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REVIEW

Autogenic mesenchymal stem cells for intervertebral disc regeneration

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Abstract

Purpose A systematic review of the literature was conducted to clarify the outcomes of autologous mesenchymal stem cells (MSC) injections for the regeneration of the intervertebral disc (IVD).

Methods The following databases were accessed: PubMed, Medline, CINAHL, Cochrane, Embase and Google Scholar bibliographic databases. Articles including previous or planned surgical interventions were excluded. Only articles reporting percutaneous autologous MSC injection to regenerate IVD in humans were included. We referred to the Coleman Methodology Score for the methodological quality assessment. The statistical analysis was performed using Review Manager Software 5.3.

Results After the databases search and cross-references of the bibliographies, seven studies were included in the present work. The funnel plot detected low risk of publication bias. The Coleman Methodology Score reported a good result, scoring 61.07 points. A total of 98 patients were enrolled, with 122 treated levels. All the patients underwent conservative therapies prior to injection. A remarkable improvement in the quality of life were reported after the treatment. The average Oswestry Disability Index (ODI) improved from "severe disability" to "minimal disability" at one year follow-up. The visual analogue scale (VAS) showed an improvement of ca. 30% at one year follow-up. Only one case of herniated nucleus pulposus was reported. No other adverse events at the aspiration or injection site were observed.

Conclusions This systematic review of the literature proved MSC injection to be a safe and feasible option for intervertebral disc regeneration in the early-degeneration stage patients. Irrespective of the source of the MSCs, an overall clinical and radiological improvement of the patients has been evidenced, as indeed a very low complication rate during the follow-up.

Keywords Mesenchymal stem cells · Regenerative medicine · Intervertebral disc degeneration · Low back pain · Spine

Introduction

Intervertebral disc (IVD) degeneration is one of the most important cause of low back pain, leading to disability and increasing financial burden [1]. Loss of disc tissue from herniation and/or surgery can accelerate the degeneration process [2]. A variety of surgical procedures have been developed to treat IVD [3, 4]. Discectomy followed by spinal fusion is considered the gold standard for the treatment of symptomatic degenerative IVD disease [5]. These surgeries reported several complications, such as dural tears, infections and epidural haematomas [6–9].

Regenerative medicine has the purpose to replace degenerated human cells, tissues and organs, restoring their physiological functions [10, 11]. One of the most interesting application of regenerative medicine is represented by stem cell applications [12]. Stem cells can be potentially committed in any tissue, thus finding wide interests, broad researches and applications in orthopaedic surgery [13, 14].

IVD ageing and degeneration are accompanied by quantitative and qualitative cells decline, attributable to both necrosis and apoptosis [15]. Numerous studies characterised the biochemical pathways and biomechanical forces involved in the IVD, offering insights and theories into the structure-function-failure relationship [16]. There are many obstacles in treating patients using stem cells: the harsh microenvironment within

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the degenerated IVD, characterised by a reduction in oxygen [17], glucose level [18] and matrix acidity [19], might limit the success of stem cell regeneration.

Up to date, there are no available systematic reviews that clarify the role of autologous mesenchymal stem cell (MSC) injections for the regeneration of the IVD. In the literature, there are a lot of preclinical, biomechanical, in vitro or animal studies concerning this topic [20–23]. Conversely, the number of clinical studies is still limited. This observation reveals that we are on the transition point between the preclinical and the clinical phase, witnessing a critical moment in the development of stem cell-related therapies.

Given these premises, the purpose of this study is to clarify the role of MSCs for the treatment of intervertebral disc degeneration, including possible benefits and disadvantages. A systematic review of the available literature was carried out to clarify indications, procedures and outcomes of autologous MSC injections for the IVD regeneration.

Materials and methods

Search strategy and data extraction

We preliminary developed a protocol to guide the research. Published studies were enrolled if they reported:

(A) Diagnosis of lumbar IVD degeneration
(B) Percutaneous injection of MSCs
(C) Minimum of one prespecified outcome of interest

A comprehensive review of the literature was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. The following databases were accessed: PubMed, Medline, CINAHL, Cochrane, Embase and Google Scholar. The research extended in a timeframe from 2010 to 2018. The following keywords were used in combination: "mesenchymal stem cells," "adipose-derived stem cells," "bone marrow-derived stem cells," "regenerative medicine," "intervertebral disc," "nucleus pulposus," "low back pain," "percutaneous injection" and "spine."

Eligibility criteria

Three independent reviewers (FM, JE, BR) separately conducted the search. Given the linguistic capabilities of the authors, all publications in English, French, Spanish, Italian and German were reviewed. According to the Oxford Centre of Evidence-Based Medicine [25], only level I to III articles were considered for inclusion. The authors started by reading all the abstracts resulting from the initial search. If no abstract was available, the study was excluded. If the abstract matched the criteria, the full text of the article was accessed. Letters or editorials, reviews or meta-analysis and expert opinions were excluded. Biomechanical, in vitro, animal and cadaveric studies were also excluded, along with articles treating patients who had undergone or planned spine surgery. Studies that performed isolated infiltrations of collagen, fibrin, glycosaminoglycans, proteoglycans and other components of the extracellular matrix were excluded. Furthermore, papers reporting infiltration of chondrocytes, fibroblasts, platelets, osteoblasts or osteoclasts or any other differenced cell lineages were also excluded. We also excluded studies that performed infiltration of cells from an allogenic transplant or using embryonal or other less-committed stem cell lineages. In the quantitative analysis, we reported only the outcomes across the follow-ups of interest (three, six, 12 months). Only articles reporting percutaneous autologous MSC injection to regenerate IVD in humans were considered for inclusion.

Data extraction

Data extraction was performed by three reviewers (FM, JE, BR). For each study, a level of evidence using published guidelines was assigned [26]. All the investigators independently extracted the following data: generalities and demographic baseline (author and year, type of study, level of evidence, number of patients and levels treated, mean age at surgery, follow-up duration, previous conservative therapies, presence of a control group), inclusion and exclusion criteria, scores (Oswestry Disability Index, ODI [27] and visual analogue scale, VAS), type and quantity of injected MSCs, complications, resumption of normal activities, radiological and clinical outcomes. Scores were recorded at baseline, at the three month, six month and 12-month follow-up.

Methodological quality assessment

The quality assessment was performed by three independent reviewers (FM, JE, BR). We referred to the Coleman Methodology Score (CMS). This score evaluates the quality of the methodology of reviews and meta-analysis and has been already validated in other studies [28, 29]. CMS evaluated the enrolled studies under ten criteria: study size, mean follow-up, surgical approach, type of study, description of diagnosis, descriptions of surgical technique, description of post-operative rehabilitation, outcome criteria, procedure of assessing outcomes and selection process [30]. This score results in a numerical evaluation ranking from 0 to 100 points. The final score can be defined as poor (< 50 points), fair (50 to 69 points), good (70 to 84 points) and excellent (85 to 100 points).

Statistical analysis

For the statistical analysis we referred to the Review Manager 5.3 software (the Nordic Cochrane Collaboration, Copenhagen). For each continuous variable, we referred to the inverse-variance statistical method. The standardized mean difference evaluated the effect misure of the samples. For each effect estimate (EE), a confidence interval (CI) of 95% was set. Student-T test was also performed. A P value < 0.5 was considered statistically significant. For the analysis, a fixed statistical method was used. A random method was used when I^2 was > 50%.

Results

From the databases search and cross-reference of the bibliographies, 910 articles were identified. First, 134 articles were rejected because of duplicated. Other 707 articles were rejected because did not focus the topic or did not match the eligibility criteria. After reading the abstracts, 69 studies were potentially eligible. After reading the remaining full-text articles, we excluded further 62 works that lacked quantitative data. This left seven publications for this study. The flowchart diagram of the literature search is shown in Fig. 1.

Methodological quality assessment

The Coleman Methodology Score reported a good result (61.07 points). This score evidenced that the main limitations of this study were represented by the low number of included patients and by the too short follow-up time. The study of Yoshikawa et al. [31] significantly and negatively influenced the overall outcome of the CMS, since it presents only two patients with a short-term follow-up. In the present study, only two RCTs were included, representing another important limitation. The CMS final value given to each publication is shown in Table 1.

Patients' demographic data

In the present study, two RCTs [32, 33], four prospective cohort studies [34–37] and one case series [31] were included. A total of 98 patients were analyzed, accounting 122 treated levels. The mean age of the studied cohort was 44.17 years (SD 12.24). All the patients underwent conservative therapies prior infiltration. Many studies did not provide any information about the duration and type of the conservative therapies. In the study of Elabd et al. [35], the patients underwent conservative therapies for 5 years before MSC treatment. In two other studies [36, 37], the patients underwent previous

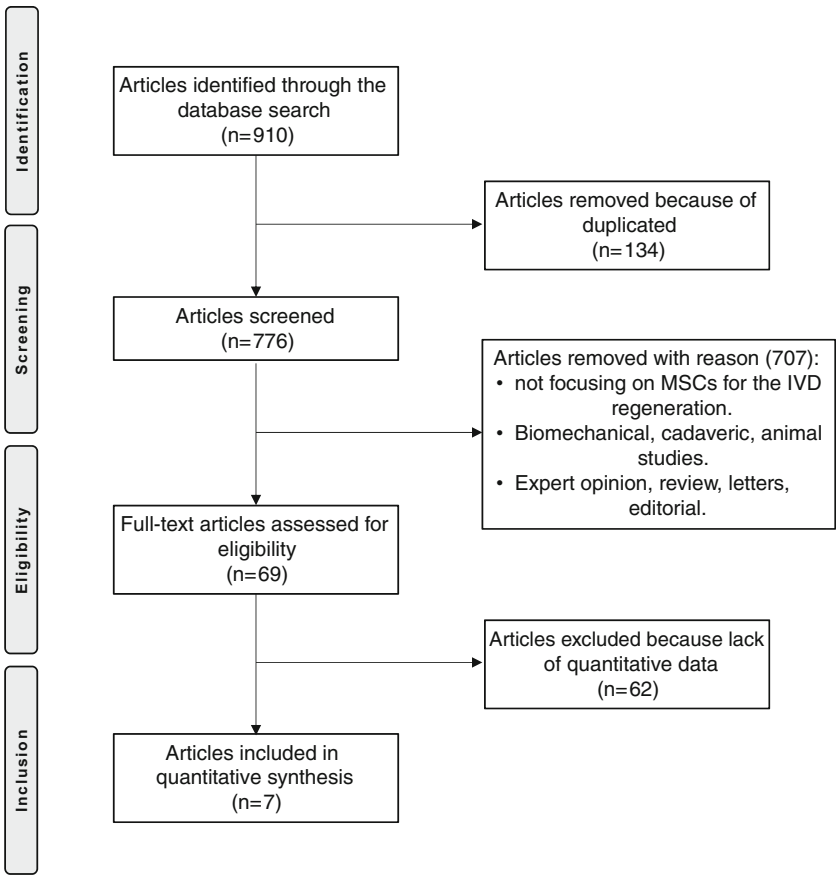


Fig. 1 PRISMA flow chart of the literature search

Table 1 Patients' demographic data

Author (year)	Criteria									
	Level of evidence	Coleman score	Patients (*n*)	Mean age (years)	Total of treated levels	Previous conservative therapies	Control group	Follow-up (months)	Inclusion criteria	Exclusion criteria
Centeno et al. (2017) [34]	II	66	33	40.3	33	Y	N	24	(1) DDD confirmed on MRI, (2) clinical diagnosis of radicular pain and (3) failed conservative treatment	(1) Active neurologic and/or endocrine disorder potentially associated with symptoms, (2) severe cardiac and/or pulmonary disease requiring medication, (3) history of active neoplasm within the past 5 years, (4) anaemia and (5) prior therapeutic intradiscal injection
Elabd et al. (2016) [35]	II	57	5	40	5	60	N	62	(1) Significant functional disability and (2) if lumbar radiculopathy is present, it is due to a chemical radiculitis secondary to an annular fissure or small protrusion	(1) Symptomatic severe central canal or foraminal stenosis, (2) previous history of lumbar spine surgery, (3) lumbar radiculopathy caused by mechanical compression, (4) spondylolisthesis/spondylolysis, (5) inflammatory or auto-immune-based pathology, (6) pregnancy and (7) bleeding disorder
Kumar et al. (2017) [32]	II	68	10	43.5	11	Y	N	12	(1) Ages 19–70, (2) low back pain < 3 months, (3) VAS > 4/10, ODI > 30%, (4) Pfirrmann stages III–IV in at least 2 levels, (5) discographic confirmation and (6) failure of previous conservative therapies	(1) Pregnancy and breastfeeding, (2) previous lumbosacral surgery, (3) herniated disc or stenosis requiring surgery, (4) Modic type 3, (5) MRI evidence of spinal infection, (6) disc space collapse > 50%, (7) uncontrolled hypertension and/or diabetes despite receiving optimal medication, (8) other serious systemic diseases and (9) allergies to hyaluronic acid
Noriega et al. (2017) [33]	II	66	12	38	19	Y	Y	12	(1) DDD of 1 or 2 lumbar discs with predominant back pain; (2) failure of previous conservative therapies; (3) stages 2, 3 and 4 of Pfirrmann; (4) decrease of disc height > 20%; (5) absence of spinal infection; (6) good performance status; and (7) ages 18–75	(1) Allergy to gentamicin or to bovine, cattle or horse serum; (2) spine deformations that may upset cell application; (3) spinal segmental instability; (4) spinal canal stenosis; (5) Modic III, BMI < 35; (6) pregnancy or breastfeeding; (7) neoplasia; (8) immunosuppression; and (9) contraindications or interactions of mepivacaine
Orozco et al. (2011) [36]	II	56	10	35	12	6	N	12	(1) Adams stages I, II and III and (2) decrease of disc height > 50%	(1) Infection signs or positive serology for HIV, (2) hepatitis and syphilis,

Table 1 (continued)

Author (year)	Criteria									
	Level of evidence	Coleman score	Patients (*n*)	Mean age (years)	Total of treated levels	Previous conservative therapies	Control group	Follow-up (months)	Inclusion criteria	Exclusion criteria
										(3) spinal segmental instability, (4) spinal canal stenosis, (5) isthmus pathology, (6) pregnancy, (7) neoplasia and (8) immunosuppression
Pettine et al. (2015) [37]	II	63	26	40	39	3	N	12	(1) Centralised chronic low back pain that increased with activity and lasted at least 6 months, (2) modified Pfirrmann score of 4–7, (3) Modic grade < 1, (4) decrease of disc height < 30%, (5) ODI score > 30/100 and (6) VAS > 4/10	(1) Abnormal neurologic exam, (2) symptomatic compressive stenosis, (3) herniation and (4) spondylolysis or any spondylolisthesis
Yoshikawa et al. (2010) [31]	III	41	2	68.5	3	Y	N	24	(1) DDD confirmed by MRI, (2) radiograph showing the vacuum phenomenon, (3) intervertebral disc instability, (4) associated pressure and spontaneous pain at the level of the degenerated intervertebral disc, (5) wearing a corset alleviates low back pain, (6) lumbar spinal stenosis and neurologic symptoms, (7) resisted conservative therapy and (8) required surgery	

ODI Oswestry Disability Index

conservative therapies three to six months. Only the study of Noriega et al. [33] presented a control group. The table of patients' demographic data is shown in Table 1.

Procedures

Bone marrow-derived MSCs harvested from the iliac crest represented the most common type of infiltrated cell [31, 33–37]. Kumar et al. [32] used adipose-derived MSCs in combination with hyaluronic acid in their study. The cells were processed, treated, expanded and cultivated in different ways in each study. Four authors [32, 34, 35, 37] reported an average of 1.5 ml (0.25–3 ml) of stem cells inoculated into the IVD. Most of the authors did not recommend any further procedure after the treatment. Only Yoshikawa et al. [31] requested to wear a corset for two weeks. The allowance for resumption of normal activities was variable: Orozco et al. [36] let the patients return to their normal activities one week after treatment, and Centeno et al. [34] requested a break of three days to four days.

Analysis of scores

Four studies analysed the Oswestry Disability Index (ODI) [32, 33, 36, 37]. An overall improvement across all the follow-up was evidenced. The mean ODI at baseline was 39.58 ± 13.42 points. After three months, the score improved to 18.7% (EE = 2.11; 95% CI = 0.57, 3.65; $P = 0.007$). At six months, the score improved to 2.1% (EE = 0.37; 95% CI = −0.14, 0.89; $P = 0.16$). At the last follow-up, the mean ODI improved to 0.98% (EE = 0.30; 95% CI = −0.33, 0.92; $P = 0.35$). The overall improvement observed from baseline to the last follow-up was 21.78% (EE = 2.67; 95% CI = 1.06, 4.28; $P = 0.001$) (Table 2).

Five studies reported the VAS [32–34, 36, 37], evidencing an overall improvement among all the follow-up. The mean pre-operative VAS was 57.08 ± 29.52 points. After three months, the score improved to 25.54% (EE = 5.90; 95% CI = 2.22, 9.59; $P = 0.002$). At six months, there was an improvement of 4.76% (EE = 1.36; 95% CI = −0.11, 2.84; $P = 0.002$). At the last follow-up, the reported VAS was 27.04 ± 15.27 points, corresponding to an improvement of −0.26% (EE = 0.23; 95% CI = −0.30, 0.76; $P = 0.40$). The overall improvement observed from baseline to the last follow-up was 30.04% (EE = 10.49; 95% CI = 2.09, 18.88; $P = 0.01$) (Table 3).

Outcomes and complications

Regarding the radiological outcomes, most of the authors [33, 36, 37] observed both qualitative and quantitative improvements in the MRI sequences. Yoshikawa et al. [31] reported higher moisture content in the treated discs at the last follow-up in the T_2-weighted MRI scans. In the study of Elabd et al. [35], a reduction of the protrusion size and a maintenance of the disc height at the last follow-up were found. Centeno et al. [34] observed a reduction in the size of disc bulges of 23% in the 85% of patients at the last follow-up. The study of Kumar et al. [32] showed an improvement of the Pfirrmann score and disc hydration. Regarding the clinical scores, all the authors reported an overall improvement along all the follow-ups, with significant relief of pain and reduction of disability. Only one case of herniated nucleus pulposus after injection was reported in the study of Centeno et al. [34]. All the other authors reported no adverse events at the aspiration or injection site.

Discussion

The main findings of this systematic review are that percutaneous injection of autologous MSCs for intervertebral disc degeneration can represent a feasible and safe option in selected patients, leading to good clinical outcomes during the follow-up period. All studies reported a high rate of patient's satisfaction, with a noticeable improvement of the quality of life. The average ODI value improved from severe disability at baseline to minimal disability at the 12-month follow-up. Compared to the values prior to treatment, the VAS showed an average improvement of 30% at the one year follow-up.

Regarding the complications, only one case of herniation of the nucleus pulposus [34] was reported. This data is ambiguous, as we did not know if the herniation represents a complication directly associated with treatment, or if it was due to the natural evolution of IVD degeneration [38–40]. Recently, Pettine et al. [41] reported the result of the same cohort of 26

Table 2 Comparison of the ODI score (pretreatment versus 12-month follow-up)

Study or Subgroup	Pre-treatment Mean	SD	Total	12 Months Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kumar et al. 2017	42.8	15.03	10	16.8	9.77	10	36.0%	1.96 [0.86, 3.07]
Noriega et al. 2016	34	7	12	22	7	12	37.7%	1.66 [0.71, 2.61]
Orozco et al. 2011	25	4.1	10	7.4	2.3	10	26.4%	5.07 [3.11, 7.03]
Pettine et al. 2014	56.5	0	26	25	0	26		Not estimable
Total (95% CI)			**58**			**58**	**100.0%**	**2.67 [1.06, 4.28]**

Heterogeneity: $Tau^2 = 1.55$; $Chi^2 = 9.67$, df = 2 (P = 0.008); $I^2 = 79\%$
Test for overall effect: Z = 3.25 (P = 0.001)

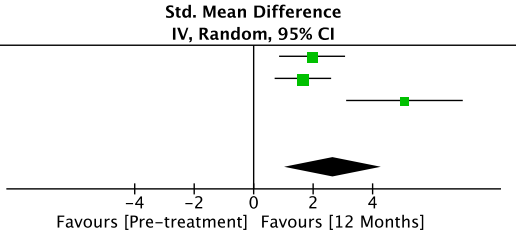
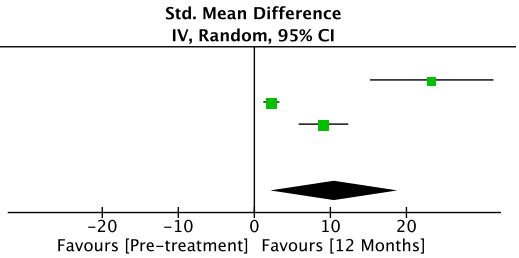


Table 3 Comparison of the VAS score (pretreatment versus 12-month follow-up)

Study or Subgroup	Pre-treatment Mean	SD	Total	12 Months Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Centeneo et al. 2017	52	0	33	6	0	33		Not estimable
Kumar et al. 2017	65	1.27	10	29	1.66	10	27.6%	23.33 [15.21, 31.44]
Noriega et al. 2016	67	7	12	47	10	12	37.1%	2.24 [1.18, 3.30]
Orozco et al. 2011	68.9	3.3	10	20	6.5	10	35.3%	9.09 [5.82, 12.35]
Pettine et al. 2014	79.3	0	26	33.2	0	26		Not estimable
Total (95% CI)			**91**			**91**	**100.0%**	**10.49 [2.09, 18.88]**

Heterogeneity: Tau² = 49.22; Chi² = 39.32, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.45 (P = 0.01)



patients over the 36-month follow-up. They confirmed no treatment-related adverse effects, with a high rate of patient's satisfaction. Concerning the feasibility of MSC injection, another recent prospective study [42] has studied the complication rate among patients undergoing to stem cell injections in different joints. This study observed 2372 patients, reporting a very low complication rate over the 26-month follow-up.

Among the various inclusion and exclusion criteria, the authors referred to the Adams [43], Pfirrmann [44] and Modic [45] scores. These scores evaluate different aspects of the vertebral segment degeneration, and by analysing them throughout the works considered in this study, we can delineate the characteristics that make a spinal segment eligible for treatment. The discography must show signs of degeneration and an IVD capable of containing stem cells: IVD with complete radial fissure cannot receive the treatment, because the non-integrity of the anulus may allow the injected stem cells to escape. The disc structure should present as inhomogeneous, with intermediate grey signal intensity at the MRI sequences. The distinction between the nucleus and anulus must be unclear, and the disc height can be normal or slightly decreased. Patients with fractures of the trabecular bone and/or with trabecular shortening and/or widening, with oedema and/or inflammation of the subchondral bone and/or with fatty replacement of the bone marrow are not suitable for treatment. It was also stated that patients should not present structural changes (such as spondylolisthesis) or an abnormal neurological examination. A good performance status is always required: while this is important to avoid publication biases, in the clinical practice, the treatment may, in the future, be extended to some of the categories that were currently excluded. As summarised, patients with low back pain due to initial IVD degeneration and low-stage radiological degeneration are eligible for infiltration with MSCs. Since these cells are not able to regenerate an expelled disc or a totally necrotic nucleus pulposus [46–48], the treatment has to be performed at the early stages of tissue degeneration. The power of regenerative medicine relies in the signalling and mutual interaction patterns between stem cells and their environment [49–51], which decreased in the advanced stages of IVD degeneration [52–54]. This degeneration can be due to several factors, but there is still a lack of consensus regarding the exact pathology of this phenomenon [55–57]. Triggering events include calcification of the endplate, infection, disc dehydration, fissure of the fibrous ring, genetic predisposition, biomechanical alteration of forces and many others [2, 58–63]. Irrespective of the leading pathogenic factor, a pro-inflammatory environment can be observed in all degenerated discs [64, 65]. MSCs can positively influence the pro-inflammatory state of the IVD: this can be achieved through a negative feedback provided by the production of anti-inflammatory cytokines, growth factors and anti-catabolic factors [51, 66–68]. A two-way communication has been observed when MSCs are in contact with the nucleus pulposus cells (NPCs) [69, 70]. The paracrine environmental signalling stimulates the MSCs to differentiate into NPC-like cells [71–73]. Concurrently, the MSC signalling can influence the reprogramming of the NPCs [50, 51, 74].

A limitation of this study is represented by the heterogeneous variety of MSCs used, the type of processing and the expansion of the stem cell lines. Further studies should also be promoting a longer follow-up time, investigating the duration of benefits and reporting also possible long-term complications. To clarify and refine the inclusion and exclusion criteria, large-scale studies enrolling a higher number of patients and procedures are required.

The regenerative medicine is strongly dependent to the progresses and developments made by other disciplines, such as the molecular biology [75, 76]. Further studies should deeply characterise the molecular signalling, differentiation, reparation and survival on the physiological IVD, as well as on the various pathological conditions. Moreover, establishing what kind of MSCs and the associated proliferation process lead to the best results, in terms of both safety and clinical outcome. We hypothesized that only a better comprehension of these aspects will correlate to better outcomes.

Conclusion

This systematic review of the literature proved MSC injection to be a safe and feasible option for the intervertebral disc regeneration in the early-degeneration stage patients. Irrespective of the source of the MSCs, an overall clinical and radiological improvement of the patients has been

evidenced, as indeed a very low complication rate during the follow-up observation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not required for this type of study

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