exploited for stem cell therapy.



**Figure 3** Sources of stem cells for degenerated disc therapy and a common protocol followed during the treatment [9]

Stem cells are isolated from the source, expanded in the culture, and then injected into the degenerated disc of the animal or human model. Further, assessment is done based on the phenotype, histology, and imaging studies [9].

### 4. Mesenchymal stem cells (MSCs)

MSCs are the multipotent cells derived from mesodermal tissues and organs, that can differentiate into several cell types, including bone, cartilage, fat, muscle, and tendons, depending on the environment and biologic signals provided. These cells can differentiate into NP-like cells in the disc and help in restoring the lost function of the NP cells thereby promoting anti-inflammatory effects [9]. In 2015, Sakai et al. [10] demonstrated that transplantation of culture-expanded autologous MSCs into the nucleus of degenerated discs slowed the degenerative process and improved annular integrity, providing proof of the concept. The most commonly used approach to identify the MSCs is based on the presence of biomarkers such as CD90(+), CD73(+), CD105(+), CD14(-), CD34(-), CD45(-), CD79(-), and HLA-DR (-)

as described by the International Society for Cellular Therapy. But this method yields a heterogeneous population of progenitor cells. Selecting a particular type of MSCs having high chondrogenic properties is very important for the success of the therapy [10,11,12]. In this regard, studies have been conducted to demonstrate the use of a specific subpopulation of MSCs having the potential to differentiate into a particular cell line [10]. The most exploited MSC subpopulations are bone marrow, adipose tissue, synovial tissue, muscle tissue, and umbilical cord due to their accessibility and proliferation rate [10,12].

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## 5. Bone-Marrow derived mesenchymal stem cells (BMSCs)

BMSCs are multipotent adult stem cells having the potential to differentiate into multiple lineages including bone (osteoblasts), tendon, cartilage (chondrocytes), fat (adipocytes), fibroblasts, endothelial cells, and smooth and cardiac muscles [42]. These stem cells can be isolated from the bone marrow aspirate (BMA). BMA is a rich source of BMSCs and other growth factors. The biomarkers that aid in the identification of BMSCs are CD271, CD105, CD44, CD90, and CD117 [12]. In 2011, Álvarez-Viejo et al. [14] reported that CD271 is the most versatile and specific marker for the isolation and characterization of BMSCs [11]. Most recently, in 2017 Jeziarska-Wozniak et al. [15] demonstrated that CD271(-) MSCs have more potential to differentiate into NP-like cells than its counterpart, CD271(+) MSCs [11]. BMSCs are well suited for both the stimulation of native disc cells and differentiation into NP-like cells (chondrocytes) [16]. BMSCs have shown the ability to produce nuclear matrix and its components *in vitro* [16,17]. In 2017, Tan et al. [18] reported that the BMSCs can successfully differentiate into chondrocytes in a biomimetic environment and the differentiation can be increased with applied mechanical and chemical stimulations. These stem cells have shown promising results when intradiscally injected into humans.

In 2017, Noriega et al. [19] conducted a randomized clinical trial to examine the intervertebral disc repair by allogeneic MSCs derived from bone marrow. They randomized 24 patients with disc degeneration and are unresponsive to conservative treatments. The test group was given with allogeneic BMSCs and the clinical outcomes of those patients were followed up for a year. When the disc quality was examined they found that the patients treated with BMSCs showed quick and significant improvement. However, this improvement was noted only in 40% of the cohort [11]. In 2019, Blanco et al. [20] conducted phase I/II clinical trials to analyze the safety, efficacy, and clinical feasibility of autologous BMSCs embedded with tricalcium phosphate as a therapeutic alternative to bone graft in patients with DDD during posterolateral spine fusion. Eleven patients were included in the study, age of the patients was within the range of 30-58yrs. At the end of the follow-up, it was found that 80% of patients achieved lumbar fusion without any adverse side effects.

These findings indicate that both allogeneic and autologous BMSCs are capable of treating the degenerated disc. However, autologous BMSCs are more preferable as they are immunologically compatible. Even though these stem cells have the potential properties to treat DDD, there are several disadvantages. Isolation of MSCs from bone marrow involves a complicated procedure and the concentration of MSCs obtained in BMA will be less compared to stem cells isolated from the adipose tissue [16]. Studies are required to address these issues so that BMSCs can be used effectively in degenerated disc therapy without any limitations.

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## 6. Adipose-derived mesenchymal stem cells (AMSCs)

AMSCs are an alternative source of MSCs other than bone marrow. These cells are easily isolated from the Stromal Vascular Fraction (SVF) of the adipose tissue [21]. AMSCs are identified based on the positive surface markers CD90, CD44, CD29, CD105, CD13, CD34, CD73, CD166, CD10, CD49e, CD59 and negative surface markers CD31, CD45, CD14, CD11b, CD19, CD56, CD146 along with other antigen-specific markers, HLA-ABC(+), STRO-1(+) and HLA DR(-) [22]. The genetic profiling studies conducted by Minogue et al. [23] depicted that AMSCs are more appropriate to treat DDD than the BMSC, as they differentiate into phenotypes more similar to NP cells [16,24].

In 2015, Xu et al. [25] conducted *in vitro* study to investigate the feasibility of AMSCs to differentiate into NP-like cells. In this study, they isolated AMSCs from healthy New Zealand rabbits and co-cultured those cells with the NP cells isolated from the allogeneic rabbit. They observed that AMSCs were able to differentiate successfully into NP-like cells in the co-culture system. AMSCs have also shown promising results when injected into humans. In 2017, Kumar et al. [26] conducted a phase I clinical trial to examine the feasibility, safety, and tolerability of AMSCs that are intradiscally implanted along with hyaluronic acid in patients suffering from chronic discogenic back pain. At the end of the trial, it was found that out of 10 patients 6 patients responded to the treatment and showed significant improvement without any adverse side effects. Among these 6 patients, 3 of them were found to have increased water content in their disc. In 2017, Comella et al. [28] conducted a phase I clinical trial to analyze the effects of stromal vascular fraction (with AMSCs)

and platelet-rich plasma (PRP) implanted in patients with DDD. The majority of patients showed a positive response to the treatment and no adverse effects were reported during the trial. Recently, in 2019 Ishiguro et al. [29] performed *in vivo* studies to analyze the regenerative efficacy of AMSCs derived tissue-engineered construct (AMSC-TEC) in rat nucleotomy model. The study reported that the nucleotomized IVD restored integrity and biomechanical functions. The disc height and endplate structure were preserved up to 6 months after the implantation.

Even though several trials have reported the successful application of AMSCs in DDD therapy, further randomized clinical trials are necessary to examine the efficacy of the treatment in humans.

## 7. Synovial mesenchymal stem cells (SMSCs)

In recent years, SMSCs have gained much attention in degenerated disc therapy as they possess a proliferation rate greater than the bone marrow and adipose-derived mesenchymal stem cells. These mesenchymal cells are found in the synovial tissue of knee joints. The synovial tissue has three regions, surface, stromal and perivascular region. But the exact location of mesenchymal cells in the synovial tissue is yet to be investigated [29,11]. The chondrogenic surface markers that help in the identification of SMSCs are the positively expressed CD73, CD90, CD105, CD106, CD166, CD271, CD29, CD44, CD56, GD2, SSEA-4, integrins  $\alpha 2$ ,  $\beta 5$  and  $\alpha 10$ , notch, Sca-1, ALDH. However, CD73(+) expresses the highest levels of *SOX9*, *ACAN*, and *COL2A1*. The increased levels of *SOX* indicate that SMSCs have the potential to differentiate into chondrogenic cells [29]. In 2010, Miyamoto et al. [30] performed *in vivo* studies in rabbits to analyze the feasibility of SMSCs in treating disc degeneration. They found that SMSCs injected into degenerated discs promoted the synthesis of NP cells and maintained the structure of the intervertebral disc. In 2018, Fernandes et al. [31] successfully demonstrated the *in vitro* differentiation of SMSCs into chondrocytes according to GMP standards.

Although SMSCs have remarkable proliferating properties they are not used to treat DDD as much as BMSCs and AMSCs. Based on the studies available, further research must be done to formulate a therapeutic protocol for DDD therapy using SMSCs [11].

## 8. Muscle derived mesenchymal stem cells (MMSCs)

MMSCs are located within skeletal muscles, they have specific properties of a stem cell such as self-renewal, differentiation into other cell types such as hematopoietic, osteogenic, chondrogenic, adipogenic, and skeletal myogenic cells [1]. MMSCs have positively expressed CD73, CD90, and CD105 and negatively expressed CD34 and CD45 surface markers that help in the identification of these chondrogenic stem cells [32]. In 2011, Zheng et al. [33] demonstrated that non-myogenic cells in the fascia of skeletal muscle can differentiate into chondrocytes, and therefore MMSCs can be used in repair and regeneration applications.

Although MMSCs can differentiate into chondrocytes there is no strong evidence depicting the efficacy of MMSCs based therapy for DDD in humans. Advanced research in this regard might give more insights into the applications of MMSCs in disc degeneration therapy.

## 9. Umbilical cord-derived mesenchymal stem cells (UMSCs)

The umbilical cord (UC) is a very good source of mesenchymal stem cells. Apart from the typical properties of a stem cell, UMSCs have several advantages such as easy, painless isolation, and rapid self-renewal ability [35]. The umbilical cord is considered medical waste, therefore there are limited ethical concerns associated with its use in clinical applications. The surface markers that are considered for the identification of UMSCs are similar to that of BMSCs, but UMSCs express negative for hematopoietic and macrophage markers [36]. The umbilical cord (UC) has four regions artery, vein, Wharton's jelly, and cord lining. In 2013, Mennan et al. [36] were successful in isolating the stem cells from all four regions of the UC and they found that all the cells showed almost equal potential to differentiate into chondrocytes. In 2013, Leckie et al. [37] conducted a randomized placebo-controlled study to determine whether the injected UMSCs improve degenerated disc in skeletally mature New Zealand white rabbits. At the end of this study, they found that there was an improvement in terms of cellularity and disc architecture in responded patients. In 2019, Yan et al. [38] demonstrated that exomes produced from the 3D cultures of the UMSCs in a hollow fiber bioreactor show improved osteochondral activity than those obtained from conventional 2D culture. This finding helps in understanding that improved regeneration potential of 3D exomes can be applied in treating cartilage-based defects like DDD. In 2021, Ekram et al. [39] have performed *in vivo* studies to analyze the effects of UMSCs in the rat intervertebral disc degeneration model. At the end of the study, they found that chondroprogenitors of UMSCs could regenerate the disc and downregulate the inflammation and pain in the treated rat model.

Most scientists concentrate on BMSCs to treat DDD but the above findings show that UMSCs have equal potential to be a choice for DDD therapy. However, further studies and clinical trials are required to validate the use of UMSCs in clinical applications.

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## 10. Induced Pluripotent stem cells (IPSCs)

IPSCs are somatic stem cells that have been reprogrammed to express the genes of embryonic stem cells [39]. This reprogramming can be done by Somatic Cell Nuclear Transfer (SCNT), cell fusion, or transduction of OSKM transcription factors (Oct3/4, Sox2, c-Myc, Klf4). IPSCs can express similar features to embryonic stem cells such as self-renewal property and ability to differentiate into many types of cells in the body. Owing to its properties such as pluripotency, patient-specific, and disease-specific, they can be used in various clinical applications as an alternative to embryonic stem cells (ESCs). This helps to overcome the ethical and legal barriers concerning ESCs [41].

Many studies have been performed to demonstrate the *In vitro* differentiation of IPSCs into NP-like cells. In 2015, K. Liu et al. [42] were successful in inducing differentiation of mouse IPSCs into NP cells with the addition of transforming growth factor-beta 1 (TGF- $\beta$ 1). Further in 2018, Tang et al [43] developed a protocol in which the IPSCs were transduced using lentivirus containing reporter gene for Green fluorescent protein and the promoter of a transcription factor. This study reported the efficient differentiation of IPSCs into NP-like cells. Recently, in 2020 Hu et al. [44] developed a new strategy to differentiate IPSCs into NP cells. They transfected the IPSCs with the GDF5 gene (a gene that induces differentiation of IPSCs into NP cells) integrated lentivirus vector and those transfected cells were co-cultured with the NP cells. Further, the obtained NP cells were prepared in a thermosensitive hydrogel. In both *In vitro* and *in vivo* studies, it was found that GDF5 expressing IPSCs encapsulated in thermosensitive hydrogel improved disc degeneration.

Despite their potential to induce chondrogenesis, IPSCs might lead to tumor formation due to their pluripotency [11]. Standard protocols and additional efficacy studies are required to properly implement IPSCs in degenerated disc therapy.

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## 11. Intervertebral disc stem cells (IVDSCs)

Both the normal and the degenerated IVD is the reservoir for stem cells and are referred to as intervertebral derived stem cells (IVDSCs). These stem cells can be isolated from the various parts of the IVD such as nucleus pulposus, annulus fibrosus, and cartilaginous endplate, and they are called nucleus pulposus stem cells (NPSCs), annulus fibrosus stem cells (APSCs), and cartilaginous endplate stem cells (CEPSCs) respectively [45]. They express the surface markers namely, *Sox2*, *Oct3/4*, *Nanog*, *CD133*, *Nestin*, and *NCAM*. The IVDSCs in the AP region has several specific markers such as *STRO-1*, *C-KIT*, *NOTCH1*, *DLL4*, and *JAG1* [44,45]. These markers aid in the isolation of IVDSCs. Some studies have reported that there is a stem cell niche (SCN) within the disc which has an extracellular matrix and neighboring stem cells. The cells isolated from SCN have typical properties of mesenchymal stem cells [44]. In 2016, Wang et al. [45] reported that the chondrogenic property is highest in the CEPSCs and then followed by AFSCs and NPSCs. Also, the CEPSCs have higher chondrogenic properties than the BMSCs [45,47,48]. When cultured in a biomimetic environment, IVDSCs showed resistance to acidic pH and hypoxic environment than AMSCs indicating that they are suitable for disc regeneration [45].

The major factors that influence the differentiation of IVDSCs are the disc microenvironment and extracellular matrix (ECM). The microenvironment of the disc is characterized by low oxygen (hypoxia), nutrient depletion, and high stress. Under hypoxia, the NPSCs express more potential to differentiate into chondrocytes but the same condition does not favor the differentiation of CEPSCs into osteocytes. Therefore, it becomes important to properly manage the hypoxemic environment in the disc according to the requirements [44,48,49]. Another influencing factor in the microenvironment is mechanical stress. *In vitro* studies have shown that tensile stress in the disc causes apoptosis of CEPSCs and NPSCs. But this tensile stress is required by the stem cells for their normal functioning. Hence it is important to properly stimulate the tensile stress in the biomimetic environment. The ECM of the disc greatly influences the phenotype and functions of the stem cells [45].

In 2010, Blanco et al. [3] conducted a study to analyze whether NPSCs and BMSCs isolated from the same patient have similar biological properties. The NPSCs were able to differentiate into chondrocytes and osteocytes as efficiently as the BMSCs. However, adipocyte was an exception. In 2016, Chen et al. [51] demonstrated that NPSCs have high regeneration potential than NP cells when transplanted into rabbits with the degenerated disc. In 2017, Huang et al. [52] performed *in vivo* studies to analyze the stimulation of stem cells with simvastatin (an antilipemic agent which enhances cell proliferation). At the end of the study, they found that simvastatin can regulate the differentiation of NPSCs by

promoting the hypoxemic condition for the stem cells to regenerate the disc. Stem cells can be easily transplanted into the target location when it is loaded to a scaffold. Scaffold helps in maintaining the microenvironment necessary for the differentiation of the stem cells. In this regard, in 2019 Wang et al. [53] conducted a study to examine the effects of hydrogel combined NPSCs when injected into the rat model with DDD. The results depicted that there was a remarkable improvement in the differentiation of NPSCs when it was combined with the 3D hydrogel and this could be an effective therapeutic strategy for DDD.

Considering the above findings, it is clear that IVDSCs have the potential to differentiate into disc cells more efficiently as they very well adapt to the disc microenvironment. Since the factors such as disc microenvironment and ECM influences the differentiation of IVDSCs it is necessary to perform further studies to formulate a standard protocol for the in-vitro differentiation of IVDSCs and test the feasibility of these cells in regenerating the degenerated disc in humans.

## 12. Selection of patients

Stem cell therapy might not work if it is applied to the wrong patient. Therefore patient cohort should be properly stratified using the magnetic resonance imaging technique. It is very important to note that stem cell therapy will be effective only in the advanced stages of disc degeneration. Patients representing Pfirrmann grade III or IV on MRI have moderate severity disc degeneration. Patients representing Pfirrmann grade II or IV on MRI have too mild or too advanced disc degeneration. Currently, patients with chronic back pain (>4 VAS) and disability index (>40 ODI) are selected for stem cell therapy. However, patients having abnormalities such as disc herniation, fracture, scoliosis, spondylolysis, spondylolisthesis are excluded. The present imaging techniques fail to efficiently identify the specific pain-generating components in the disc. In this regard, new imaging techniques are being developed. It includes T1 $\rho$  and T2 relaxation times, and chemical exchange saturation transfer (CEST) [54].

**Table 1** Safety and efficacy are important [54]

Safety	Efficacy
The long-term retention of the stem cells in the disc has to be studied under the physiological environment.	The selected protocol should help in the long-term relaxation of symptoms, restoration of the disc structure, and biomechanical functions.
Acute, chronic, and systemic toxicity should be evaluated both <i>In vivo</i> and <i>In vitro</i> .	Experimental control, cost, and results in the early stages should be balanced with biological complexity and clinical relevance at the later stages.
The delivery of the stem cells to the target site should not be invasive.	The model system should mimic the physical, chemical, mechanical, and biological environment of the disc.
Multiple administration should be avoided.	The effects of age, sex, and species on the efficacy of the treatment in animal models should be considered.
The genetic stability of the cells should be manipulated <i>In vitro</i> .	Human-sourced cells should be incorporated for better efficacy.
Autologous therapies are preferable as they pose less risk compared to allogeneic cells.	There should be clearly defined success benchmarks for each experiment.

## 13. Conclusion

Degenerative disc disease is indeed a critical condition that requires immediate care and treatment. Although conventional treatments are available none of them provide a complete cure for the disease. Due to the flourishing knowledge about stem cells and their behaviour *in vitro* and *in vivo*, their application in regenerative medicine is gaining a lot of attention. The pre-clinical and clinical studies conducted on animal and human models show that certain stem cells such as mesenchymal stem cells (MSCs), Induced pluripotent stem cells (iPSCs), and Intervertebral disc stem cells

(IVDSCs) in our body have the capability to reverse or halt disc degeneration. If the pathogenesis, treatment protocol, success rate are clearly understood then stem cell therapy can replace the current treatments for DDD. However, till now animal studies and a few human studies with a limited population have been tested for stem cell therapy for DDD. Therefore, randomized clinical trials and further research is necessary to understand the behavior of stem cells in the disc environment along with the safety, and feasibility of stem cell therapy for DDD. All these seem to be achievable in the field of stem cell therapy which in turn can enhance human life.

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## Compliance with ethical standards

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### *Disclosure of conflict of interest*

There are no conflicts of interest to disclose.

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## References

- [1] Hemanta D, Jiang XX, Feng ZZ, Chen ZX, Cao YW. Etiology for degenerative disc disease. *Chinese Medical Sciences Journal*. 1 Sep 2016; 31(3):185-91.
- [2] Feng Y, Egan B, Wang J. Genetic factors in intervertebral disc degeneration. *Genes & diseases*. 1 Sep 2016; 3(3): 178-85.
- [3] Vasiliadis ES, Pneumaticos SG, Evangelopoulos DS, Papavassiliou AG. Biologic treatment of mild and moderate intervertebral disc degeneration. *Molecular Medicine*. 2014; 20(1): 400-409.
- [4] Kepler CK, Ponnappan RK, Tannoury CA, Risbud MV, Anderson DG. The molecular basis of intervertebral disc degeneration. *The Spine Journal*. 1 Mar 2013; 13(3): 318-30.
- [5] Meisel HJ, Agarwal N, Hsieh PC, Skelly A, Park JB, Brodke D, Wang JC, Yoon ST, Buser Z. Cell therapy for treatment of intervertebral disc degeneration: a systematic review. *Global spine journal*. May 2019; 9(1\_suppl): 39S-52S.
- [6] Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it?. *Spine*. 15 Aug 2006; 31(18): 2151-61.
- [7] Loibl M, Wuertz-Kozak K, Vadala G, Lang S, Fairbank J, Urban JP. Controversies in regenerative medicine: Should intervertebral disc degeneration be treated with mesenchymal stem cells?. *JOR spine*. Mar 2019; 2(1): e1043.
- [8] Longo UG, Papapietro N, Petrillo S, Franceschetti E, Maffulli N, Denaro V. Mesenchymal stem cell for prevention and management of intervertebral disc degeneration. *Stem cells international*. 2012 Jan 1; 2012.
- [9] Gou S, Oxentenko SC, Eldrige JS, Xiao L, Pingree MJ, Wang Z, Perez-Terzic C, Qu W. Stem cell therapy for intervertebral disk regeneration. *American journal of physical medicine & rehabilitation*. 1 Nov 2014; 93(11): S122-31.
- [10] Sakai D, Andersson GB. Stem cell therapy for intervertebral disc regeneration: obstacles and solutions. *Nature Reviews Rheumatology*. Apr 2015; 11(4): 243.
- [11] Loibl M, Wuertz-Kozak K, Vadala G, Lang S, Fairbank J, Urban JP. Controversies in regenerative medicine: Should intervertebral disc degeneration be treated with mesenchymal stem cells?. *JOR spine*. 2019 Mar; 2(1): e1043.
- [12] Pérez-Silos V, Camacho-Morales A, Fuentes-Mera L. Mesenchymal stem cells subpopulations: application for orthopedic regenerative medicine. *Stem cells international*. 2016 Oct.
- [13] Taldone S, Schulman IH, Balkan W, Hare JM. Allogeneic versus Autologous Source: Comparative Effects. In *Stem Cell and Gene Therapy for Cardiovascular Disease*. 1 Jan 2016 151-168.
- [14] Álvarez-Viejo M, Menéndez-Menéndez Y, Otero-Hernández J. CD271 as a marker to identify mesenchymal stem cells from diverse sources before culture. *World journal of stem cells*. 26 Mar 2015; 7(2): 470.
- [15] Jezierska-Wozniak K, Barczewska M, Habich A, Wojtacha P, Badowska W, Maksymowicz W, Wojtkiewicz J. The feasibility of the CD271+ and CD271–mesenchymal stromal cell enrichment toward nucleus pulposus-like cells. *Folia histochemica et cytobiologica*. 2017; 55(3): 114-23.

- [16] Zeckser J, Wolff M, Tucker J, Goodwin J. Multipotent mesenchymal stem cell treatment for discogenic low back pain and disc degeneration. *Stem cells international*. 11 Jan 2016.
- [17] Grad S, Alini M, Eglin D, Sakai D, Mochida J, Mahor S, Collin E, Dash B, Pandit A. Cells and biomaterials for intervertebral disc regeneration. *Synthesis lectures on tissue engineering*. 25 Jun 2010; 5(1): 1-04.
- [18] Tan AR, Hung CT. Concise review: Mesenchymal stem cells for functional cartilage tissue engineering: Taking cues from chondrocyte-based constructs. *Stem cells translational medicine*. Apr 2017; 6(4): 1295-303.
- [19] Noriega DC, Ardura F, Hernández-Ramajo R, Martín-Ferrero MÁ, Sánchez-Lite I, Toribio B, García-Sancho J. Intervertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial. *Transplantation*. 2017; 101(8): 1945-1951.
- [20] Blanco JF, Villarón EM, Pescador D, da Casa C, Gómez V, Redondo AM, López-Villar O, López-Parra M, Muntión S, Sánchez-Guijo F. Autologous mesenchymal stromal cells embedded in tricalcium phosphate for posterolateral spinal fusion: results of a prospective phase I/II clinical trial with long-term follow-up. *Stem cell research & therapy*. 2019 Dec; 10(1): 1-8.
- [21] Vadalà G, Russo F, Ambrosio L, Loppini M, Denaro V. Stem cells sources for intervertebral disc regeneration. *World journal of stem cells*. 26 May 2016; 8(5): 185.
- [22] Mildmay-White A, Khan W. Cell surface markers on adipose-derived stem cells: a systematic review. *Current Stem Cell Research & Therapy*. 1 Aug 2017; 12(6): 484-92.
- [23] Minogue BM, Richardson SM, Zeef LA, Freemont AJ, Hoyland JA. Characterization of the human nucleus pulposus cell phenotype and evaluation of novel marker gene expression to define adult stem cell differentiation. *Arthritis & Rheumatism*. Dec 2010; 62(12): 3695-705.
- [24] Gilbert HT, Hoyland JA, Richardson SM. Stem cell regeneration of degenerated intervertebral discs: current status (update). *Current pain and headache reports*. 1 Dec 2013; 17(12): 377.
- [25] Xu J, Qi DL, Pang XJ, Jing CW. Rabbit nucleus pulposus cells facilitate differentiation of adipose-derived stem cells into nucleus pulposus-like cells. *Indian journal of cancer*. 2015 Nov 1; 52(5): 17.
- [26] Kumar H, Ha DH, Lee EJ, Park JH, Shim JH, Ahn TK, Kim KT, Ropper AE, Sohn S, Kim CH, Thakor DK. Safety and tolerability of intradiscal implantation of combined autologous adipose-derived mesenchymal stem cells and hyaluronic acid in patients with chronic discogenic low back pain: 1-year follow-up of a phase I study. *Stem cell research & therapy*. 2017 Dec; 8(1): 1-4.
- [27] Comella K, Silbert R, Parlo M. Effects of the intradiscal implantation of stromal vascular fraction plus platelet rich plasma in patients with degenerative disc disease. *Journal of translational medicine*. 2017 Dec; 15(1): 1-8.
- [28] Ishiguro H, Kaito T, Yarimitsu S, Hashimoto K, Okada R, Kushioka J, Chijimatsu R, Takenaka S, Makino T, Sakai Y, Moriguchi Y. Intervertebral disc regeneration with an adipose mesenchymal stem cell-derived tissue-engineered construct in a rat nucleotomy model. *Acta biomaterialia*. 15 Mar 2019; 87: 118-29.
- [29] Campbell DD, Pei M. Surface markers for chondrogenic determination: a highlight of synovium-derived stem cells. *Cells*. 2012 Dec; 1(4): 1107-20.
- [30] Miyamoto T, Muneta T, Tabuchi T, Matsumoto K, Saito H, Tsuji K, Sekiya I. Intradiscal transplantation of synovial mesenchymal stem cells prevents intervertebral disc degeneration through suppression of matrix metalloproteinase-related genes in nucleus pulposus cells in rabbits. *Arthritis research & therapy*. 2010 Dec; 12(6): 1-3.
- [31] Fernandes TL, Kimura HA, Pinheiro CC, Shimomura K, Nakamura N, Ferreira JR, Gomoll AH, Hernandez AJ, Bueno DF. Human synovial mesenchymal stem cells good manufacturing practices for articular cartilage regeneration. *Tissue Engineering Part C: Methods*. 2018 Dec 1; 24(12): 709-16.
- [32] Owston H, Giannoudis PV, Jones E. Do skeletal muscle MSCs in humans contribute to bone repair? A systematic review. *Injury*. 1 Dec 2016; 47: S3-15.
- [33] Li G, Zheng B, Meszaros LB, Vella JB, Usas A, Matsumoto T, Huard J. Identification and characterization of chondrogenic progenitor cells in the fascia of postnatal skeletal muscle. *Journal of molecular cell biology*. 1 Dec 2011; 3(6): 369-77.
- [34] Liu LT, Huang B, Li CQ, Zhuang Y, Wang J, Zhou Y. Characteristics of stem cells derived from the degenerated human intervertebral disc cartilage endplate. *PloS one*. 18 Oct 2011; 6(10): e26285.

- [35] Nagamura-Inoue T, He H. Umbilical cord-derived mesenchymal stem cells: their advantages and potential clinical utility. *World journal of stem cells*. 26 Apr 2014; 6(2): 195.
- [36] Mennan C, Wright K, Bhattacharjee A, Balain B, Richardson J, Roberts S. Isolation and characterisation of mesenchymal stem cells from different regions of the human umbilical cord. *BioMed research international*. 2013 Oct.
- [37] Leckie SK, Sowa GA, Bechara BP, Hartman RA, Coelho JP, Witt WT, Dong QD, Bowman BW, Bell KM, Vo NV, Kramer BC. Injection of human umbilical tissue-derived cells into the nucleus pulposus alters the course of intervertebral disc degeneration *in vivo*. *The Spine Journal*. 1 Mar 2013; 13(3): 263-72.
- [38] Yan L, Wu X. Exosomes produced from 3D cultures of umbilical cord mesenchymal stem cells in a hollow-fiber bioreactor show improved osteochondral regeneration activity. *Cell biology and toxicology*. Dec 2019; 9: 1-4.
- [39] Ekram S, Khalid S, Bashir I, Salim A, Khan I. Human umbilical cord-derived mesenchymal stem cells and their chondroprogenitor derivatives reduced pain and inflammation signaling and promote regeneration in a rat intervertebral disc degeneration model. *Molecular and Cellular Biochemistry*. Apr 2021; 17: 1-5.
- [40] Ohnuki M, Takahashi K. Present and future challenges of induced pluripotent stem cells. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 19 Oct 2015; 370(1680): 20140367.
- [41] Singh VK, Kumar N, Kalsan M, Saini A, Chandra R. Mechanism of induction: induced pluripotent stem cells (iPSCs). *Journal of stem cells*. 2015; 10(1): 43.
- [42] Liu Y, Fu S, Rahaman MN, Mao JJ, Bal BS. Native nucleus pulposus tissue matrix promotes notochordal differentiation of human induced pluripotent stem cells with potential for treating intervertebral disc degeneration. *Journal of biomedical materials research Part A*. Mar 2015; 103(3): 1053-9.
- [43] Tang R, Jing L, Willard VP, Wu CL, Guilak F, Chen J, Setton LA. Differentiation of human induced pluripotent stem cells into nucleus pulposus-like cells. *Stem cell research & therapy*. 2018 Dec; 9(1): 1-2.
- [44] Hu A, Xing R, Jiang L, Li Z, Liu P, Wang H, Li X, Dong J. Thermosensitive hydrogels loaded with human-induced pluripotent stem cells overexpressing growth differentiation factor-5 ameliorate intervertebral disc degeneration in rats. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. 2020 Jul; 108(5): 2005-16.
- [45] Hu B, He R, Ma K, Wang Z, Cui M, Hu H, Rai S, Wang B, Shao Z. Intervertebral disc-derived stem/progenitor cells as a promising cell source for intervertebral disc regeneration. *Stem cells international*. 18 Dec 2018.
- [46] Sobajima S, Kim JS, Gilbertson LG, Kang JD. Gene therapy for degenerative disc disease. *Gene therapy*. 2004 Feb; 11(4): 390-401.
- [47] Blanco JF, Graciani IF, Sanchez-Guijo FM, Muntión S, Hernandez-Campo P, Santamaria C, Carrancio S, Barbado MV, Cruz G, Gutierrez-Cosío S, Herrero C. Isolation and characterization of mesenchymal stromal cells from human degenerated nucleus pulposus: comparison with bone marrow mesenchymal stromal cells from the same subjects. *Spine*. 15 Dec 2010; 35(26): 2259-65.
- [48] Liu LT, Huang B, Li CQ, Zhuang Y, Wang J, Zhou Y. Characteristics of stem cells derived from the degenerated human intervertebral disc cartilage endplate. *PloS one*. 18 Oct 2011; 6(10): e26285.
- [49] Li H, Tao Y, Liang C, Han B, Li F, Chen G, Chen Q. Influence of hypoxia in the intervertebral disc on the biological behaviors of rat adipose-and nucleus pulposus-derived mesenchymal stem cells. *Cells Tissues Organs*. 2013; 198(4): 266-77.
- [50] Yao Y, Deng Q, Song W, Zhang H, Li Y, Yang Y, Fan X, Liu M, Shang J, Sun C, Tang Y. MIF plays a key role in regulating tissue-specific chondro-osteogenic differentiation fate of human cartilage endplate stem cells under hypoxia. *Stem cell reports*. 9 Aug 2016; 7(2): 249-62.
- [51] Chen X, Zhu L, Wu G, Liang Z, Yang L, Du Z. A comparison between nucleus pulposus-derived stem cell transplantation and nucleus pulposus cell transplantation for the treatment of intervertebral disc degeneration in a rabbit model. *International Journal of Surgery*. 1 Apr 2016; 28: 77-82.
- [52] Huang Z, Zhang L, Feng X, Chen T, Bi S. A new *in vivo* method to retard progression of intervertebral disc degeneration through stimulation of endogenous stem cells with simvastatin. *Medical hypotheses*. 1 Apr 2017; 101: 65-6.

- [53] Wang F, Nan LP, Zhou SF, Liu Y, Wang ZY, Wang JC, Feng XM, Zhang L. Injectable hydrogel combined with nucleus pulposus-derived mesenchymal stem cells for the treatment of degenerative intervertebral disc in rats. *Stem cells international*. 15 Oct 2019.
- [54] Smith LJ, Silverman L, Sakai D, Le Maitre CL, Mauck RL, Malhotra NR, Lotz JC, Buckley CT. Advancing cell therapies for intervertebral disc regeneration from the lab to the clinic: Recommendations of the ORS spine section. *JOR spine*. 2018 Dec; 1(4): e1036.