Systematic Review

Do Regenerative Medicine Therapies Provide Long-Term Relief in Chronic Low Back Pain: A Systematic Review and Metaanalysis

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Background: Several cell-based therapies have been proposed in recent years the management of low back pain, including the injection of medicinal signaling cells or mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP). However, there is only emerging clinical evidence to support their use at this time.

Purpose: To assess the effectiveness of MSCs or PRP injections in the treatment of low back and lower extremity pain.

Study Design: A systematic review and metaanalysis of the effectiveness of PRP and MSCs injections in managing low back and lower extremity pain.

Data Sources: PubMed, Cochrane Library, US National Guideline Clearinghouse, prior systematic reviews, and reference lists. The literature search was performed from 1966 through June 2018.

Study Selection: Randomized trials, observational studies, and case reports of injections of biologics into the disc, epidural space, facet joints, or sacroiliac joints.

Data Extraction: Data extraction and methodological quality assessment were performed utilizing Cochrane review methodologic quality assessment and Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) and Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR). The evidence was summarized utilizing principles of best evidence synthesis on a scale of 1 to 5.

Data Synthesis: Twenty-one injection studies met inclusion criteria. There were 12 lumbar disc injections, 5 epidural, 3 lumbar facet joint, and 3 sacroiliac joint studies

Results: Evidence synthesis based on a single-arm metaanalysis, randomized controlled trials (RCTs), and observational studies, disc injections of PRP and MSCs showed Level 3 evidence (on a scale of Level I through V). Evidence for epidural injections based on single-arm metaanalysis, a single randomized controlled trial and other available studies demonstrated Level 4 (on a scale of Level I through V) evidence. Similarly, evidence for lumbar facet joint injections and sacroiliac joint injections without metaanalysis demonstrated Level 4 evidence (on a scale of Level I through V)..

Limitations: Lack of high quality RCTs.

Conclusion: The findings of this systematic review and single-arm metaanalysis shows that MSCs and PRP may be effective in managing discogenic low back pain, radicular pain, facet joint pain, and sacroiliac joint pain, with variable levels of evidence in favor of these techniques.

Key Words: Chronic low back pain, regenerative therapy, medicinal signaling or mesenchymal stem cells, platelet-rich plasma, disc injection, lumbar facet joint injections, sacroiliac joint injections

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The growing number of modalities for management of chronic low back pain, along with the prevalence of this condition, has contributed to its high socioeconomic burden (1-4). Growing costs, in conjunction with the alleged low quality of some studies has had a negative impact on care health policy (1-13). In an assessment of U.S. spending on personal health care and public health, Dieleman et al (3) demonstrated that out of 155 defined conditions, low back and neck pain showed the second highest increase in spending, estimated to be around $57.2 billion (uncertainty interval $47.4 billion - $64.4 billion), from 1996 to 2013. In addition, low back and neck pain were the conditions that received the third highest level of health care spending, estimated at $87.6 billion in the context of a total of $183.5 billion spent for musculoskeletal disorders (3,4).

Diagnostic studies have demonstrated that the most common sources of low back pain include the intervertebral discs, the zygapophysial (facet), and the sacroiliac joints (13-19). Discogenic pathology, with or without internal disc derangement, has been estimated to contribute from 16.9% to 39% of cases of chronic low back pain without radiculopathy. In addition, lumbar disc disorders may manifest as disc prolapse, protrusion, extrusion, and herniation (13). According to the literature, the prevalence of symptomatic lumbar disc herniation is approximately 1% to 3%, whereas the prevalence of lumbar radiculopathy and sciatica is 0.98% (13-21). Similarly, the lumbosacral facet joints are well-recognized generators of chronic low back and referred lower extremity pain. Controlled studies have shown that the facets are responsible for generating low back pain that is not radicular or discogenic in 16% to 41% of cases (14). In addition, studies based on controlled diagnostic blocks have implicated the sacroiliac joints in 10% to 25% of low back pain cases without disc herniation, discogenic pain, or radiculitis (15).

Pain related to disc degeneration, disc herniation, and facet or sacroiliac joint pathology may be self-limited, but in a significant proportion of patients, this pain may become chronic, requiring the extensive treatment applications. Many of the decisions made in the management of these disorders are not supported by randomized controlled trials (RCTs) or well-designed observational studies (22).

Treatment modalities in the management of chronic lumbosacral pain include, conservative management with physical therapy, pharmacological therapy, interventional and intradiscal as well as surgical intervention through fusion or disc replacement. Multiple regulations have put in place to improve the standard of care and reduce healthcare costs (10,14-17,23-54). It is known that in disc degeneration, inflammatory cytokines produced by macrophages or disc cells play important roles in pain generation (55-66). As a result, in addition to traditional treatments, several cell-based therapies have recently been proposed including injections of medicinal signaling cells or mesenchymal stem cells (MSCs) or platelet-rich plasma (PRP). Evidence regarding these therapies has emerged from the basic sciences and has been translated into clinical research through controlled trials.

The available literature includes 4 systematic reviews and multiple additional manuscripts that assess the role of regenerative medicine therapies in treating lumbosacral degenerative disorders (58-66). Wang et al (58) studied the efficacy of intervertebral disc regeneration using stem cells in a systematic review and metaanalysis of controlled animal trials. Khan et al (59) performed a systematic review on the use of mesenchymal stem cells (MSCs) in spinal cord injury, intervertebral disc repair, and spinal fusion and concluded that MSCs possess an immune-modulatory role and can be used safely and effectively for spinal cord injury and disc repair (59). In a consensus statement on biologic treatments for orthopedic injury, LaPrade et al (63) discussed the evidence supporting the potential use of biologics for promotion of healing and function in patients with musculoskeletal injury. Basso et al (60) performed a systematic review of the clinical evidence of regenerative medicine in intervertebral disc degeneration with a focus on the role of PRP and MSCs. This review encompassed 7 articles on regenerative therapies that studied a combined population of only 104 patients. It also summarized the literature highlighting the potential of intradiscal injection of MSC or PRP in treating chronic low back pain due to underlying degenerative disc disease. Wu et al (61) conducted a systematic review and a single-arm metaanalysis of 6 reports on cell-based therapies for lumbar discogenic pain, and concluded that these therapies were associated with improvements in pain and disability scores.

However, the roles of biologicals in epidural injections, lumbar facet joint injections, and sacroiliac joint injections remains to be defined. The following systematic review and metaanalysis was therefore undertaken to evaluate the effectiveness of regenerative medicine therapies and their potential applications in the management of chronic low back pain.

1.0 Methods

The present systematic review was performed based on methodological and reporting quality of systematic reviews as described by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and A Measurement Tool to Assess Systematic Reviews (AMSTAR) (67-70). The step-wise compliance of PRISMA checklist was utilized (67,68).

This review focuses on the effectiveness of regenerative therapy in managing lumbosacral disorders which have resulted in chronic pain.

1.1 Eligibility Criteria

1.1.1 Types of Trials

- Randomized controlled trials
- Observational studies
- Case reports

1.1.2 Types of Participants

Patients in chosen trials had been suffering with chronic low back and/or lower extremity pain secondary to disc herniation, discogenic pathology without disc herniation, radiculitis or facet joint arthropathy, spinal stenosis, post-surgery syndrome, lumbar facet joint pain and sacroiliac joint pain.

1.1.3 Types of Interventions

Intradiscal, intraarticular, epidural and sacroiliac joint injections.

1.1.4 Types of Outcome Measures

- The primary outcome parameter was pain relief.
- The secondary outcome measure was functional status improvement.

1.2 Data Sources

All available trials in all languages, from all countries, providing appropriate management with outcome evaluations were considered for inclusion. Searches were performed from the following sources without language restrictions:

1. PubMed from 1966
   www.ncbi.nlm.nih.gov/pubmed
2. Cochrane Library
   www.thecochranelibrary.com
3. US National Guideline Clearinghouse (NGC)
   www.guideline.gov/
4. Previous systematic reviews and cross references
5. Clinical Trials
   www.clinicaltrials.gov/
6. All other sources including non-indexed journals and abstracts

The search period was from 1966 through June 2018.

1.3 Search Strategy

Search criteria were extensive, covering chronic low back pain of various origins along with multiple methods of injection of biologicals including PRP and stem cells.

Search strategy was as follows: (((((((((((((((chronic low back pain) OR chronic mid back OR upper back pain) OR disc herniation) OR discogenic pain) OR herniated lumbar discs) OR nerve root compression) OR lumbosciatic pain) OR postlaminectomy) OR lumbar surgery syndrome) OR radicular pain) OR radiculitis) OR sciatica) OR spinal fibrosis) OR spinal stenosis) AND ((((((((((epidural injection) OR platelet rich plasma injection or stem cell injection) OR epidural perineural injection) OR interlaminar epidural) OR intraarticular platelet rich plasma) OR stem cells) OR nerve root blocks) OR periradicular infiltration) OR transforaminal injection) OR platelet rich plasma OR stem cells) OR intradiscal injections or PRP or stem cells or sacroiliac joint or ligament injections or PRP or stem cells))) AND ((meta-analysis [pt] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp])))

1.4 Data Collection and Analysis

This review focused on all types of evaluations of PRP and stem cell injections. All studies that provided appropriate management and included outcome evaluations and statistical evaluations were reviewed. Book chapters, case reports, and reports without an appropriate diagnosis were excluded from consideration.

1.4.1 Inclusion Criteria

This review focused only on studies of effectiveness. The population of interest was patients suffering from chronic low back pain. Patients with acute trauma, fractures, malignancies, and inflammatory diseases were excluded.

All randomized trials with appropriate statistical calculations were utilized. Observational studies with a sample size of at least ten subjects were included.

1.4.2 Data Collection Process

Two review authors independently, in an unblinded, standardized manner, developed a search strategy, searched for relevant literature, selected manuscripts, and extracted data from the included studies. Disagreements were resolved by discussion between the 2 reviewers; if no consensus could be reached, a third author was called in to break the tie. If there was a conflict of interest regarding a reviewed manuscript (concerning authorship), or if the reviewer was also one of the authors or had any other type of conflict, the involved reviewer did not review the manuscript for methodologic quality assessment.

1.5 Data Synthesis and Analysis

Data synthesis and analysis were performed, including assessment of the risk of bias or quality of individual studies, outcomes assessment, and qualitative and quantitative analysis.

1.5.1 Risk of Bias of Individual Studies

The quality of each individual article used in this analysis was assessed using the Cochrane Review rating system (Appendix Table 1) (71) and Interventional Pain Management Techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment Tool (IPM – QRB) for randomized controlled trials (Appendix Table 2) (72), and Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for nonrandomized or observational studies (IPM-QRBNR) (Appendix Table 3) (73).

Utilizing the Cochrane Review criteria, studies meeting at least 9 of the 13 inclusion criteria were considered high-quality. Those meeting 5 to 8 criteria were considered moderate-quality, and those meeting fewer than 5 criteria were considered low quality and were excluded.

Based on the IPM-QRB and IPM-QRBNR criteria, studies meeting the inclusion criteria but scoring less than 16 were considered low quality and were excluded, studies scoring from 16 to 31 were considered moderate quality; and studies scoring from 32 to 48 were considered high quality and were included.

Methodologic quality assessment of each manuscript was performed by 2 review authors. The assessment was carried out independently in an unblinded, standardized manner to assess the methodologic quality and internal validity of all the studies considered for inclusion. If discrepancies occurred, a third reviewer performed an assessment, and a consensus was reached. Further remaining issues were discussed by all reviewers and were then resolved.

1.5.2 Outcome of the Studies

For the present analysis, either 50% relief from the baseline pain score or a change of at least 3 points on an 11-point pain scale of 0 to 10 was considered clinically significant. For functional status improvement, a change of 30% or more on disability scores or 50% improvement from baseline was considered clinically significant.

A study was judged to be positive if the relevance and effectiveness of the regenerative injection therapy of interest was demonstrated with either a control group or upon comparison from baseline to follow-up. A negative study was defined as one where no difference was seen between the treatments or where no improvement from baseline could be measured. Reference point measurements were considered at 3 months, 6 months, and one year.

1.6 Analysis of Evidence

The analysis of the evidence was performed based on best-evidence synthesis and was modified and collated using multiple available criteria, including the Cochrane Review criteria and United States Preventive Task Force (USPSTF) criteria as illustrated in Table 1 (74). The analysis was conducted using 5 levels of evidence ranging from strong to opinion- or consensus-based. The results of best evidence as per grading were utilized. At least 2 of the review authors independently, in an unblinded, standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus was attained. If there were any conflicts of interest (e.g., authorship), the reviewers of interest were recused from assessment and analysis.

1.6.1 Metaanalysis

The metaanalysis was performed using Comprehensive Metaanalysis version 3.0 (Biostat Inc., Englewood, NJ). For pain and functional status improvement data, the studies were reported as standardized mean differences (SMD) with 95% confidence intervals (CI). Data were plotted with forest plots to evaluate treat-

Table 1. *Qualitative modified approach to grading of evidence.*

Level I	Strong	Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness
Level II	Moderate	Evidence obtained from at least one relevant high quality randomized controlled trial or multiple relevant moderate or low quality randomized controlled trials
Level III	Fair	Evidence obtained from at least one relevant high quality nonrandomized trial or observational study with multiple moderate or low quality observational studies
Level IV	Limited	Evidence obtained from multiple moderate or low quality relevant observational studies
Level V	Consensus Based	Opinion or consensus of large group of clinicians and/or scientists for effectiveness as well as to assess preventive measures, adverse consequences, effectiveness of other measures.

Adapted from Manchikanti L, Falco FJE, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. Pain Physician 2014; 17:E319-E325 (74).

ment effects. Heterogeneity was interpreted through I^2 statistic.

Random-effects model (single-arm) metaanalysis was planned to assess net changes in the same outcome variable (61,75). Heterogeneity among the effect sizes of individual studies was assessed using the I^2 index and Q statistic. Heterogeneity analyzed with the I^2 statistic was defined as low (25%–50%), moderate (50%–75%), or high (>75%) (76). Subgroup analyses were conducted based on follow-up periods (6 vs. 12 months or more) and the injected biologic solution type (stem cell vs. PRP). We conducted meta-regression analysis to identify factors related to a decrease in the pain score following therapy.

All analyses were based on each modality of treatment and the solution injected. Short-term improvement was defined as any improvement lasting for at least 3 months, and long-term improvement was described as that lasting for 6 months or longer. Meta-analysis was performed only when at least 3 studies were available and included an appropriate sample size of at least 10 for nonrandomized studies.

2.0 Results

2.1 Study Selection

Figure 1 shows a flow diagram of the study selection using the PRISMA study selection process (67,68).

Based on the search criteria, 26 manuscripts were identified and considered for inclusion (62,77-101). A total of 23 studies met the inclusion criteria (62,77-81,83-86,89-101) following the removal of duplicate publications (78,79). Three studies on stem cell therapy were excluded due to the inclusion of fewer than 10 participants (82,87,88). Of the remaining twenty studies, one utilized 3 modalities of treatment (92).

2.2 Methodologic Quality and Risk of Bias Assessment

Of the 21 manuscripts meeting inclusion criteria (62,77,80,81,83-86,89-101), 5 were randomized trials (85,90,94,95,101). Appendix Tables 4 and 5 show the methodologic quality assessment and risk of bias in each of these trials utilizing the Cochrane review criteria and the IPM-QRB criteria respectively (85,90,94,95,101). Assessment by the Cochrane review criteria showed that all of the trials were high-quality. However, assessment by IPM-QRB showed only 4 trials to be of high quality (85,90,94,101), with the remaining one trial of moderate quality (95).

Appendix Table 6 shows the assessment of the included nonrandomized or observational studies, including case reports, utilizing IPM-QRBNR criteria. Sixteen studies were included in this category for various types of regenerative medicine injection procedures in the lumbosacral spine (62,77,80,81,83,84,86,89,91-93,96-100). However, none of these were shown to be of high quality. The majority were moderate-quality (62,77,80,81,83,84,86,89,91-93,96,98-100) with one low-quality study (97).

2.3 Lumbar Disc Injections

Evidence of the effectiveness of PRP injections and injections of MSCs has been assessed through systematic reviews, randomized trials, and multiple observational studies.

2.3.1 Platelet-Rich Plasma

Our search identified multiple manuscripts on the utilization of PRP for intradiscal injections. These included a systematic review (60) and 6 individual studies, of which one was an RCT (90), and 5 were observational studies (80,81,89,91,92). The systematic review

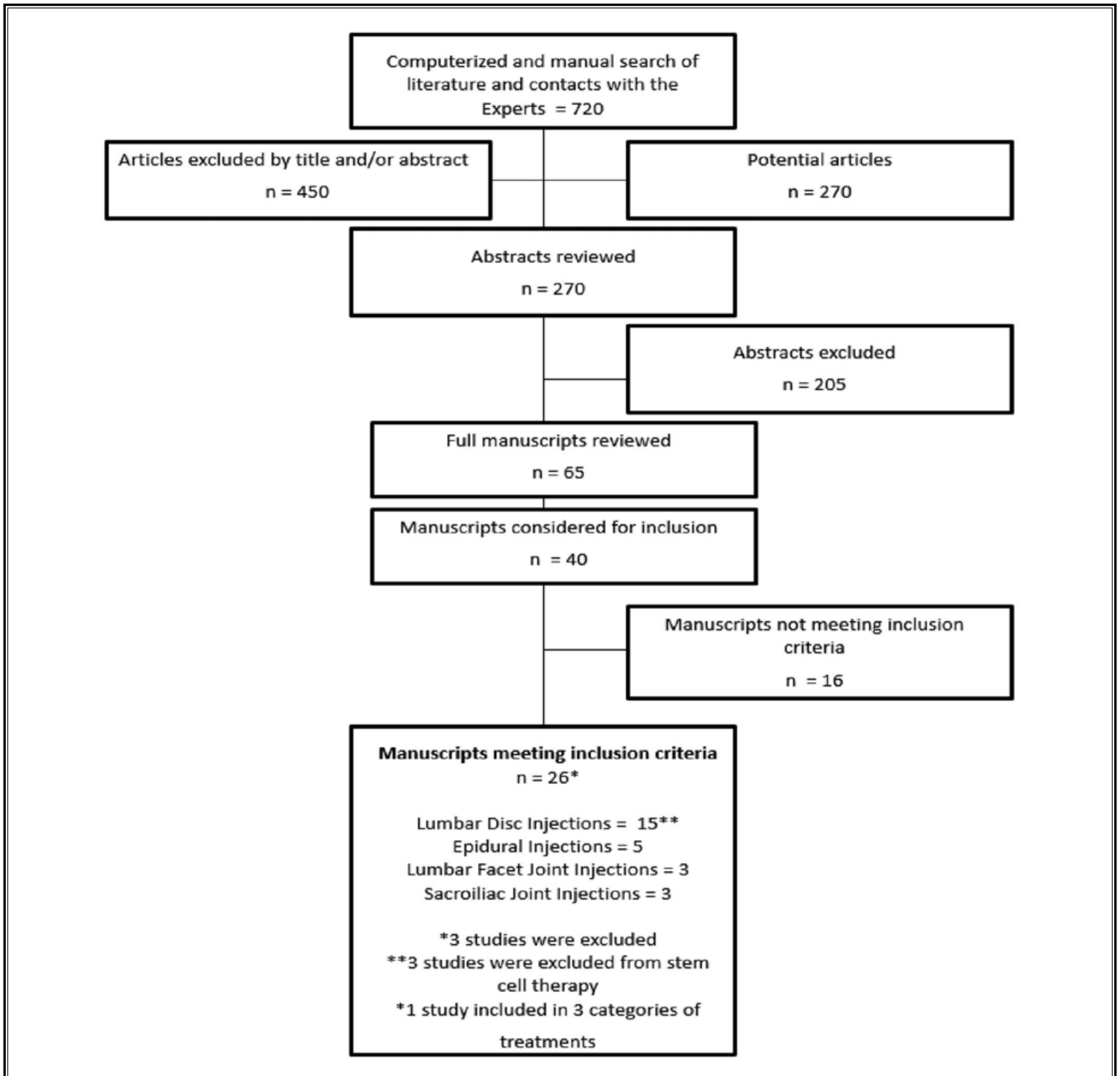

Fig. 1. *Flow diagram illustrating published literature evaluating regenerative therapies in lumbosacral disorders.*

(60) included the RCT (90) and 2 of the observational studies (81,91). Methodologic quality assessment and risk of bias assessment showed the RCT (90) to be of high quality based on the Cochrane review criteria and IPM-QRB criteria as shown in Appendix Tables 4 and 5. All the observational studies were shown to be of moderate quality (80,81,89,91,92) as assessed by IPM-QRBNR criteria and shown in Appendix Table 6.

Study characteristics are described in Table 2. Appendix Table 7 shows the study details of the numerical rating scale (NRS) and the visual analog scale (VAS) data at various follow-up time points.

As this search revealed only one RCT of interest (90), a 2-arm metaanalysis was not feasible. Thus, a single-arm metaanalysis was performed with inclusion of all studies. However, as demonstrated in Appendix

Table 2. ***Characteristics and outcomes of studies of PRP in intervertebral disc degeneration.***

Study Details	Chronicity of Injury and Biologic Used	Follow-up Period	Conclusions
Tuakli-Wosornu et al, 2016 (90) Lumbar discogenic pain Prospective, double-blind, randomized controlled study, n=47	Chronic PRP injections	One year	Intradiscal injections of PRP x1 showed significant improvement at 8-week follow-up, with maintained improvement compared to controls at 1-year follow-up.
Monfett et al, 2016 (89) Lumbar discogenic pain, lumbar disc degeneration Prospective trial, n=29	Chronic PRP injections	2 years	Intradiscal PRP injections show continued safety and improvements in pain and function at 2 years post-procedure
Navani et al, 2018 (80) Lumbar discogenic pain Prospective case series n=14	Chronic PRP, single injection, 2mL injected up to 3 disc levels	18 months	At 18 months, 11 patients remained for survey compared to 13 patients surveyed at 6 months. VAS relief was (>=50%) in 100% of patients at 18 months (n=11/11) and in 85% of patients (n=11/13) at 6 months.
Akeda et al, 2017 (91) Lumbar discogenic pain Preliminary clinical trial, n=14	Chronic PRP injections	12 months	Intradiscal injection of autologous PRP releasate in patients with low back pain was safe with no adverse events observed during follow-up The results showed reduction in mean pain scores at one month, sustained throughout the observation periods of 6 months and 12 months.
Levi et al, 2016 (81) Lumbar discogenic pain Prospective trial, n=8	Chronic PRP, single injection	6 months	Single or multiple levels (up to 5) of discogenic pain injected with PRP showed encouraging improvement, with more patients developing improvement over time. Cohort up to 6 months.
Kirchner and Anitua, 2016 (92) Lumbar disc degeneration Observational retrospective pilot study, n=86	Chronic PRGF-Endoret	6 months	Fluoroscopy-guided infiltrations of intervertebral discs and facet joints with PRGF in patients with chronic LBP resulted in significant pain reduction assessed by VAS. The results showed reduction of the VAS over time. The study ended at 6 months with 91% of the patients showing an excellent score, 8.1% showing moderate improvement, and 1.2% showing lack of response.

PRP = platelet-rich plasma; PRGF = plasma rich in growth factors; VAS = Visual Analog Scale; SF-36= 36-item Short Form Survey

Table 7, study details of the RCT were only available for 8 weeks. Consequently, the data from the RCTs was not included in long-term assessment. Figure 2 shows single-arm metaanalysis of decreased pain score data after 6-month follow-up. Five of the studies assessed showed a decrease in pain scores following treatment with a pooled sample size of 165 (80,81,89,91,92). The pooled mean difference in pain scores from baseline to 6-month follow-up was 40.631 ± 14.00 points (95% CI: -68.07 to -13.19, P < 0.0001, I^2 97.8%). Heterogeneity across studies was high (I^2 = 98%).

Figure 3 shows pain relief data on the 12-month follow-up. Three studies were included showing a decrease in pain scores after treatment with a pooled sample size of 57 (80,89,91). The pooled mean difference in pain scores from baseline to the 12-month follow-up was 36.408 ± 8.114 points (95% CI: -62.311 to -20.51 P < 0.003, I^2 82.9%). Heterogeneity across studies was high (I^2 = 83%). The authors of the 3 studies utilized different tools for functional improvement, and detailed data was not available. As a result, a metaanalysis of functional improvement data was not feasible.

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Akeda et al 2017	-43.000	7.691	59.152	-58.074	-27.926	-5.591	0.000
Monfett et al 2016	-16.600	4.888	23.890	-26.180	-7.020	-3.396	0.001
Navani et al 2018	-40.120	5.235	27.406	-50.381	-29.859	-7.664	0.000
Kirchner and Anitua 2016	-76.000	2.183	4.767	-80.279	-71.721	-34.807	0.000
Levi et al 2016	-26.600	6.217	38.647	-38.784	-14.416	-4.279	0.000
	-40.631	14.001	196.032	-68.073	-13.190	-2.902	0.004

Heterogeneity

Q-Value	df(Q)	p-value	I-squared	Tau squared	Tau
187.85	4	0.0001	97.782	949.782	30.817

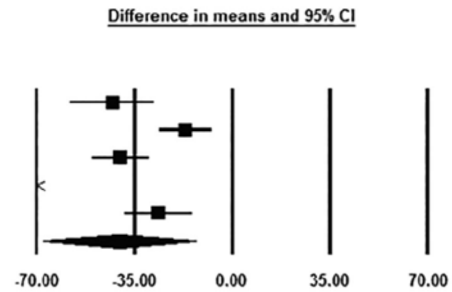

Fig. 2. *Decreased pain score (numerical rating scale or visual analog scale, 0-100) after treatment (6-month follow-up data) of lumbar disc injections of PRP.*

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Akeda et al 2017	-46.000	8.580	73.616	-62.816	-29.184	-5.361	0.000
Monfett et al 2016	-21.900	4.963	24.629	-31.627	-12.173	-4.413	0.000
Navani et al 2018	-43.230	4.674	21.847	-52.391	-34.069	-9.249	0.000
	-36.408	8.114	65.839	-52.311	-20.505	-4.487	0.000

Heterogeneity

Q-Value	df(Q)	p-value	I-squared	Tau squared	Tau
11.711	2	0.003	77.166	82.923	12.653

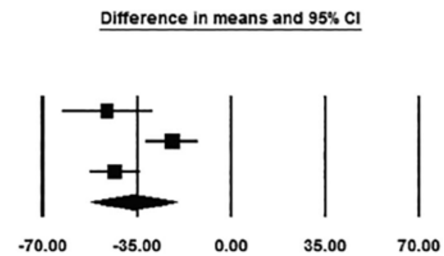

Fig. 3. *Pain scores (numerical rating scale or visual analog scale, 0-100) after treatment (12-month follow-up data) with lumbar disc PRP injections.*

2.3.2 Mesenchymal Stem Cells or Medicinal Signalling Cells

Mesenchymal stem or medicinal signally cell (MSCs) therapy has been studied with multiple pre-clinical, clinical studies along with systematic reviews (60-62,77-79,82-88). In a systematic review, Basso et al (60) reviewed 3 manuscripts (79,82,84) exploring MSCs use in intervertebral disc disease. The second systematic review, a single arm metaanalysis by Wu et al (61), included 6 studies which were eligible for the review (62,78,82-84,87). Our search criteria identified a total of 9 manuscripts studying cell-based therapies for lumbar discogenic low back pain (62,77-79,82-88). Of these, there was one RCT (85), 3 manuscripts reporting a single study (77-79), 2 studies that each included 2 patients (87,88), and one study that included 9 patients (82). Consequently, 6 studies met inclusion criteria (62,77,83-86). The methodologic quality and risk of bias assessment of these studies showed high quality evidence for one RCT (85) based on both Cochrane review criteria and IPM-QRB criteria as shown in Appendix Tables 4 and 5. Five observational studies meeting inclusion criteria showed moderate quality (62,77,83,84,86) utilizing IPM-QRBNR criteria as shown in Appendix Table 6.

Appendix Table 8 shows the study features of cell therapy in discogenic pain presenting the average numerical rating scale (NRS) or visual analog scale (VRS) at different time points. Appendix Table 9 shows the average Oswestry Disability Index (ODI) at various time points for all the studies. Table 3 shows the characteristics and outcomes of the stem cell therapy in lumbar discogenic pain studies.

With only a single RCT (85), a 2-arm metaanalysis was not feasible. A single-arm metaanalysis was thus performed utilizing the 6 available studies including one RCT (62,77,83,84,85,86).

Table 3. *The characteristics and outcomes of the included studies of stem cell therapy in disc degeneration.*

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Noriega et al, 2017 (85) Sample size = 24 Follow-up = 12 months RCT	24 patients with chronic low back pain with lumbar disc degeneration and unresponsive to conservative treatments were randomized into 2 groups. Patient age (yrs) mean age ± SE = 38±2 s	Allogeneic bone marrow MSCs by intradiscal injection or a sham infiltration of paravertebral musculature with anesthetic	The intervention group received allogeneic bone marrow MSCs by intradiscal injection of 25 X 10, 6 cells per segment under local anesthesia	VAS, ODI, MRI, SF-12	• MSC-treated patients displayed a quick and significant improvement in all algofunctional indices versus the controls. • Both lumbar pain and disability were significantly reduced at 3 months and improvement was maintained at 6 and 12 months. Overall there was an average 28% improvement in pain and disability one-year after the intervention. • Only 5 of the 12 outcomes in patients (40%) receiving MSCs were described as perfect treatment with 100% improvement.	• 28% improvement in all patients • 40% of patients perfect result • Positive result
Pettine et al, 2015, 2016, 2017 (77-79) Sample size =26 Follow-up=3 years Prospective, open-label, non-randomized, 2-arm study	26 patients presented with symptomatic moderate to severe discogenic low back pain Patient age (yrs)= 18–61 years (median 40)	Autologous bone marrow concentration (nonexpanded)	2–3mL of bone marrow concentrate was injected in lumbar disc (1.66_106/mL)	ODI, VAS, and MRI	• The average ODI and VAS scores were reduced to 22.8 and 24.4 at 3 months. After 36 months, 6 patients proceeded to surgery. • After 36 months, 20 of the 26 patients reported average ODI and VAS improvement to 17.5 ± 32 and 21.9 ± 4.4 respectively. • One year MRI indicated 40% of patients improved one modified Pfirrmann Grade and no patient worsened radiographically.	• At 36-month follow-up, 6 of 26 patients progressed to surgery. The remaining 20 patients (77%) reported significant ODI and VAS improvements. • Authors concluded that there were no adverse effects and the study provided evidence of safety and feasibility of intradiscal BMC therapy.
Coric et al, 2013 (83) Sample size =15 Follow-up=1 year Prospective cohort	15 patients with single-level, symptomatic lumbar DDD from L-3 to S-1 and medically refractory low back pain Patient age (yrs)= 19–47 years (median 40)	Expanded allogeneic juvenile chondrocyte cells	Mean 1.3mL (1–2 mL, 107/ mL) cells solution was injected in the center of the disc space	ODI and NRS scores, 36-item Short Form Health Survey and MRI	• The mean ODI, NRS, and SF-36 physical component summary scores all improved significantly from baseline • Ten (77%) of these 13 patients exhibited improvements on MRI. Of these, the HIZ was either absent or improved in 8 patients (89%) by 6 months • Of the 10 patients who exhibited radiological improvement at 6 months, findings continued to improve or were sustained in 8 patients at the 12-month follow-up • Only 3 patients (20%) underwent total disc replacement by the 12-month follow-up due to persistent, but not worse than baseline, LBP	• The results of this prospective cohort are promising with 77% of patients improving • Positive result

Table 3 (cont.). *The characteristics and outcomes of the included studies of stem cell therapy in disc degeneration.*

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Orozco et al, 2011 (84) Sample size =10 Follow-up=1 year Pilot phase 1 trial	10 patients with degenerative disc disease and persistent low-back pain (>6 months; decrease of disc height >50%;) Patient age (yrs)= 35_7 (mean_SD)	Autologous expanded bone marrow–derived mesenchymal stem cells	23±5X106 autologous expanded BMSCs was injected into the nucleus pulposus area	ODI and VAS scores and MRI	• Patients exhibited rapid improvement of pain and disability (85% of maximum in 3 months) that approached 71% of optimal efficacy • This study confirmed feasibility and safety with identification of strong indications of clinical efficacy	• Authors concluded that MSC therapy may be a valid alternative treatment for chronic back pain caused by degenerative disc disease. • They also concluded that advantages over current gold standards include simpler and more conservative intervention without surgery, preservation of normal biomechanics, and same or better pain relief
Kumar et al, 2017 (86) Sample size = 10 Follow-up = 1 year Phase 1 study	10 patients with chronic low back pain lasting for more than 3 months with a minimum intensity of 4/10 on a visual analog scale and disability level ≥ 30% on the Oswestry Disability Index. Patient age (yrs)=between 19 & 70	Combined hyaluronic acid derivative and adipose-tissue derived mesenchymal stem cells (AT-MSCs)	A single intradiscal injection at a dose of 2 X 107 cells/disc (N=5) or 4 X 107 cells/disc (N=5)	VAS, ODI, Short-form 36, lumbar spine x-ray, MRI	• VAS, ODI, and SF-36 scores significantly improved in both groups receiving both low and high cell doses, and did not differ significantly between the 2 groups ● At 12-month follow-up 7 patients reported 50% or greater improvement in VAS ● 6 patients achieved treatment success with pain reduction of 50% or greater and improvement on disability scores on ODI • Among 6 patients who achieved significant improvement in VAS, ODI, and SF-36, 3 patients were determined to have increased water content based on an increased apparent diffusion coefficient on diffusion MRI	60% significant improvement with no adverse effect • Authors concluded that combined implantation of AT-MSCs and hyaluronic acid derivative in chronic discogenic low back pain is safe and tolerable • Positive result
Mochida et al (82) Sample size =9 Follow-up=3 years Prospective clinical study	9 patients with Pfirrmann grade III disc degeneration and posterior lumbar intervertebral fusion. Patient age (yrs)=20-29 years	Autologous cultured nucleus pulposus chondrocytes that cocultured with MSCs	One million activated autologous NP cells were injected into the degenerated disc 7 d after fusion surgery	JOA and MRI	• Clinical outcomes based on Japanese Orthopedic Association (JOA) scoring system for low back pain showed significant improvement from 14.2 ± 4.8 points preoperatively to 27.2 ± 1.6 points at 3 years after transplantation of the activated NP cells (maximum possible score of 29 points) • The JOA scoring system also showed improvement in low back pain subscale from 1.2 ± 0.5 points preoperatively to 2.7 ± 0.2 points at 3 years after the transplantation with maximum possible score of 3 points for no pain • No adverse effects were observed during the -year follow-up period	• Significant improvement in function and pain scores was reported • This study confirmed the safety of activated NP cell transplantation, and the findings suggest the minimal efficacy of this treatment to slow the further degeneration of human intervertebral discs

Table 3 (cont.). *The characteristics and outcomes of the included studies of stem cell therapy in disc degeneration.*

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Meisel et al, 2006 (62) Sample size =12 Follow-up=2 years	Patients with discogenic pain after repeat discograms. Patients were treated with cell therapy at least 3 months post the endoscopic. Patient age (yrs)= 18–75 years	Autologous cultured disc-derived chondrocytes (from surgical treatment of their disc prolapse)	Cells are injected into disc approximately 12 weeks following discectomy. The cell dose was not mentioned	ODI and VAS scores and MRI	• The median total Oswestry Score was 2 in the autologous disc chondrocyte transplantation (ADCT) group compared with 6 in the control group. Decreases in the Disability index in autologous disc chondrocyte transplantation (ADCT)-treated patients correlated with the reduction of low back pain • Decreases in disc height over time were only found in the control group, and of potential significance, intervertebral discs in adjacent segments appeared to retain hydration when compared to those adjacent to levels that had undergone discectomy without cell intervention	• Significant improvement • Positive result

RCT = randomized controlled trial; BMSCs= Bone marrow derived stem cells; MSCs=mesenchymal stem cells; JOA = Japanese Orthopedic Association; MRI = magnetic resonance imaging; NP = nucleus pulposus; DDD=degenerative disc disease; BMC = bone marrow concentrate; LBP=low back pain; NRS = Numerical Rating Scale; ODI = Oswestry Disability Index; VAS =Visual Analog Scale; SD=standard deviation; SF-12=12-item short-form survey; HIZ-high intensity zone

Based on a single arm analysis, Fig. 4 shows changes in the pain scores. Inclusion of the 6 studies revealed a pooled sample size of 71 (62,79,83-86). The pooled mean difference of the decrease in pain scores from baseline to the 12 month follow-up was 36.943 points (95% CI: -49.855 to -24.030, $P < 0.001$. Heterogeneity across studies was high (I^2 =86%).

Figure 5 shows the functional scores. Six studies showed an Oswestry Disability Index (ODI) assessment (62,79,83-85,100,). The data was available for 12 months. The pooled mean difference in disability scores from baseline to the 12-month follow-up was a 26.342 point decrease (95% CI: -32.359 to -20.325, $P < 0.001$). Heterogeneity across studies was moderate (I^2 =55%).

2.4 Epidural Injections

Multiple biologics have been administered epidurally in the management ofradicular pain (92,98-101). However, studies have been preliminary and there has been only one randomized, double blind, reference-controlled study (101). The other studies have been observational, either prospective or retrospective (92,98-100). There have not been any systematic reviews assessing epidural injections with biologics. Methodologic quality and risk of bias assessment of included studies of epidural injections showed one RCT of high quality (101) based on Cochrane review criteria and IPM-QRB criteria as shown in Appendix Tables 4 and 5. The assessment of observational studies by IPM-QRBNR demonstrated moderate quality for all the studies as shown in Appendix Table 6 (92,98-100). Appendix Tables 10 and 11 list pain relief and disability data.

Since there was only one randomized, double blind, controlled trial (101), a 2-arm systematic review was not feasible. Consequently, a single-arm systematic review and metaanalysis was performed (Fig. 6).

Table 4 shows summary characteristics of lumbar epidural injections of PRP studies.

2.5 Lumbar Facet Intraarticular Injections

Of the 3 available studies, only one was randomized comparing PRP to a local anesthetic combined with a corticosteroid (94). Methodologic quality assessment of lumbar facet intraarticular injections showed that one RCT (94) was of high quality by Cochrane review quality and IPM-QRB criteria as shown in Appendix Tables 4 and 5. The other 2 studies (92,93) demonstrated moderate quality based on IPM-QRBNR criteria as shown in Appendix Table 6. Of the 3 studies, 2 were performed

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Coroc D 2013	-22.330	1.030	1.061	-24.349	-20.311	-21.680	0.000
Kumar H 2017	-36.000	6.609	43.679	-48.953	-23.047	-5.447	0.000
Meisel HJ 2006	-41.450	8.509	72.403	-58.127	-24.773	-4.871	0.000
Noriega DC 2017	-20.000	11.768	138.486	-43.065	3.065	-1.700	0.089
Orozco L 2011	-48.900	7.288	53.115	-63.184	-34.616	-6.710	0.000
Pettine K, 2015	-53.400	7.920	62.726	-68.923	-37.877	-6.742	0.000
	-36.943	6.588	43.401	-49.855	-24.030	-5.608	0.000

Heterogeneity

Q-Value	df(Q)	p-value	I-squared	Tau squared	Tau
35.678	5	0.000	85.989	204.543	14.302

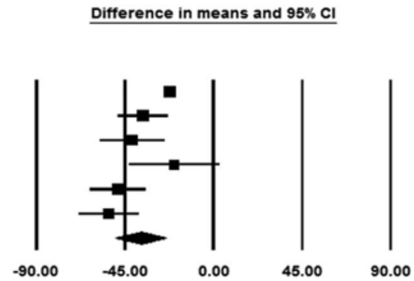

Fig. 4. *Changes in pain score (numerical rating scale or visual analog scale, 0-100) after treatment (12 months follow data) of cell therapy of lumbar disc.*

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Coric D 2013	-27.649	0.555	0.308	-28.737	-26.561	-49.818	0.000
Kumar H 2017	-26.000	5.672	32.172	-37.117	-14.883	-4.584	0.000
Meisel HJ 2006	-41.190	7.438	55.324	-55.768	-26.612	-5.538	0.000
Noriega DC 2017	-12.000	9.523	90.688	-30.665	6.665	-1.260	0.208
Orozco L 2011	-17.600	4.699	22.081	-26.810	-8.390	-3.745	0.000
Pettine KA 2015	-33.900	8.393	70.442	-50.350	-17.450	-4.039	0.000
	-26.342	3.070	9.425	-32.359	-20.325	-8.580	0.000

Heterogeneity

Q-Value	df(Q)	p-value	I-squared	Tau squared	Tau
11.1922	5	0.048	55.324	26.461	5.144

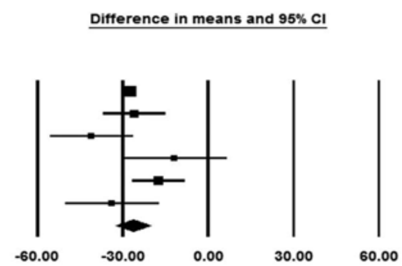

Fig. 5. *Changes in Oswestry Disability Index (ODI) after treatment (12 months follow data) of cell therapy of lumbar disc.*

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
HS Kumar 1976	-49.500	3.852	14.835	-57.049	-41.951	-12.852	0.000
Becker C 2007	-54.500	5.256	27.625	-64.801	-44.199	-10.369	0.000
Kirchner 2016	-76.000	2.183	4.767	-80.279	-71.721	-34.807	0.000
	-60.278	9.691	93.906	-79.272	-41.285	-6.220	0.000

Heterogeneity

Q-Value	df (Q)	p-value	I-squared	Tau squared	Tau
43.082	2	0.0001	95.358	266.285	16.318

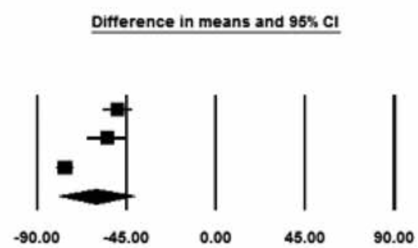

Fig. 6. *Changes in pain scores (0-100) after treatment (6 months follow data) of epidural PRP injections.*

by one group of authors with a sample size of 19 (93) and 46 (94). The third study by Kirchner and Anitua (92) was a complicated study with multiple injections (intradiscal, facet joint, as well as transforaminal) and reported excellent results. Because of the limitations, we were unable to perform a metaanalysis on these studies. The summary characteristics of these studies are listed in Table 5.

2.6 Sacroiliac Joint Injection

The effectiveness of biologicals, specifically PRP, was studied in one RCT (95) and 2 observational studies

Table 4. *Summary of lumbar epidural injection PRP studies published to date*

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Becker et al, 2007 (101) Sample size=84 Follow-up = 6 months Randomized controlled trial	84 patients with chronic lumbar radicular pain Patient age (yrs)=29-81 (mean 53.9)	IL-1 RA-enriched autologous conditioned serum (Orthokine; Autologous conditioned serum (ACS)	Transforaminal or perineural injection of ACS once per week for 3 consecutive weeks. Perineural space was approached through interlaminar space with injection of 1 mL of local anesthetic and autologous serum in Group 3. Group 1 and 2 received 1 mL of local anesthetic plus 10 mg of triamcinolone or 5 mg of triamcinolone	VAS, ODI	• Patients in all 3 groups improved comparably. Results were significant within each treatment group from week 12 to the final evaluation at week 26, injections with ACA showed a consistent pattern of superiority over both triamcinolone groups with VAS, with no significant difference for ODI among the groups	• ACS showed similar response to triamcinolone injection with local anesthetic initially; however, with significant improvement at 26 weeks with pain relief, but not with function. Results similar to local anesthetic and steroid injections • One of the limitations in this trial is that of multiple injections
Centeno et al, 2017 (99) Sample size=470 Follow-up=2 years Prospective registry	Patients suffering with lumbar radicular pain and MRI findings that were consistent with symptoms.	Platelet lysate	• Transforaminal or interlaminar epidural injection under fluoroscopic guidance. The final injectate consisted of plasma lysate 50% by volume, 4% lidocaine at 25% by volume, and compounded preservative free 100 to 200 nanograms per mL of hydrocortisone at 25% by volume • For transforaminal and interlaminar epidural injections, 3 to 5 cm3 volume was injected	Numeric Pain Score (NPS), Modified Single Assessment Numeric Evaluation (SANE) rating, Functional Rating Index (FRI)	• Patients treated with platelet lysate epidurals reported significantly lower NPS and FRI change scores at all time points compared to baseline • Posttreatment FRI change score means exceeded the minimal clinically important difference beyond one month • Average modified SANE rating showed 49.7% improvement at 24 months posttreatment • 29 or 6.3% patients reported mild adverse events related to treatment.	• Positive results with registry presenting real world data. • A large proportion of patients withdrawn • 36% of the patients failed to provide baseline NPS data • Information on number of procedures is unknown • 26% of the patients failed to show any significant improvement
Kumar et al, 2015 (100) Sample size=20 patients Follow-up= 6 months Prospective evaluation	20 patients with unilateral lumbar radiculopathy	Autologous conditioned serum (ACS)	• Interlaminar injection with 2 mL of contrast followed by 2 mL of ACS • A maximum of 3 injections at 7 days interval were given based on the clinical response • 20 patients received number of injections ranging from 1 to 3	VAS, ODI	• There was significant improvement in pain relief and function with VAS improving from 6.95 to 2.0 and ODI improving from 27.9 to 8.5. • 5 patients (20%) had complications which were immediate and systematic rather than local and were of short duration lasting less than 30 minutes	• Positive results with injection of ACS with disease modifying course with reduction of pain and disability • Small sample size with injection of contrast, which may diminish the effect of ACS

Table 4 (cont.). *Summary of lumbar epidural injection PRP studies published to date*

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Kirchner and Anitua, 2016 (92) Sample size=86 patients Follow-up = 6 months Observational retrospective pilot study	86 patients 47 females: age range 22 to 81, median age 58 39 males: age range 29 to 79 years, median age 55	86 patients each received one intradiscal, one intraarticular facet and one transforaminal epidural injection of plasma rich in growth factors	Transforaminal injection of 2 mL of activated PRGF after intradiscal injection of 4 mL of PRGF and facet joint infiltration	VAS	• At the end of the study (6 months), 90.7% of the patients showed an excellent score, 8.1% showed a moderate VAS score, and 1.2% of patients were included in the ineffective score group • There were no major adverse events	• Approximately 90% of the patients improved after 6 months • Positive study • Results are unreliable because of observational study and multiple injections into the disc, facet joint and with transforaminal application • Number of injections are unknown
Bhatia & Chopra, 2016 (98) Sample size=10 patients Follow-up=3 months Prospective evaluation	10 patients with findings of lumbar disc herniation/ prolapse in MRI, or either sex with age less than 65 years	Platelet-rich plasma	Interlaminar epidural injection with 2 mL of PRP	VAS and ODI	Patients who had received epidural injections of autologous PRP showed improvements in their scores of evaluation tools. Improvement was sustained during the 3 month study period and was not associated with any complications.	Autologous PRP can be considered as a good alternative to epidural steroids and surgery in management of patients with chronic prolapsed intervertebral disc.

ODI = Oswestry Disability Index; VAS =Visual Analog Scale; PRGF=platelet-rich growth factor; PRP=platelet-rich plasma

(96,97). The methodologic quality and risk of bias assessment of sacroiliac joint injections showed an RCT (95) of high quality based on the Cochrane review criteria and moderate quality based on IPM-QRB criteria as shown in Appendix Tables 4 and 5. Of the 2 observational studies (96,97), one was of moderate quality (96) and the second one was of low quality (97) as shown in Appendix Table 6.

Because of only a single RCT and a total of 3 studies (95-97), a metaanalysis could not be performed. Table 6 describes a summary of the studies of sacroiliac joint PRP injections.

2.7 Assessment of Evidence

Evidence was assessed for intradiscal injections, epidural injections, lumbar facet joint injections, and sacroiliac joint injections.

2.7.1 Intradiscal Injections

Evidence for intradiscal injections was based on the injected biological, either PRP or MSCs.

2.7.1.1 Platelet-Rich Plasma

Based on the available evidence, including one high-quality RCT (90) with multiple moderate-quality observational studies (80,81,89,91,92), a single-arm metaanalysis and evidence from a systematic review (60), the qualitative evidence is Level III (on a scale of Level I through V) using a qualitative modified approach to grading of evidence based on best-evidence synthesis.

2.7.1.2 Mesenchymal Stem Cells

Based on the available evidence with a high-quality RCT (85), multiple moderate-quality observational studies (62,77,83,84,86), a single-arm metaanalysis, and 2 systematic reviews (60,61), the qualitative evidence is Level III (on a scale of Level I through V) using a qualitative modified approach to grading of evidence based on best evidence synthesis.

Table 5. *Summary of lumbar facet joint PRP studies published to date.*

Study Details	Methods	Results	Conclusion
Wu et al, 2017 (94) Sample size=46 Follow-up=6 months Prospective randomized trial Chronic facet joint pain	46 patients with lumbar facet syndrome were randomized to intra-articular injections of PRP versus LA/corticosteroid Outcomes were assessed with VAS, ODI, and RMDQ	• Back pain improved in both groups immediately and at one month follow-up • At 3 months, back pain relief was superior in PRP injection group compared to steroid group • Functional status improvement was observed in both groups; however, at 3 months, there was significant improvement in PRP group compared to steroid group • Highest objective success rate with over 50% pain relief in 81% was found at 3 and 6 months after treatment, whereas highest success rate in 85% of the patients in the steroid group dissipated after one month	• There was significant improvement in both groups in short-term. However, improvement was long lasting for 6 months in PRP group • Positive study • Limited with a small number of patients
Wu et al, 2016 (93) Sample size=19 Follow-up=3 months Prospective clinical evaluation Chronic facet joint pain	19 patients with lumbar facet syndrome given intra-articular injections of PRP Outcomes were assessed with VAS, ODI, and RMDQ	• 79% of the patients reported satisfactory improvement with good or excellent at 3 month follow-up after injection of PRP • ODI and RMDQ were also significantly improved. There were no adverse events. A positive small study of intraarticular injection of autologous PRP	Positive results in a study with a small number of patients and relatively short follow-up of 3 months
Kirchner and Anitua, 2016 (92) Sample size=86 Follow-up = 6 months Observational retrospective pilot study, n=86 humans Facet Joint Syndrome	One intradiscal, one intra-articular facet, and one transforaminal epidural injection of PRGF under fluoroscopic guidance-control were carried out in 86 patients with chronic LBP.	VAS showed a statistically significant drop at 1, 3, and 6 months after the treatment ($P < 0.0001$) except for the pain reduction between the 3rd and 6th month whose signification was lower ($P < 0.05$).	• Positive study with multiple drawbacks with multiple injections in each setting with injection into disc, facet joint, and epidural space • Extremely high positive results in a low quality observational study

VAS=visual analog scale; ODI=Oswestry Disability Index; RMDQ=Roland Morris Disability Questionnaire; PRP=platelet-rich plasma; PRGF=platelet-rich growth factor; LBP=low back pain

2.7.2 Epidural Injections

Based on one high-quality RCT (101), multiple relevant moderate-quality observational studies (92,98-100) and a single-arm metaanalysis, the qualitative evidence is Level IV (on a scale of Level I through V) using a qualitative modified approach to grading of evidence based on best evidence synthesis.

2.7.3 Lumbar Facet Joint Injections

Based on one high-quality RCT (94) and 2 moderate-quality observational studies (92,93), the qualitative evidence for facet joint injections with PRP is Level IV (on a scale of Level I through V) using a qualitative modified approach to grading of evidence based on best evidence synthesis.

2.7.4 Sacroiliac Joint Injection

Based on one high-quality RCT (95), one moderate-quality observational study (96), and one low-quality case report (97), the qualitative evidence is Level IV (on a scale of Level I through V) using a qualitative modified approach to grading of evidence based on best evidence synthesis.

3.0 Discussion

This systematic review identified one RCT in each category of regenerative medicine for lumbosacral procedures (intradiscal injections with PRP or MSCs, lumbar epidural injections, lumbar facet joint injections, and sacroiliac joint injections). Single-arm metaanalysis for disc injections and epidural injections were included.

Table 6. *Summary of sacroiliac joint injection PRP studies published to date.*

Study Details	Methods	Results	Conclusion
Singla et al, 2017 (95) Sample size=40 Follow-up=3 months Prospective, randomized open blinded endpoint study Chronic low back pain with sacroiliac joint pathology	Patients were randomized into 2 groups with one group receiving 1.5 mL of methylprednisolone 40 mg/mL and 1.5 mL of 2% lidocaine with 0.5 mL of saline, whereas, PRP group receiving 3 mL of leukocyte free PRP with 0.5 mL of calcium chloride with ultrasound guided sacroiliac joint injection Outcomes were assessed with Visual Analog Scale (VAS) scores, Oswestry Disability Index (ODI), Short Form-12	• At 3-month follow-up, 90% of the patients reported satisfactory relief with PRP; whereas, satisfactory relief was observed in 25% of the patients receiving steroids. • A strong association was observed in patients receiving PRP and showing a reduction of VAS of greater than 50% from baseline	• Positive first prospective, randomized study • Small number of patients
Navani & Gupta, 2015 (96) Sample size=10 (4 males, 6 females) with sacroiliac joint pain of greater than 6 months duration Age Distribution=5 patients below 40 and 5 patients over 40 Sacroiliac joint pain	Sacroiliac joint injection under fluoroscopic guidance with PRP	• All patients improved 3 months post injection and maintained low pain levels not requiring any additional treatment up to 6 months post injection • SF-36 demonstrated improvement in both physical component summary scores and mental component summary scores in all patients • No adverse events	A positive case series of 10 patients
Ko et al, 2017 (97) Sample size=4 Follow-up=2 yrs. Case series	Sacroiliac joint injection with PRP under ultrasound Outcomes were assessed with Short form, McGill Pain Questionnaire, Numeric Rating Scale (NRS), Oswestry Disability Index (ODI)	• At 12-month follow-up there was marked improvement in joint stability, a statistically significant reduction in pain, and improvement in quality of life • The clinical benefits of PRP were still significant at 4 years post treatment	PRP showed long lasting positive results in this short case series of 4

PRP-platelet-rich plasma; SF-36= 36-item short form health survey;

The study demonstrated Level III (on a scale of Level I through V) evidence for intradiscal injections of PRP and MSCs, and Level IV (on a scale of Level I through V) evidence for epidural injections, lumbar facet joint injections, and sacroiliac joint injections based on qualitative evidence synthesis on a scale of Level I through V. There were no included studies of MSCs for epidural administration, lumbar facet joint injections, or sacroiliac joint injections.

This is the first systematic review assessing various therapeutic modalities of regenerative medicine inclusive of current analyses in the available literature. The results of the present investigation are comparable to those previously published for intradiscal injections (60,61); however, systematic reviews of epidural injections, facet joint injections and sacroiliac joint injections are not available.

Chronic low back pain is complex with involvement of the intervertebral discs, zygapophysial joints, and sacroiliac joints, all of which have been implicated as common causes based on studies using controlled diagnostic techniques. While the therapeutic role of regenerative medicine in discogenic pain is better established, the role of these therapies in epidural injections, facet joint injections and sacroiliac joint injections, though promising, is less clear. Degenerative disc disease and age-related debilitating disorders have a prevalence of more than 90% in people older than 50 years (102). Degenerative disc disease is a result of the combined effects of aging, adverse loading, dehydration, cellular apoptosis, and other imbalances in tissue metabolism (103). With reduction in matrix anabolism, there is an increased expression of prolonged-inflammatory cytokines and proteolytic enzymes (104). Disc degeneration involves changes in the composition of the extracellular matrix and loss of nucleus pulposus cells leading to morphological and functional abnormalities. The intervertebral disc is a dynamic structure having minimal vascular support and poor regenerative potential, especially after disruption of its metabolic homeostasis (105,106). Consequently, a potential therapeutic strategy involves augmenting the nucleus pulposus cell population in effort to restore the normal biologic function and matrix sufficiency. Currently the gold standard for treatment of intervertebral disc disease is fusion surgery using multiple techniques (6-8,107,108). The results of multiple analyses of the effectiveness of fusion procedures show that these types of surgery do not preserve the intervertebral disc, and they are not superior to other conservative modalities including epidural injections (109). Most conservative treatments based on physical therapy, injection therapy, or intradiscal therapies do not reverse the degenerative cascade (16,39-50,110-113). But because biological therapies offer the possibility of preventing or inhibiting degenerative changes of the intervertebral disc, they may represent a better treatment alternative (58,113,114). It has been postulated that the ideal interventional or biologic therapy should resolve nociceptive discogenic pain, slow or reverse the catabolic metabolism within the intervertebral disc environment and should provide partial or complete restoration of disc tissue (115).

The 12 studies included in our systematic review with single-arm meta-analysis included 2 high-quality RCTs (85,92), one using PRP (92) and the other using MSCs (85). These studies showed significant improvements in pain relief and functional status while demonstrating limited improvements in promoting regeneration and the reversal of degenerative processes. There has been significant activity in recent years with intensified efforts in the application of tissue engineering and regenerative medicine that have demonstrated effectiveness in preclinical studies (58,59). Preclinical research has been focused around 3 biological approaches to addressing the problem of degenerative disc disease - stimulation of anabolic processes, modulation of catabolic processes, and the provision of new cell growth in regeneration (116). Tissue-engineered cellular therapy has focused on chondrocytes (117), stem cell replacement therapy (118), and the injection of PRP. Biological approaches are appealing because of their minimal invasiveness and reduced costs in comparison to surgical interventions, including fusion. Based on the available literature, MSCs are known for their self-renewal ability as well as their capacity to sustain nearby cellular activity (119). Furthermore, they can differentiate into osteoblasts, adipocytes, chondroblasts, and cells with the phenotypic features of the intervertebral disc under proper in vitro conditions (120,121). MSCs may be derived from bone marrow, adipose, or umbilical cord tissue (122). At this time, there is limited literature evidence to determine which source of MSCs is superior (122). Some authors favor the use of adipose tissue because of its relatively higher concentration of MSCs, ease of harvesting, and its superior differentiation into the intervertebral disc phenotype (123,124). However, the capability of bone-marrow-derived MSCs to differentiate into nucleus-pulposus-like cells and their ability to stimulate production of new cell matrix when co-cultured (125) has also been described. In this regard, Mochida et al (82) tested this theory in intervertebral disc repair with activated nucleus pulposus cell transplantation over a 3-year prospective clinical study of its safety. Others investigators have also tested implantation of MSCs (62,77,83-86).

Some researchers have investigated the role of MSCs in healing and regeneration by studying autologous bone marrow MSC migration into the injured intervertebral disc. In a study of the homing process of MSCs, evidence was provided suggesting that although MSCs are recruited during disc degeneration, only a limited number of MSCs migrate to the intervertebral disc, presumably because of the disc's avascular nature (126). Wang et al (58) performed a systematic review and metaanalysis of using animal control trials to investigate the efficacy of intervertebral disc regeneration with stem cells. They demonstrated that stem cells, transplanted into the intervertebral disc in the quadruped animals, decelerate or arrest the intervertebral disc degenerative process. Yim et al (127), in a systematic review of comparative controlled studies regarding the potential benefits of using MSCs in disc degeneration, showed that all types of MSCs (bone marrow, adipose, or synovial tissue derived) demonstrated a significant inhibition of disc degeneration with a better quality of repair compared to non-MSC treatments. In addition, multiple in vitro and in vivo studies have demonstrated the effects of growth factors in regulating intervertebral disc cell proliferation and chondrogenic matrix metabolism (128). This suggests that the efficacy of intradiscal MSC injection could be enhanced by combining it with growth factors such as those found in PRP. Alternatively, PRP may be injected independently which produces similar results.

Platelet-rich plasma has been defined as a growth factors cocktail with the potential to promote nucleus pulposus cell differentiation and the reconstitution of human nucleus pulposus tissue (129-132). Among the available literature, Chen et al (131) created an ex vivo porcine model of a degenerative intervertebral disc to test the regenerative ability of 3 different therapeutic regimens, including MSCs, PRP, and MSC/PRP combined treatments. Formica et al (132) in their assessment of preclinical studies on the role of PRP injection in intervertebral disc degeneration, included 6 in vitro and 6 in vivo studies. The included studies showed positive histological results along with MRI analysis and the in vivo studies highlighted the therapeutic effects of PRP. As shown in our assessment, 6 clinical studies have yielded positive results, demonstrating that PRP can be helpful when used alone, producing results similar to MSCs in terms of regeneration and cell proliferation (80,81,89-92,131).

The next most pressing area of investigation involves the role that epidural PRP or MSCs injection plays in the treatment of disc herniation, any associated radiculopathy, radiculopathy without disc herniation, and in other biochemical and mechanical disorders (16,17,133). The nucleus pulposus contains a variety of inflammatory pain mediators, including phospholipase A2, nitric oxide, and prostaglandin E. In addition, cytokines such as interleukin IL-1 have been identified as mediators of inflammatory and degenerative changes (15-18,60). It has been hypothesized that the disc material, with inflammatory substances, causes direct toxic injury to the nerve root by chemical mediation which subsequently amplifies intra- and extraneural inflammation. This results in venous congestion and conduction block (133,134). Of the multiple cytokines identified within the disc, IL-1 appears to be of special interest regarding its role in the causation of lower back pain (135). Strategies for inhibiting the biological activities of IL-1 include the use of IL-1 receptor antagonist (RA), soluble forms of IL-1 receptors, and type-1 cytokines such as IL-4, IL-10, and IL-13 that inhibit synthesis of IL-1 and/or increase the synthesis of IL-1ra (60). The therapeutic use of cytokine inhibitors and growth factors was proposed in the late 1970's and early 1980's (136). In fact, some of the proponents of epidural injections believe that epidural injections produce anti-inflammatory effects with or without the use of steroids (39,109,137,138) since the role of steroids in epidural injections for managing discogenic pain continues to be debated and remains controversial (138).

With significant developments in biologicals as an evolutionary model, PRP and its derivatives, along with MSCs, have been proposed for epidural administration. Autologous condition serum (ACS) preparations have been described as a source of anti-inflammatory cytokines, including IL-4, IL-10, IL-13, and IL-1ra and also contain elevated concentrations of growth factors like fibroblast growth factor (FGF-2), hepatocyte growth factor (HGF), and transforming growth factor beta (TGF-β1) (135). ACS contains high concentrations of IL-1ra, an antagonist to IL-1 that is a "biochemical sensitizer" of nerve roots in radiculopathy (100,101,139). Consequently, ACS has been considered as a promising new treatment option for patients with radicular pain. ACS has been studied in one RCT (101) and in a prospective assessment (100). Similarly, the epidural injection of PRP with its multiple growth factors has also been studied (98). In addition, multiple other innovations including plasma lysate (99) and plasma rich in growth factors (PRGF-Endoret) (92) have been studied for epidural use. However, the literature has been tainted with flawed studies providing inadequate evidence. Despite this, present single arm metaanalysis did show moderate results with Level IV (on a scale of Level I through V) evidence using epidural injections of PRP or its derivatives.

Results of lumbar facet and sacroiliac intraarticular injections of biologics have demonstrated similar outcomes as those seen in the use of biologics for peripheral joints (140-144). The literature reports a significant increase in the levels of pro-inflammatory cytokines such as growth related oncogene-a (GRO-a), soluble intercellular adhesion molecule-1 (sICAM-1), interferon-c (IFN-c), tumor necrosis factor-a (TNF-a), interleukin (IL)-1b, IL-6, and IL-17 (94,145,146). Because of its high concentration of activated growth factors and cytokines including platelet-derived growth factor (PDGF), TGF-β, fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF-1), connective tissue growth factor (CTGF), and epidermal growth factor (EGF), as well as bioactive proteins, PRP has been used to promote the healing of tendons, ligaments, muscle, and bone (94,148,149). These elements within PRP act as humoral mediators to induce an anti-inflammatory effect and to facilitate the natural healing cascade by promoting cell proliferation, migration and differentiation, protein transcription, extracellular matrix regeneration, angiogenesis, and collagen synthesis (94,150-153). Based on this evidence, some investigators have recommended PRP as the most appropriate option for the treatment of lumbar facet joint syndrome. Three clinical studies have been presented which assessed the role of PRP injection into the facet joints and included one RCT (92-94); however, there are no studies evaluating the role of MSCs injections into the facet joints. The effectiveness of PRP use in sacroiliac joint pain was also evaluated in 3 studies which included one RCT as well as 2 case reports (95-97). However, there are no studies exploring the role of MSCs in sacroiliac joint treatment.

This systematic review has multiple advantages in comparison with the existing studies, as it is the largest of its nature thus far, and it includes epidural injections, lumbar facet joint injections, and sacroiliac joint injections of biologicals. Due to limitations, this review utilized a single-arm metaanalysis to evaluate the effect of biologics from baseline through treatment.

This review has several limitations. Despite extensive search criteria and inclusion of databases and trials, only 21 studies met our inclusion criteria and were incorporated into in this systematic review and metaanalysis. While this appears to be a robust number, after apportioning based on the treatment and type of injection, the number of studies was reduced to 6 for intradiscal PRP injections (80,81,89-92), 6 for intradiscal MSCs (62,77,83-86), 5 for epidural injections (92,98-101), 3 for lumbar facet joint injections (92-94), and 3 for sacroiliac joint injections (95-97). In addition, the majority of these studies were observational studies and case reports with significant heterogeneity and were performed on only a small number of patients. Other disadvantages include lack of valid or reliable selection criteria for the patients with discogenic pain. Further, there are no significant reports on quality of content of injectate, technical and other complications of discography, and diffusion or bulk flow of injectate to site of inflammation. Finally, there is no data reporting on clinically meaningful results and we have virtually no data reporting on clinically meaningful results, whereas we have some data on statistically meaningful results.

4.0 Conclusion

The findings of this systematic review and single-arm meta-analysis demonstrate that MSCs and PRP may be effective in managing discogenic low back pain, radicular pain, facet joint pain, and sacroiliac joint pain, with variable levels of evidence. The evidence is Level III (on a scale of Level I through V) for intradiscal injections versus Level IV (on a scale of Level I through V) evidence for epidural, facet joint, and sacroiliac joint injections. More studies are warranted to better understand the role of MSCs and PRP in mediating or modulating beneficial effects in low back related pain.

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Appendix

Appendix Table 1

Appendix Table 2

Appendix Table 3

Appendix Table 4

Appendix Table 5

Appendix Table 6

Appendix Table 7

Appendix Table 8

Appendix Tables 9 to 11

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