



## Systematic Reviews /Meta-analyses

## Stem cell therapy for degenerative disc disease: A systematic review of preclinical evidence, clinical translation, and future directions



Vinicius Ricieri Ferraz, MD<sup>a</sup>, Carlos R. Goulart, MD<sup>b</sup>, Maria Fernanda Ricieri Ferraz Franco de Souza, MD<sup>c</sup>, Marcelo Ochoa Coelho de Souza Furlan, MD<sup>d</sup>, Philippe Mercier, MD, PhD<sup>e</sup>, Tobias A. Mattei, MD, FACS<sup>e,\*</sup>

<sup>a</sup> Chief Neurosurgeon of Spine Surgery, Dr. José de Carvalho Florence Hospital, Rua Saigiro Nakamura, 800 - Vila Industrial, São José dos Campos, São Paulo, 12220-280, Brazil

<sup>b</sup> Division of Neurological Surgery, Essentia Health, 502 E 2nd St, Duluth, 55805, MN, USA

<sup>c</sup> Division of Neurology, Irmandade Da Santa casa de Misericórdia de Santos, Av. Dr. Cláudio Luiz da Costa, 50 - Jabaquara, Santos - SP, 11075-101, São Paulo, Brazil

<sup>d</sup> Pontifical Catholic University of Paraná, School of Medicine, Rua Imaculada Conceição 1155, Prado Velho, Curitiba, Paraná, 80215-901, Brazil

<sup>e</sup> Division of Neurological Surgery, Saint Louis University School of Medicine, 1008 S. Spring Avenue, 3rd Floor, Saint Louis, MO, 63110, USA

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## ABSTRACT

**Background:** Degenerative disc disease (DDD) is a leading contributor to chronic low back pain and global disability. Existing therapies, from conservative management to spinal fusion, do not reverse the underlying molecular degeneration, leaving a critical treatment gap. Given its regenerative capabilities the advent of stem-cell therapy may constitute an ideal solution to fulfill such a therapeutic gap.

**Methods:** This PRISMA-compliant systematic review evaluates stem cell-based strategies for intervertebral disc regeneration by examining preclinical evidence, clinical translation, and future directions. Searches of PubMed, Scopus, Web of Science, and related databases (from January 2000–May 2025) identified studies reporting on pain (Visual Analogue Scale), function (Oswestry Disability Index), and structural outcomes (MRI).

**Results:** Preclinical models uniformly demonstrate meaningful regeneration, including restoration of disc height and extracellular matrix. Clinical evidence, however, is limited: thirteen low to moderate-quality trials show modest, albeit statistically significant, improvements in pain and disability, without compelling imaging proof of biological repair. Short to mid-term safety appears acceptable.

**Conclusions:** The use of stem-cell therapy for treatment of degenerative disc disease is constrained by the somewhat hostile and avascular microenvironment of the intervertebral disc. Existing trials exhibit significant methodological weaknesses which substantially impair their application to the daily clinical practice. Future progress will likely depend on incorporating biomaterial-assisted delivery systems, cell-free exosome approaches, biological scaffolds and gene-editing technologies aimed at engineering the disc niche rather than simply focusing on cell replacement.

## Introduction

*The pathophysiological cascade of degenerative disc disease*

Intervertebral disc degeneration is a complex and progressive condition influenced by many genetic, mechanical, and biological factors [1,2]. It involves a cascade of cellular and molecular changes leading to structural and functional failure of the disc [1,3]. The process begins in the gelatinous nucleus pulposus (NP) with the critical loss of pro-

teoglycans, particularly aggrecan [4,5]. Aggrecan, a large and highly charged proteoglycan, attracts water into the disc, generating the osmotic pressure required to resist axial load [6,7]. As aggrecan degrades and fragments due to enzymatic activity, the disc dehydrates and loses both turgor and height [4,6].

During the degenerative process the extracellular matrix (ECM) also undergoes marked structural remodeling. The flexible Type II collagen typical of a healthy nucleus pulposus (NP) is gradually replaced by

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\* Corresponding author. Tobias A Mattei, Saint Louis University School of Medicine, 1008 S. Spring Avenue, 3rd Floor, St. Louis, MO 63110, USA.

E-mail address: [tobias.mattei@health.slu.edu](mailto:tobias.mattei@health.slu.edu) (T.A. Mattei).

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stiffer and fibrous Type I collagen, reducing the disc's shock-absorbing capacity and blurring the boundary between the NP and the annulus fibrosus (AF) [1,3,5]. This degradation occurs in an increasingly hostile biochemical environment, characterized by elevated levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- $\alpha$ ), and catabolic enzymes, including matrix metalloproteinases (MMPs) and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) [1,5,6]. These mediators accelerate matrix breakdown, with TNF- $\alpha$  levels increasing up to 2- to 6-fold in some cases [5].

This inflammatory environment, coupled with a limited nutrient supply in the largely avascular disc, contributes to widespread cell senescence and apoptosis [3,8]. The resident disc cells, chondrocyte-like cells in the NP and fibroblast-like cells in the AF, which are responsible for maintaining matrix homeostasis, decline in number and function, ultimately impairing matrix homeostasis [5]. In advanced stages, up to 50% of the disc cells may become necrotic [5]. This decline in the cellular population affects the disc intrinsic capacity for repair to delay the ongoing degradation. This matrix loss has a profound impact upon the spinal biomechanics, increasing mechanical stress, which in turn promotes further cell death and inflammation, accelerating matrix breakdown in a vicious cycle [1]. This results in the clinically relevant disc height loss, annular fissures, bulging, and eventual herniation of nuclear material into the spinal canal, causing nerve root compression and associated inflammatory changes [4,6].

Ultimately disc degeneration is a dynamic disease process that appears to be exceptionally difficult to interrupt, highlighting why traditional treatments have proven insufficient.

#### Historical evolution of treatments

The historical evolution of treatment for degenerative disc disease (DDD) underscores a persistent therapeutic gap, which ultimately prompted a turn towards modern regenerative medicine approaches. From antiquity to the present, treatment paradigms have progressed from rudimentary symptom management to advanced surgical interventions, yet they consistently fall short of addressing the underlying biology of the pathological process. Early descriptions, including those in the Edwin Smith Papyrus (circa 1550 BC) and the writings of Hippocrates, emphasized palliative measures for low back pain such as rest, traction, heat, and massage [9,10]. Contemporary conservative management, still the first-line approach, involve non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and structured physical therapy [5,11,12]. While these strategies may be successful to provide symptom relief, they do not modify the underlying degenerative trajectory of the disease [5].

The 20th century marked a surgical paradigm shift in the management of advanced DDD. Early laminectomies were performed for traumatic injuries as early as in the 19th century [9,13]. The modern era of disc surgery began with the pioneering discectomies of Fedor Krause in 1908 and, most notably, William Mixter and Joseph Barr in 1934 [5,14]. Their seminal publication in the *New England Journal of Medicine* established a definitive link between herniated disc material and the clinical syndrome of sciatica, identifying nerve root compression as a surgically treatable entity [14,15]. This discovery ushered in the era of discectomy, which later evolved into microdiscectomy. In cases of more advanced degeneration accompanied by segmental instability, spinal fusion (arthrodesis) became the standard. Initially developed in the early 20th century, in part as a treatment for spinal deformities secondary to tuberculosis, fusion aims to stabilize the spine by eliminating motion at the affected segment through vertebral arthrodesis [16,17].

While these procedures offer effective relief of pain and improvement of neurological deficits, they are inherently non-restorative. Discectomy is ablative, removing disc fragments that cause neural compression, whereas fusion provides mechanical stability. Neither approach addresses the loss of viable disc cells, degradation of the extracellular

matrix, or sustained inflammatory signaling [5,18]. This inability to reverse or halt the degenerative cascade defines the "treatment gap" that regenerative strategies, particularly stem cell-based therapies, seek to overcome.

Through complementary mechanisms, intradiscal mesenchymal stromal cell (MSC) therapy counteracts the two central hallmarks of DDD, cellular depletion and a catabolic and pro-inflammatory micro-environment. After injection, MSCs can survive the disc's hypoxic milieu, adopt a nucleus-pulposus-like phenotype, and synthesize aggrecan and type II collagen, thereby re-establishing osmotic pressure and hydration. Furthermore, its robust paracrine signaling releases anti-inflammatory cytokines (IL-10, TGF- $\beta$ ) and trophic factors (IGF-1, GDF-5), which suppress MMP/ADAMTS activity, inhibit apoptosis, and stimulate residual disc cells to resume extracellular-matrix production. Finally, recent studies suggests that MSC-derived extracellular vesicles further modulate innate immunity and block nociceptive nerve ingrowth, amplifying analgesic effects. Large-animal studies and early-phase clinical trials consequently demonstrate partial recovery of disc height alongside significant, sustained reductions in pain and disability [18]

Given the increasing interest in the use of regenerative medicine, and the use of stem-cell therapy, the goal of this systematic review is to identify the available pre-clinical and clinical evidence regarding the use of stem-cell therapy for the treatment of DDD.

## Methods

### Rationale and objectives of the systematic review

The profound limitations of historical and current treatments for DDD underscore the urgent need for novel therapeutic strategies that can target the biological origins of the disease. Stem cell therapy has emerged as a leading candidate with the potential to fill this treatment gap. This systematic review was undertaken to critically evaluate and synthesize the current preclinical and clinical evidence supporting the use of stem cell therapy for intervertebral disc (IVD) regeneration. The primary objectives were defined using the Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) framework:

- Population (P): The review included studies involving (1) human subjects with symptomatic lumbar DDD and (2) preclinical animal models with surgically or chemically induced DDD.
- Intervention (I): The intervention of interest was intradiscal administration of stem cells, including mesenchymal stem cells (MSCs) from bone marrow, adipose tissue, or umbilical cord sources; induced pluripotent stem cells (iPSCs); and related biologics such as stem cell-derived exosomes.
- Comparison (C): Comparator groups included placebo (eg, saline injection), no treatment, or other standard-of-care or biologic therapies (eg, hyaluronic acid).
- Outcomes (O): The primary outcomes were:
  - Clinical: Primary endpoints included pain reduction, most commonly assessed via the Visual Analogue Scale (VAS), and improvement in functional status, typically measured by the Oswestry Disability Index (ODI). Safety outcomes were reported as the incidence of adverse events.
  - Radiographic/Biological: Structural outcomes included changes in disc height index (DHI) and T2-weighted MRI signal intensity. In animal models, additional endpoints included histological evidence of extracellular matrix (ECM) restoration—specifically proteoglycan and Type II collagen content—and preservation of cellular morphology.
- Study Design (S): Eligible study designs included preclinical controlled animal studies and all human clinical trials, including randomized controlled trials (RCTs) and non-randomized prospective or retrospective studies.

This systematic review was conducted and reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 statement [19–21].

### Eligibility criteria

Study selection was guided by the PICOS framework outlined above. Inclusion criteria were as follows: (1) studies involving human subjects with discogenic low back pain or animal models of DDD; (2) intradiscal administration of stem cell therapy as the primary intervention; (3) presence of a comparator group (eg, placebo, no treatment, or alternative therapy); (4) reporting of at least 1 relevant outcome—clinical (eg, Visual Analogue Scale [VAS], Oswestry Disability Index [ODI], or safety) or biological (eg, MRI-based metrics, histological findings); and (5) publication as a full-text article in English. The search was restricted to studies published between January 1, 2000 and May 7, 2025.

Exclusion criteria were: (1) case reports, narrative reviews, letters to the editor, and conference abstracts; (2) studies with incomplete or inaccessible outcome data; and (3) studies involving patients with prior spinal fusion at the target level.[20]

### Information sources and search strategy

A comprehensive literature search was conducted across multiple electronic databases to identify relevant preclinical and clinical studies. Databases included PubMed, MEDLINE (via Ovid), Google Scholar, Web of Science, Scopus, Embase, ScienceDirect, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy integrated Medical Subject Headings (MeSH) with relevant keywords to maximize sensitivity. A representative PubMed search string was as follows:

*“Intervertebral Disc Degeneration”[Mesh] OR “Low Back Pain”[Mesh] OR “discogenic pain” AND (“Mesenchymal Stem Cell Transplantation”[Mesh] OR “Stem Cell Transplantation”[Mesh] OR “stem cells” OR “regenerative medicine” OR “progenitor cells”) AND (“Animals”[Mesh] OR “Clinical Trial”).*

Additionally, the reference lists of all included studies and relevant review articles were manually screened to capture any studies not identified through the database search.

### Study selection

Study selection was performed in two phases by independent reviewers. In the initial phase, titles and abstracts of all retrieved records were screened to exclude studies that clearly did not meet inclusion criteria. In the second phase, full-text articles of the remaining records were reviewed for final eligibility based on the predefined PICOS framework. Discrepancies between reviewers at any stage were resolved by consensus, with adjudication by a third senior reviewer when necessary.

### Data extraction

A standardized data extraction form, developed in Microsoft Excel, was used to systematically collect relevant information from each included study. Two reviewers independently extracted the data, and any discrepancies were resolved by consensus. The following data items were extracted:

- Study identifiers: First author and year of publication.
- Study characteristics: Study design (eg, RCT, cohort study, animal model) and country of origin.
- Population: Sample size, species (for animal studies), diagnosis (eg, chronic discogenic LBP, Pfirrmann grade), age and sex.
- Intervention: Cell type (eg, autologous or allogeneic, bone marrow-derived MSC, adipose-derived MSC), cell dose and delivery method (eg, direct injection, hydrogel carrier).
- Comparator: Details of the control group intervention (eg, saline, hyaluronic acid, sham procedure).

- Follow-up: Duration of the follow-up period.
- Outcomes: Baseline and follow-up data for VAS, ODI, MRI T2 signal, DHI, histological scores, and reported adverse events.

### Risk of bias assessment

The methodological quality and risk of bias for each included study were independently evaluated by two reviewers. Randomized controlled trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, while nonrandomized clinical studies were evaluated with the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool. For preclinical animal studies, the SYRCLE’s Risk of Bias tool—specifically designed for animal research—was employed. Disagreements were resolved through discussion and consensus, with input from a third reviewer when necessary. These assessments informed the appraisal of the overall strength and reliability of the evidence.

## Results

### Study selection

The systematic search across 8 electronic databases identified 3,845 records. After removal of 1,210 duplicates, 2,635 unique records remained for title and abstract screening. Of these, 2,540 were excluded as irrelevant based on predefined inclusion criteria. The full texts of the remaining 95 articles were reviewed in detail. Sixty-four studies were excluded for the following reasons: 23 were review articles or case reports, 18 lacked an appropriate comparator group, 15 had incomplete outcome data, and 8 were not published in English. Ultimately, 31 studies met the inclusion criteria and were included in the systematic review, comprising 18 preclinical animal studies and 13 human clinical studies. Inter-rater agreement between the 2 reviewers was 82% during title-and-abstract screening and rose to 99% at the full-text assessment stage; any discrepancies were adjudicated by a third author who was not involved in the initial screening. The study selection process is depicted in the PRISMA 2020 flow diagram (Fig. 1).

### Characteristics of included studies

The 13 included clinical studies, published between 2011 and 2025, enrolled a total of 1,299 patients. Study designs comprised 5 randomized controlled trials and 8 prospective or retrospective cohort or pilot studies. The most common diagnosis was chronic discogenic low back pain unresponsive to at least 6 months of conservative management, with intervertebral disc degeneration (typically classified as Pfirrmann grade III–V). Interventions were heterogeneous, employing both autologous and allogeneic mesenchymal stem cells (MSCs) derived from bone marrow (BM-MSCs), adipose tissue (ASCs), or umbilical cord tissue (UC-MSCs). Administered cell doses ranged from  $2 \times 10^6$  to  $4 \times 10^7$  cells per disc. Follow-up durations varied from 12 months to 6 years. Primary outcomes across studies consistently included pain, measured by the VAS and functional disability, measured by the ODI. Detailed characteristics of the included clinical studies are summarized in Table 1.

The 18 included preclinical studies utilized various animal models, most commonly rabbit ( $n=9$ ), rat ( $n=6$ ), and sheep ( $n=2$ ). Degeneration was typically induced via annulus fibrosus puncture or nucleus pulposus aspiration. Interventions predominantly involved BM-MSCs, often delivered within a carrier such as atelocollagen or hyaluronic acid gel. Outcomes focused on radiographic changes (DHI and MRI T2 signal) and detailed histological analysis. A summary of key preclinical studies is presented in Table 2.

### Risk of bias assessment

The overall methodological quality of the included clinical studies was low to moderate. Among the 5 RCTs, only 3 were assessed as having

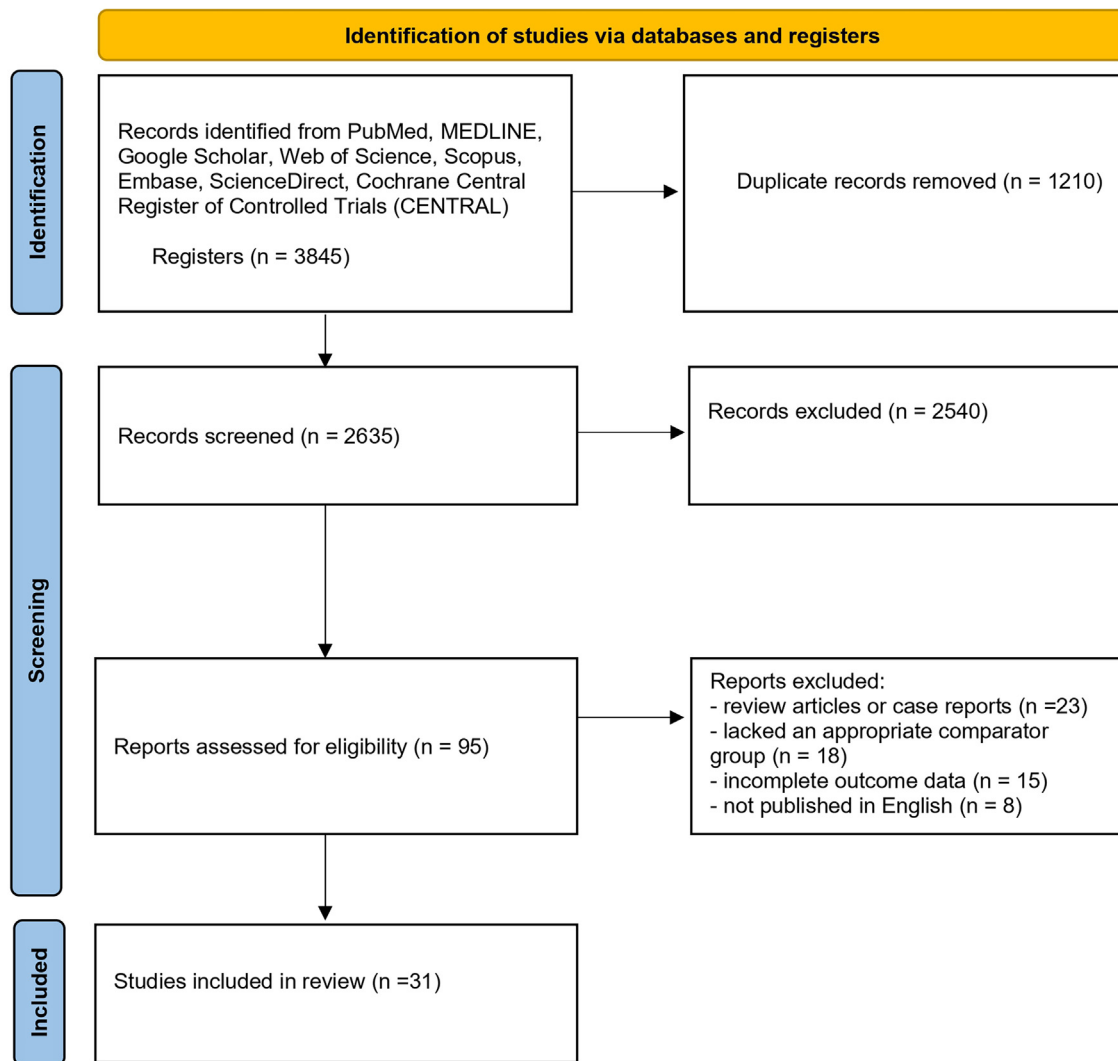


Fig. 1. PRISMA 2020 flow diagram for study selection.

a low risk of bias using the RoB 2 tool. Recurrent shortcomings included inadequate randomization or allocation concealment procedures, absence of participant or personnel (performance bias), and incomplete outcome reporting (attrition bias). All 8 nonrandomized studies were graded as having a moderate to serious risk of bias using the ROBINS-I tool, primarily due to uncontrolled confounders and selection bias.

Preclinical evidence was similarly limited. Using SYRCLE's tool, only 4 of 18 animal studies (22%) documented random group assignment, and none described blinding of investigators or outcome assessors, conditions that heighten performance and detection bias and likely exaggerate treatment effects.

Collectively, these methodological weaknesses curtail the credibility of reported benefits and highlight the need for rigorously designed, adequately powered trials to clarify the true therapeutic value of stem-cell-based interventions for DDD.

#### Synthesis of efficacy and safety

##### Preclinical efficacy

The preclinical evidence provides a robust proof-of-concept for the regenerative potential of MSCs in the setting of DDD. Across various animal models—from small rodents to large mammals such as sheep—single intradiscal injections of MSCs consistently slow, and in some cases partially reverse the degenerative process [5,22]. Key outcomes reported

include restoration of disc height, improved (brighter) T2-weighted signal on MRI scans indicative of disc rehydration, and detailed histological confirmation of enhanced ECM production, specifically of proteoglycans and Type II collagen [23,24]. Two principal mechanisms have been proposed: (1) differentiation of transplanted MSCs into chondrocyte-like cells that secrete new matrix, and (2) paracrine modulation, whereby MSCs release anabolic factors (eg, TGF- $\beta$ ) and anti-inflammatory cytokines that stimulate remaining native disc cells and mitigate the degenerative microenvironment [5,25,26].

##### Clinical translation

In stark contrast to the robust regenerative effects observed in preclinical models, the clinical evidence for stem-cell therapy for treatment of DDD in humans is significantly more modest. Efficacy in human trials has primarily been assessed using patient-reported outcome measures (PROMs) with pain (VAS) and functional disability (ODI) serving as the principal endpoints. Several of the included trials demonstrates a statistically significant improvement in VAS and ODI, at 6, 12, and 24-month follow-up compared to baseline or control groups [20,22,27–29]. Furthermore, 1 meta-analysis reported a mean reduction of 41.62 on the VAS in the MSC therapy group [22], while another group found a significant improvement in ODI across 7 studies [30].

However, the clinical significance of these changes is often unclear, and the results are not uniformly positive. The largest RCT to date, Beall

**Table 1**  
Characteristics of included clinical studies on stem cell therapy for IVD degeneration

First author	Study design	Patient population (n, diagnosis)	Intervention (cell type, dose, delivery)	Comparator	Follow-up	Key outcomes (VAS, ODI)
Orozco et al. [31]	Pilot Study	n=10; Chronic LBP, lumbar DDD (intact AF)	Autologous expanded BM-MSCs; Dose not specified; Intradiscal injection	None (single arm)	12 months	Significant improvement in VAS and ODI (85% of max improvement at 3 mo).
Elabd et al. [36]	Case Series	n=5; Chronic LBP, DDD	Autologous hypoxic cultured BM-MSCs; 15.1–51.6 million cells; Intradiscal injection	None (single arm)	4–6 years	No adverse events; self-reported overall improvement in strength and mobility.
Noriega et al. [32]	RCT	n=24; Chronic LBP, single-level DDD	Allogeneic BM-MSCs; 25×10 <sup>6</sup> cells; Intradiscal injection	Sham infiltration of paravertebral muscle with anesthetic	12 months	Significant improvement in algofunctional indices vs. controls.
Pettine et al. [33]	Prospective Case Series	n=26; Chronic LBP, DDD (Pfirrmann IV-VII)	Autologous bone marrow concentrate (BMC); 2mL; Intradiscal injection	None (single arm)	36 months	Significant improvement in VAS and ODI from baseline (82.1 to 21.9 and 56.7 to 17.5, respectively).
Kumar et al. [37]	Phase I Trial	n=10; Chronic discogenic LBP (>3 mo)	Autologous AT-MSCs + HA; Low dose (2×10 <sup>7</sup> ) or High dose (4×10 <sup>7</sup> ); Intradiscal injection	None (dose-escalation)	12 months	Significant improvement in VAS and ODI in both dose groups.
Centeno et al. [38]	Prospective Registry Study	n=33; LBP and disc degeneration with posterior disc bulge	Autologous AT-MSCs. Dose not specified; Intradiscal injection	None (single arm)	72 months	Significant improvement in Numeric Pain Score (NPS) and Functional Rating Index (FRI)
Centeno et al. [39]	Retrospective Case Series	n=470; Lumbar radicular pain	Autologous platelet lysate; Dose not specified; Epidural injection	None (single arm)	24 months	Significant improvement in NPS and FRI.
Akeda et al. [40]	Prospective Case Series	n=14; Chronic LBP more than 3 months, 1 or more DDD. At least 1 symptomatic disc, confirmed by discography	PRP releasate, isolated from clotted PRP, was injected into the center of the nucleus pulposus.	None (single arm)	12 months	Pain scores before treatment (VAS, 7.5±1.3; RDQ, 12.6±4.1) decreased at 1 month, and was generally sustained (6 months after treatment: VAS, 3.2±2.4, RDQ; 3.6±4.5 and 12 months: VAS, 2.9±2.8; RDQ, 2.8±3.9; p<.01, respectively)
Pettine et al. [33]	Prospective Case Series	n=26; Discogenic LBP	Autologous BMC into the center of the nucleus pulposus.	None (single arm)	24 months	92% avoided surgery through 12 months, 21 (81%) avoided surgery through 2 years. Of the 21 patients, average ODI and VAS scores were reduced to 19.9 and 27.0 at 3 months and to 18.3 and 22.9 at 24 months, respectively (p<.001). Twenty patients had follow-up MRI at 12 months, of whom 8 had improved by at least 1 Pfirrmann grade, while none of the discs worsened.
Amirdelfan K et al. [41]	RCT, multicenter, 13 clinical sites	n=100; chronic LBP, moderate DDD at 1 level from L1 to S1.	3:3:2:2 ratio to receive 6 million MPCs with HA, 18 million MPCs with HA, HA vehicle control, or saline control (placebo) treatment.	Saline or HA carrier	36 months	Significant improvement in VAS and ODI scores.
Beall DP et al. [34]	RCT, multicenter, 49 clinical sites	n=404; chronic LBP, moderate DDD at 1 level from L1 to S1.	Allogeneic MPCs ± HA; 6×10 <sup>6</sup> or 18×10 <sup>6</sup> ; Intradiscal injection	Saline or HA carrier	36 months	MPC+HA treatment showed a significant reduction in CLBP and greater improvement in quality of life (QOL)
Pers YM et al. [42]	RCT	n=114; Chronic LBP, single-level DDD	Allogeneic BM-MSCs; 20 million cells; Intradiscal injection	Sham injection	12 months	Did not meet primary endpoint for VAS/ODI improvement. Procedure was safe.
Kim KD et al. [43]	Single-arm Study	n=352; posterolateral LDH and unilateral radiculopathy/radicular leg pain for greater than 6 weeks.	Single-dose injection of SI-6603 (condoliase) vs sham	Sham injection	13 months	Significantly improving radicular leg pain at Week 13 and was generally well tolerated in patients with LDH.

LBP, low back pain; DDD, degenerative disc disease; AF, annulus fibrosus; BM-MSC, bone marrow-derived mesenchymal stem cell; AT-MSC, adipose tissue-derived mesenchymal stem cell; hUCMSC, human umbilical cord MSC; HA, hyaluronic acid; BMC, bone marrow concentrate; MPC, mesenchymal precursor cell; VAS, visual analogue scale; ODI, Oswestry disability index; RCT, randomized controlled trial.

et al. [34] with 404 patients, failed to meet its primary composite endpoint for overall treatment success, although it did show a significant reduction in LBP in a prespecified subgroup of patients with a shorter duration of symptoms. This underscores a key challenge in the field: although there is evidence of therapeutic benefit, effects are often moderate and may be confined to select patient populations.

Most critically, there is a profound lack of evidence for true biological regeneration in human intervertebral discs. Unlike the consistent radiographic and histologic improvements observed in animal studies, most clinical trials have failed to demonstrate significant or sustained increases in disc height or hydration on MRI [31]. While some studies report improvements in Pfirrmann grade in a subset of patients, these

findings are inconsistent and fall short of the structural restoration seen in preclinical models [32,33].

#### Safety

Available clinical data suggest a favorable short to medium-term safety profile for stem cell–based therapies in DDD. Across the 13 included clinical trials, there were no reports of tumor formation or other serious adverse events directly attributed to the cell therapy itself [31,33,34]. The most commonly reported adverse events were transient, mild-to-moderate back pain and musculoskeletal pain at the injection site, which typically resolved with conservative management [34].

**Table 2**  
Summary of key preclinical animal studies on stem cell therapy for IVD regeneration

First author year or model	Animal model	Degeneration induction method	Intervention (cell type, delivery)	Key findings (histology, MRI, biomechanics)
Sakai et al. [44]	Rabbit	NP aspiration	Autologous BM-MSCs in atelocollagen gel	<b>Histology:</b> MSCs differentiated into chondrocyte-like cells expressing COL2, KS.
Crevensten et al. [45]	Rat (coccygeal)	Normal disc (no induction)	Allogeneic BM-MSCs in hyaluronan gel	<b>Histology:</b> Allogeneic MSCs survived for at least 4 weeks in the NP.
Zhang et al. [46]	Rabbit	Not specified	BM-MSCs	<b>Histology:</b> Increased proteoglycan content in treated discs.
Chun et al. [47]	Rabbit	Induced degeneration	MSC therapy	<b>Finding:</b> Therapy may be more effective in later stages of degeneration.
Sakai et al. [23]	Rabbit	NP aspiration	Autologous BM-MSCs in atelocollagen gel	<b>MRI:</b> Partial restoration of disc height and hydration (T2 signal).
Nishimura & Mochida [48]	Rat	Not specified	Autologous NP cells	<b>MRI:</b> Slowed disc degeneration, preserved disc height and hydration.
Hiyama et al. [49]	Canine	Disc degeneration model	MSCs	<b>Finding:</b> Demonstrated potential for MSCs in a larger animal model.
Henriksson et al. [50]	Pig (xenogeneic)	Not specified	Human BM-MSCs	<b>Histology:</b> Transplanted human MSCs survived in the porcine IVD.
Fan et al. [51]	Mouse	Disc degeneration model	AAV-CRISPR/Cas9 targeting Ctnnb1	<b>Histology:</b> $\beta$ -catenin depletion preserved IVD structure and reduced MMP13/ADAMTS5.
Zhang et al. [52]	Rat	Tail puncture	ZNF865-overexpressing hASCs	<b>MRI/DHI:</b> Increased disc height and proteoglycan content.
Zheng et al. [53]	Rat	Disc degeneration model	CRISPR-Cas9 targeting Ntn1	<b>Outcome:</b> Pain relief observed.
Wei et al. [54]	Mouse	Genetic knockout	Chsy3 knockout	<b>Histology:</b> Accelerated degeneration, highlighting Chsy3 as a potential target.
Stover et al. [55]	Rat	Degenerated IVD conditioned media	dCas9-KRAB targeting AKAP150	<b>Outcome:</b> Eliminated nociceptive neuronal activity.
Cambria et al. [56]	Rat	Stretching stimuli	CRISPR-Cas9 KO of TRPV4	<b>Outcome:</b> Reversed upregulation of inflammatory cytokines IL-6 and IL-8.
Yim et al. [22]	Rabbit	Puncture, aspiration	BM-MSCs, AT-MSCs	<b>MRI/DHI:</b> Consistent evidence of increased disc space height.
Shu et al. [27]	Sheep	Annular lesion model of disc degeneration	MSCs.	<b>Histology:</b> MSCs induced a strong recovery in discal pathology with a reduction in cumulative histopathology degeneracy over a 3 months recovery period but no recovery in carrier injected discs.
		Toluidine blue and H&E staining were used to evaluate cellular morphology: (i) disc structure/lesion morphology; (ii) proteoglycan depletion; (iii) cellular morphology; (iv) blood vessel in-growth; (v) cell influx into lesion; and (vi) cystic degeneration/chondroid metaplasia.	Three study groups were examined: 5x5mm lesion; 6x20mm lesion; and 6x20mm lesion plus mesenchymal stem cell (MSC) treatment.	
Miyamoto et al. [57]	Rabbit	Puncture, aspiration	Synovial MSCs	<b>Finding:</b> synthesis of the remaining nucleus pulposus cells to type II collagen and inhibition of expressions of degradative enzymes and inflammatory cytokines, maintaining the structure of the intervertebral disc.
Ishiguro et al. [58]	Rat	ADSC-TEC implantation into a rat total-nucleotomized disc space	ADSC-TEC	<b>Finding:</b> ADSC-TEC implantation into IVDs preserved the disc height, endplate, and annulus fibrosus structure, and showed similar biomechanical characteristics to the sham group at postoperative 6 weeks. The structure was maintained until 6 months.

NP, nucleus pulposus; BM-MSC, bone marrow-derived mesenchymal stem cell; AT-MSC, adipose tissue-derived mesenchymal stem cell; COL2, type II collagen; KS, keratin sulfate; DHI, disc height index; AAV, adeno-associated virus.

A rare but serious complication is postprocedural discitis (infection of the disc), which was reported in isolated cases and has an incidence comparable to other intradiscal procedures like discography. Although the risk of an immune reaction to allogeneic cells remains a theoretical concern, no clinically significant immune reactions have been reported in trials utilizing allogeneic MSCs - likely due to the inherent immunomodulatory properties of MSCs and the relative immune privilege of the intervertebral disc [23,35].

## Discussion

### Therapeutic potential and translational barriers in stem cell therapy

This systematic review highlights both the considerable potential and the significant translational hurdles of stem cell therapy for inter-

vertebral disc regeneration. The principal finding is a marked disconnect between the consistent regenerative effects in preclinical animal studies and the modest, and often inconclusive, results observed in human trials. Animal models have reliably demonstrated that mesenchymal stem cells (MSCs) can survive within the disc space, differentiate into matrix-producing cells, and exert paracrine effects that promote structural and functional restoration [5,22,24]. These findings have established a robust biological proof-of-concept and generated substantial momentum for clinical translation.

However, human clinical data present a more tempered reality. While the therapy appears to be safe in the short-to-medium term, is well tolerated, and provides statistically significant reductions in pain and disability for some patients, these improvements are often modest and of uncertain clinical significance [28,30]. More critically, the radiographic hallmark of regeneration seen in animals—such as restoration

of disc height and hydration—has not been consistently replicated in humans [31]. This translational gap underscores the complexity of human DDD and the limitations of current preclinical models in fully capturing its pathophysiology. The present state of the field is therefore one of cautious optimism: stem cell therapy shows some promise as a safe and potentially beneficial intervention for select patients with DDD, but it has yet to deliver on its goal of true disease modification for the broader population with DDD.

#### *Translational research: limitations of preclinical models in human disc repair*

The disconnect between preclinical efficacy and outcomes in clinical studies can be attributed to several fundamental challenges that differentiate the human DDD from experimental animal models. The single greatest obstacle is the profoundly hostile microenvironment of the degenerated human intervertebral disc—avascular, hypoxic, acidic, hyperosmotic, and continuously subjected to mechanical loading [5,24]. The environment is unfavorable for the transplanted cells leading to poor survival, limited engraftment, and regenerative function. A substantial portion of the transplanted cells likely undergo apoptosis shortly after injection, restricting their therapeutic window and potential for both direct matrix production and sustained paracrine signaling [59,60].

Another key reason for this translational gap is the species-scale mismatch between commonly used animal models and humans [59,60]. Preclinical studies are often conducted in small animals—such as rats or rabbits—whose discs are structurally and biologically distinct from those of adult humans [59]. These animals possess small discs with shorter nutrient diffusion distances, making the nutritional challenge far less severe. Furthermore, many of these species retain regenerative notochordal cells into adulthood, a cell type that disappears from human discs shortly after birth [59]. Additionally cellular metabolism, matrix synthesis rates, and mechanical loading environment are also fundamentally different. Consequently, these animal models, while valuable for initial proof-of-concept, poorly replicate the chronic, avascular, and biomechanically complex nature of the human intervertebral disc degeneration. Large animal models, such as sheep or goats, offer a more representative platform and are essential as an intermediate step before clinical translation [59].

Other translational barriers include technical issues related to the injection process (especially cell leakage) and patient selection. Degenerated discs are often structurally compromised with fissures and tears. This can allow injected cells to leak from the disc space into the surrounding epidural area, which has been linked to adverse effects such as osteophyte formation and secondary neural impingement [5]. Additionally, accurate patient selection remains a major limitation. It is well-established that the correlation between radiographic evidence of disc degeneration and the clinical symptom of low back pain is, at best, inconsistent [5]. Many individuals with severe radiographic degeneration are asymptomatic, while others with mild changes experience debilitating pain [5]. This makes it exceedingly difficult to identify which patients have pain that is truly "discogenic" and are therefore most likely to benefit from a biologically targeted therapy for DDD. Most clinical trials include patients with chronic low back pain and Pfirrmann grades III–V, but without precise phenotyping, the therapeutic signal may be obscured by other common non-discogenic sources of pain such as facet arthropathy or myofascial dysfunction.

#### *Limitations*

Several limitations related to the present literature on stem-cell therapy for DDD warrant consideration. First, despite an exhaustive search strategy, publication bias cannot be excluded; studies reporting positive results are more likely to appear in the literature than those with null or negative findings. Second, substantial heterogeneity in study populations, stem-cell sources, dosing regimens, and outcome measures pre-

cluded a formal meta-analysis for most endpoints, so that we focused primarily on providing a qualitative synthesis. Third, restricting inclusion to English-language publications may have omitted pertinent studies published in other languages. Finally, risk-of-bias appraisal revealed significant methodological shortcomings in the majority of included studies, thereby tempering the confidence and generalizability of our conclusions.

#### **Conclusions**

Stem cell therapy for intervertebral disc regeneration represents a paradigm shift away from palliative and surgical interventions toward a biological restorative approach. This systematic review demonstrates that while the field is built on a strong foundation of preclinical evidence showing clear regenerative potential, its translation to the clinical practice is in its infancy. The current evidence from clinical studies, derived from a small number of methodologically flawed trials, suggests that intradiscal stem cell injection is safe in the short-to-medium term and can provide modest improvements in pain and function, but it has not yet proven to be a truly disease-modifying therapy capable of robustly regenerating the degenerated human disc.

The significant disconnect between preclinical promising results and the questionable outcomes of clinical studies highlights the formidable challenge posed by the hostile microenvironment of the degenerated human IVD and the inherent limitations of existing animal models. The future of the field will depend on overcoming these barriers. The trajectory of research is clearly moving toward greater biological and engineering sophistication, focusing on strategies that can engineer a more supportive niche for cell regeneration within the intervertebral disc.

The ultimate success of IVD regeneration will likely rely not on a single magic bullet, but on integrated combination of the therapies. One can envision a future where patient-derived iPSCs are genetically engineered with CRISPR to enhance their anabolic output and resistance to inflammation, and then delivered into the disc space within a custom-designed, mechanically supportive hydrogel scaffold that is also loaded with nutrient-releasing microspheres and anti-inflammatory exosomes. While this vision remains distant, it represents the logical culmination of the research trends outlined in this review.

Realizing this future will require more robust evidence from well-designed, multicenter, randomized controlled trials with long-term follow-up and rigorous methodology. Only then can the therapeutic promise of regenerative medicine be fully validated as a viable solution to the treatment gap in patients with chronic low back pain and DDD.

#### **Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### **References**

- [1] Kos N, Gradisnik L, Velnar T. A brief review of the degenerative intervertebral disc disease. *Med Arch* 2019;73(6):421–4. [cited 2022 Nov 16] Available from: <https://pubmed.ncbi.nlm.nih.gov/32082013/>.
- [2] Raj PP. Intervertebral disc: anatomy-physiology-pathophysiology-treatment. *Pain Pract Off J World Inst Pain* 2008;8(1):18–44.
- [3] Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? *Spine (Phila Pa 1976)* 2006;31(18):2151–61.
- [4] Cheung KMC, Karppinen J, Chan D, et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. *Spine (Phila Pa 1976)* 2009;34(9):934–40.
- [5] Urban JPG, Roberts S. Degeneration of the intervertebral disc. *Arthritis Res Ther* 2003;5(3):120.
- [6] Videman T, Gibbons LE, Battié MC, et al. The relative roles of intragenic polymorphisms of the vitamin d receptor gene in lumbar spine degeneration and bone density. *Spine (Phila Pa 1976)* 2001;26(3):E7–12.
- [7] Sivan SS, Wachtel E, Roughley P. Structure, function, aging and turnover of aggrecan in the intervertebral disc. *Biochim Biophys Acta* 2014;1840(10):3181–9.

- [8] Risbud MV, Shapiro IM. Role of cytokines in intervertebral disc degeneration: pain and disc content. *Nat Rev Rheumatol* 2014;10(1):44–56.
- [9] Luoma K, Riihimäki H, Luukkonen R, Raininko R, Viikari-Juntura E, Lamminen A. Low back pain in relation to lumbar disc degeneration. *Spine (Phila Pa 1976)* 2000;25(4):487–92.
- [10] Le Maitre CL, Pockert A, Buttle DJ, Freemont AJ, Hoyland JA. Matrix synthesis and degradation in human intervertebral disc degeneration. *Biochem Soc Trans* 2007;35(4):652–5.
- [11] Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet* 2017;389(10070):736–47. [cited 2022 Nov 15] Available from: <https://pubmed.ncbi.nlm.nih.gov/27745712/>.
- [12] Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. *Pain Physician* 2013;16(2 Suppl):S49–283.
- [13] Truumees E. A history of lumbar disc herniation from Hippocrates to the 1990s. *Clin Orthop* 2015;473(6):1885–95.
- [14] Mixter WJ, Barr JS. Rupture of the intervertebral disc with involvement of the Spinal canal. *N Engl J Med* 1934;211(5):210–15.
- [15] Speechley M. The last great health disciplines turf war, 1990–2020. *CMAJ Can Med Assoc J J Assoc Medicale Can* 1993;148(1):77–80.
- [16] Videman T, Battié MC, Gibbons LE, Maravilla K, Manninen H, Kaprio J. Associations between back pain history and lumbar MRI findings. *Spine (Phila Pa 1976)* 2003;28(6):582–8.
- [17] Masuda K, Oegema TR, An HS. Growth factors and treatment of intervertebral disc degeneration. *Spine (Phila Pa 1976)* 2004;29(23):2757–69.
- [18] Richardson SM, Kalamegam G, Pushparaj PN, et al. Mesenchymal stem cells in regenerative medicine: focus on articular cartilage and intervertebral disc regeneration. *Methods* 2016;99:69–80. [cited 2024 Dec 4] Available from: <https://pubmed.ncbi.nlm.nih.gov/26384579/>.
- [19] Page M, McKenzie J, Bossuyt P, bmj JB. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.com* 2021. [cited 2024 Dec 12]; Available from: <https://www.bmj.com/content/372/bmj.n71.short>.
- [20] Pieper D, Rombey T. Where to prospectively register a systematic review. *Syst Rev* 2022;11(1):8.
- [21] Banno M, Tsujimoto Y, Kataoka Y. Proportion of systematic review protocols registered outside of the international prospective register of systematic reviews (PROSPERO): a short report. *Ann Clin Epidemiol* 2022;4(2):49–52.
- [22] Yim RLH, Lee JTY, Bow CH, et al. A systematic review of the safety and efficacy of mesenchymal stem cells for disc degeneration: insights and future directions for regenerative therapeutics. *Stem Cells Dev* 2014;23(21):2553–67. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/25050446/>.
- [23] Sakai D, Mochida J, Iwashina T, et al. Regenerative effects of transplanting mesenchymal stem cells embedded in atelocollagen to the degenerated intervertebral disc. *Biomaterials* 2006;27(3):335–45. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/16112726/>.
- [24] Wei A, Shen B, Williams L, Diwan A. Mesenchymal stem cells: potential application in intervertebral disc regeneration. *Transl Pediatr* 2014;3(2):71. [cited 2025 Nov 12] Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4729108/>.
- [25] Tekari A, May RD, Frauchiger DA, Chan SCW, Benneker LM, Gantenbein B. The BMP2 variant L51P restores the osteogenic differentiation of human mesenchymal stromal cells in the presence of intervertebral disc cells. *Eur Cell Mater* 2017;33:197–210. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/28266688/>.
- [26] Vadalà G, Ambrosio L, Russo F, Papalia R, Denaro V. Interaction between mesenchymal stem cells and intervertebral disc microenvironment: from cell therapy to tissue engineering. *Stem Cells Int* 2019;2019:2376172. [cited 2025 Nov 12] Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7294366/>.
- [27] Shu CC, Smith MM, Smith SM, Dart AJ, Little CB, Melrose J. A histopathological scheme for the quantitative scoring of intervertebral disc degeneration and the therapeutic utility of adult mesenchymal stem cells for intervertebral disc regeneration. *Int J Mol Sci* 2017;18(5):1049. [cited 2025 Nov 12] Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5454961/>.
- [28] Zhang W, Wang D, Li H, et al. Mesenchymal stem cells can improve discogenic pain in patients with intervertebral disc degeneration: a systematic review and meta-analysis. *Front Bioeng Biotechnol* 2023;11. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/37397969/>.
- [29] Yolcu YU, Moinuddin FM, Wahood W, Alvi MA, Qu W, Bydon M. Use of regenerative treatments in treatment of lumbar degenerative disc disease: a systematic review. *Clin Neurol Neurosurg* 2020;195. Aug 1 [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/32442808/>.
- [30] Randy R, Yosua K, Guntara A, Hardiansyah NP. Stem cells therapy as a treatment for discogenic low back pain: a systematic review. *Int J Spine Surg* 2025;19(2):156–167. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/39779251/>.
- [31] Orozco L, Soler R, Morera C, Alberca M, Sánchez A, García-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. *Transplantation*. 2011;92(7):822–8.
- [32] Noriega DC, Ardua F, Hernández-Ramajo R, et al. Intervertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial. *Transplantation* 2017;101(8):1945–51. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/27661661/>.
- [33] Pettine KA, Suzuki RK, Sand TT, Murphy MB. Autologous bone marrow concentrate intradiscal injection for the treatment of degenerative disc disease with three-year follow-up. *Int Orthop* 2017;41(10):2097–103. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/28748380/>.
- [34] Beall DP, Bae HW, DePalma MJ, et al. Efficacy and safety of allogeneic mesenchymal precursor cells with and without hyaluronic acid for treatment of chronic low back pain: a prospective, randomized, double blind, concurrent-controlled 36-month study. *Spine J* 2025;25(9):1997–2013. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/40174800/>.
- [35] De Luca P, Castagnetta M, de Girolamo L, et al. Intervertebral disc and endplate cell characterisation highlights annulus fibrosus cells as the most promising for tissue-specific disc degeneration therapy. *Eur Cell Mater* 2020;39:156–70. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/32125689/>.
- [36] Elabd AM, Elabd OM. Relationships between forward head posture and lumbo-pelvic sagittal alignment in older adults with chronic low back pain. *J Bodyw Mov Ther* 2021;28:150–6. [cited 2025 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/34776134/>.
- [37] Kumar H, Ha DH, Lee EJ, et al. 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 Res Ther* 2017;8(1):262. 8:1. [cited 2025 Nov 12] Available from: <https://stemcellres.biomedcentral.com/articles/10.1186/s13287-017-0710-3>.
- [38] Centeno C, Markle J, Dodson E, et al. Treatment of lumbar degenerative disc disease-associated radicular pain with culture-expanded autologous mesenchymal stem cells: a pilot study on safety and efficacy. *J Transl Med* 2017;15(1). [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/28938891/>.
- [39] Centeno C, Markle J, Dodson E, et al. The use of lumbar epidural injection of platelet lysate for treatment of radicular pain. *J Exp Orthop* 2017;4(1):38. [cited 2025 Nov 12] Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5701904/>.
- [40] Akeda K, Ohishi K, Masuda K, et al. Intradiscal injection of autologous platelet-rich plasma releasate to treat discogenic low back pain: a preliminary clinical trial. *Asian Spine J* 2017;11(3):380–9. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/28670405/>.
- [41] Amirdeflan K, Bae H, McJunkin T, et al. Allogeneic mesenchymal precursor cells treatment for chronic low back pain associated with degenerative disc disease: a prospective randomized, placebo-controlled 36-month study of safety and efficacy. *Spine J* 2021;21(2):212–30. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/33045417/>.
- [42] Pers YM, Soler-Rich R, Vadalà G, et al. Allogenic bone marrow-derived mesenchymal stromal cell-based therapy for patients with chronic low back pain: a prospective, multicentre, randomised placebo controlled trial (RESPINE study). *Ann Rheum Dis* 2024;83(11):1572–83. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/39393844/>.
- [43] Kim KD, Ahadian F, Hassanzadeh H, et al. A phase 3, randomized, double-blind, sham-controlled trial of SI-6603 (condoliase) in patients with radicular leg pain associated with lumbar disc herniation. *Spine J* 2024;24(12):2285–96. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/39168360/>.
- [44] Sakai T, Sairyo K, Takao S, Nishitani H, Yasui N. Incidence of lumbar spondylolysis in the general population in Japan based on multidetector computed tomography scans from two thousand subjects. *Spine (Phila Pa 1976)* 2009;34(21):2346–50.
- [45] Crevensten G, Walsh AJL, Ananthakrishnan D, et al. Intervertebral disc cell therapy for regeneration: mesenchymal stem cell implantation in rat intervertebral discs. *Ann Biomed Eng* 2004;32(3):430–4. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/15095817/>.
- [46] Zhang YG, Guo X, Xu P, Kang LL, Li J. Bone mesenchymal stem cells transplanted into rabbit intervertebral discs can increase proteoglycans. *Clin Orthop Relat Res* 2005;430(430):219–26. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/15662327/>.
- [47] Chun HJ, Kim YS, Kim BK, et al. Transplantation of human adipose-derived stem cells in a rabbit model of traumatic degeneration of lumbar discs. *World Neurosurg* 2012;78(3–4):364–71. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/22381275/>.
- [48] Nishimura K, Mochida J. Percutaneous reinsertion of the nucleus pulposus. An experimental study. *Spine (Phila Pa 1976)* 1998;23(14):1531–9. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/9682309/>.
- [49] Hiyaama A, Mochida J, Iwashina T, et al. Transplantation of mesenchymal stem cells in a canine disc degeneration model. *J Orthop Res* 2008;26(5):589–600. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/18203202/>.
- [50] Henriksson HB, Svanvik T, Jonsson M, et al. Transplantation of human mesenchymal stem cells into intervertebral discs in a xenogeneic porcine model. *Spine (Phila Pa 1976)* 2009;34(2):141–8. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/19112334/>.
- [51] Fan Y, Zhao L, Lai Y, Lu K, Huang J. CRISPR-Cas9-mediated loss of function of  $\beta$ -catenin attenuates intervertebral disc degeneration. *Mol Ther Nucleic Acids* 2022;28:387–96. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/35505959/>.
- [52] Zhang H, Yang S, Wang L, et al. Time course investigation of intervertebral disc degeneration produced by needle-stab injury of the rat caudal spine: laboratory investigation. *J Neurosurg Spine* 2011;15(4):404–13. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/21721872/>.
- [53] Zheng B, Li S, Xiang Y, et al. Netrin-1 mediates nerve innervation and angiogenesis leading to discogenic pain. *J Orthop Translat* 2022;39:21. [cited 2025 Nov 12] Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9804017/>.
- [54] Wei L, Cao P, Xu C, et al. Chondroitin synthase-3 regulates nucleus pulposus degeneration through actin-induced YAP signaling. *FASEB J* 2020;34(12):16581–600. [cited 2025 Nov 12] Available from: <https://pubmed.ncbi.nlm.nih.gov/33089528/>.
- [55] Stover JD, Farhang N, Berrett KC, Gertz J, Lawrence B, Bowles RD. CRISPR epigenome editing of AKAP150 in DRG neurons abolishes degenerative IVD-induced neuronal activation. *Mol Ther* 2011;15(4):404–13. [cited 2025 Nov 12] Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5589089/>.

- [56] Cambria E, Arlt MJE, Wandel S, et al. TRPV4 Inhibition and CRISPR-Cas9 knock-out reduce inflammation induced by hyperphysiological stretching in Human annulus fibrosus cells. *Cells* 2020;9(7). [cited 2025 Nov 12]Available from: <https://pubmed.ncbi.nlm.nih.gov/32708074/>.
- [57] Miyamoto T, Muneta T, Tabuchi T, et al. 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 Res Ther* 2010;12(6). [cited 2025 Nov 12]Available from: <https://pubmed.ncbi.nlm.nih.gov/21054867/>.
- [58] Ishiguro H, Kaito T, Yarimitsu S, et al. Intervertebral disc regeneration with an adipose mesenchymal stem cell-derived tissue-engineered construct in a rat nucleotomy model. *Acta Biomater* 2019;87:118–29. [cited 2025 Nov 12]Available from: <https://pubmed.ncbi.nlm.nih.gov/30690206/>.
- [59] McDonnell EE, Wilson N, Barcellona MN, et al. Preclinical to clinical translation for intervertebral disc repair: effects of species-specific scale, metabolism, and matrix synthesis rates on cell-based regeneration. *JOR Spine* 2023;6(3). [cited 2025 Nov 12]Available from: <https://pubmed.ncbi.nlm.nih.gov/37780829/>.
- [60] De Luca P, Castagnetta M, de Girolamo L, et al. Intervertebral disc and endplate cell characterisation highlights annulus fibrosus cells as the most promising for tissue-specific disc degeneration therapy. *Eur Cell Mater* 2020;39:156–70. [cited 2025 Nov 12]Available from: <https://pubmed.ncbi.nlm.nih.gov/32125689/>.