

Regenerative Approaches to Low Back Pain (LBP)

A review of the literature to treating common conditions of the lumbar spine

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Regenerative Approaches to Low Back Pain (LBP)

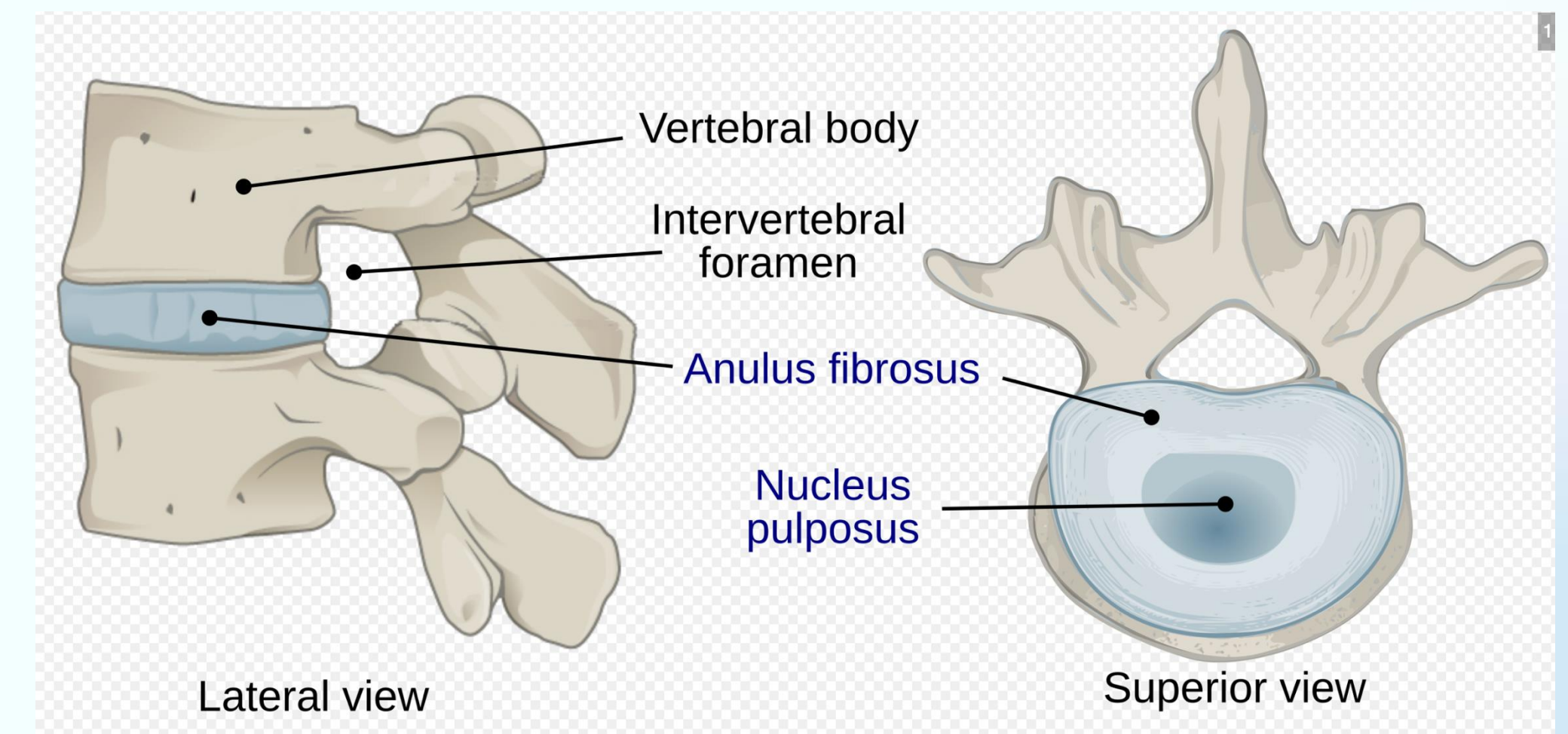
Outline

- Discuss regenerative interventions for common conditions of the low back:
 - Degenerative disc disease (DDD)
 - Facet arthropathy
 - Radiculopathy
- Evaluate the various regenerative medicine tools for common conditions including the following:
 - Platelet rich platelet
 - “Stem cells”
 - Umbilical cord derived
 - Adipose derived
 - Bone marrow

Pain generators of the low back

Degenerative Disc Disease: Pathophysiology

- Progressive loss of intervertebral disc height
 - Combination of loss of nucleus pulposus cell density
 - Reduction in ECM
 - Loss of load bearing capacity
 - Annular compression
- Vertebral body osteophyte development
- Disc herniation (bulge, extrusion, sequestration) and the resultant exposure of the nucleus pulposus is a highly inflammatory process (PLA2) that results in pain, generally non-radicular



https://en.wikipedia.org/wiki/Intervertebral_disc

Pain generators of the low back

Degenerative Disc Disease: Treatments

- Non-procedural
 - Exercise therapy (supervised/non-supervised)
 - Pharmacologic (non-opioid (NSAID, acetaminophen, SSRI/SNRI), opioid)
 - Spinal manipulation, acupuncture, massage, photobiomodulation, temperature exposure (hot/cold)
- Procedural
 - Intra-discal injections
 - Corticosteroid
 - Ozone
 - Methylene Blue
 - PRP
 - Stem cell
 - Epidural injections (ESI)
 - Radiofrequency Neurotomy (Intrasept)

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Corticosteroid
 - Reduces inflammation, effective for short term pain relief (1-3 months) with limited long term benefit. Increased risk of infection. No regenerative capacity.
- O2-O3 (Ozone)
 - Increases oxygen content in tissues, stimulates fibroblasts, interrupts inflammatory cascade. Improves pain and function in MA/SR. “Promising but insufficient to recommend strongly.”
- Methylene Blue
 - Neuroleptic effect, anti-inflammatory effect, however its impact on chronic LBP and long term effects have not fully been elucidated.

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Platelet Rich Plasma (PRP)
 - Includes several growth factors and cytokines (PDGF, VEGF, IGF-1, TGF-B1) which can help reduce inflammation and reduce MMPs.
 - **Peng et al., 2023** — systematic review / pooled analysis of intradiscal PRP studies.
 - 6 total studies: 3 RCTs, 3 prospective single arm trials (PSAT)
 - Review concluding intradiscal PRP is **generally safe and may reduce pain/improve function** in discogenic LBP, but highlighted small study sizes and variable quality; called for higher-quality RCTs.
 - **Kawabata et al., 2024** — intradiscal administration of autologous PRP (clinical study, Journal of Spine/related journal).
 - Prospective clinical safety/efficacy study targeting patients with Modic-type or MC1 disc changes/discogenic pain; **reported safety and improvements in pain/function in selected patients** (small sample, single-center).

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Platelet Rich Plasma (PRP)

Intradiscal_PRP_Studies_Clinical			
PRP Details	Comparator	Follow-up	Key Result
Autologous PRP injected after provocative discography	Sham (contrast)	8 weeks – 1 year	Improved pain/function vs control at 8 wks; sustained in some at 1 yr
Autologous PRP single intradiscal injection	None	6 months	~47% achieved ≥50% pain reduction and ≥30% ODI improvement
Follow-up of earlier PRP cohort	—	5–9 years	Sustained improvements; ~29% progressed to surgery
Autologous PRP	—	up to 12 months	Reported effective for pain and disability improvement
Autologous leukocyte-poor PRP, 2 mL per disc	None	48 weeks	Significant improvements in pain and function
High-concentration (>10×) PRP	Historical	1 year+	Clinically meaningful improvements; safe
Intradiscal PRP	Control	1 year	No significant improvement vs control
Various PRP preparations	Varied	short–mid term	Generally safe; some pain/function benefit; need better RCTs
Autologous PRP intradiscal	None	6–12 months	Safe, with improvements in selected patients
PRP vs BMC vs placebo	Placebo, BMC	multi-year	Framework for head-to-head trials
Intradiscal PRP for Modic I LBP	None	6 months	MRI and symptom improvements
PRP alone or combined (ozone, PELD)	Varied	short–mid term	Mixed results; some added benefit, others none

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Platelet Rich Plasma (PRP): Final Statements
 - Several promising studies but with small study populations, limited RCTs, and no significant long term outcome studies.
 - Safety profile is high. Efficacy in reducing pain and improving function.
 - “Lumbar Disc Injections: Based on the available evidence regarding the use of platelet-rich plasma (PRP), including one high-quality randomized controlled trial (RCT), multiple moderate-quality observational studies, a single-arm meta-analysis and evidence from a systematic review, the qualitative evidence has been assessed as Level III (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best-evidence synthesis.” ASIPP, 2019
- PRP preparations continue to be variable

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Mesenchymal Stem Cells/Medicinal Signaling Cells/Mesenchymal Stromal Cells (MSC)
 - Various sources including bone marrow, adipose tissue, and umbilical cord tissue.
 - MSC's have the capacity to differentiate into NP cells, can promote the proliferation of NPCs, support the synthesis of the ECM, and have anti-inflammatory factors that can suppress inflammation.

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- “Clinical Efficacy and Safety of Human Mesenchymal Stem Cell Therapy for Degenerative Disc Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials”
 - 3 studies included
 - Amirdelfan 2021
 - Noriega 2021
 - Noriega 2017

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Amirdelfan, 2021: “Allogeneic mesenchymal precursor cells treatment for chronic low back pain associated with degenerative disc disease: a prospective randomized, placebo- controlled 36-month study of safety and efficacy”
- “Allogeneic mesenchymal precursor cells (MPC)”
 - Allogeneic mesenchymal precursor cells (MPCs) were defined as a proprietary, allogeneic population of **bone marrow-derived stromal cells**. They were specifically selected for the **cell surface marker Stro-3+** and possessed immunomodulatory properties and the **ability to secrete anti-inflammatory factors**.
- Multicenter study across 13 sites, RCT, single intradiscal injection
- 4 groups, 100 participants, 3:3:2:2 ratio
 - Group 1: 6 million MPCs + HA
 - Group 2: 18 million MPCs + HA
 - Group 3: HA alone
 - Group 4: saline

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Amirdelfan, 2021: allogeneic mesenchymal precursor cells (MPC)
 - Outcomes: VAS, ODI over 36 months
 - Results:
 - MP treated patients showed significant differences in VAS and ODI scores than controls.
 - No difference between MP treated groups
 - **No difference in Treatment Emergent Adverse Events (TEAE) or Serious Adverse Events (SAE) across groups.**

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Noriega 2017: “Inter-vertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial”
- “allogeneic mesenchymal bone marrow cells”
 - “The bone marrow cells were obtained from (5) healthy donors, purified, and expanded for 24–27 days (3 passages)”
- 24 patients randomized into 2 groups:
 - T: 25 million aMSC injected directly into the IVD, single level
 - C: sham infiltration of paraspinal musculature with mepivacaine

Regenerative approaches to LDH

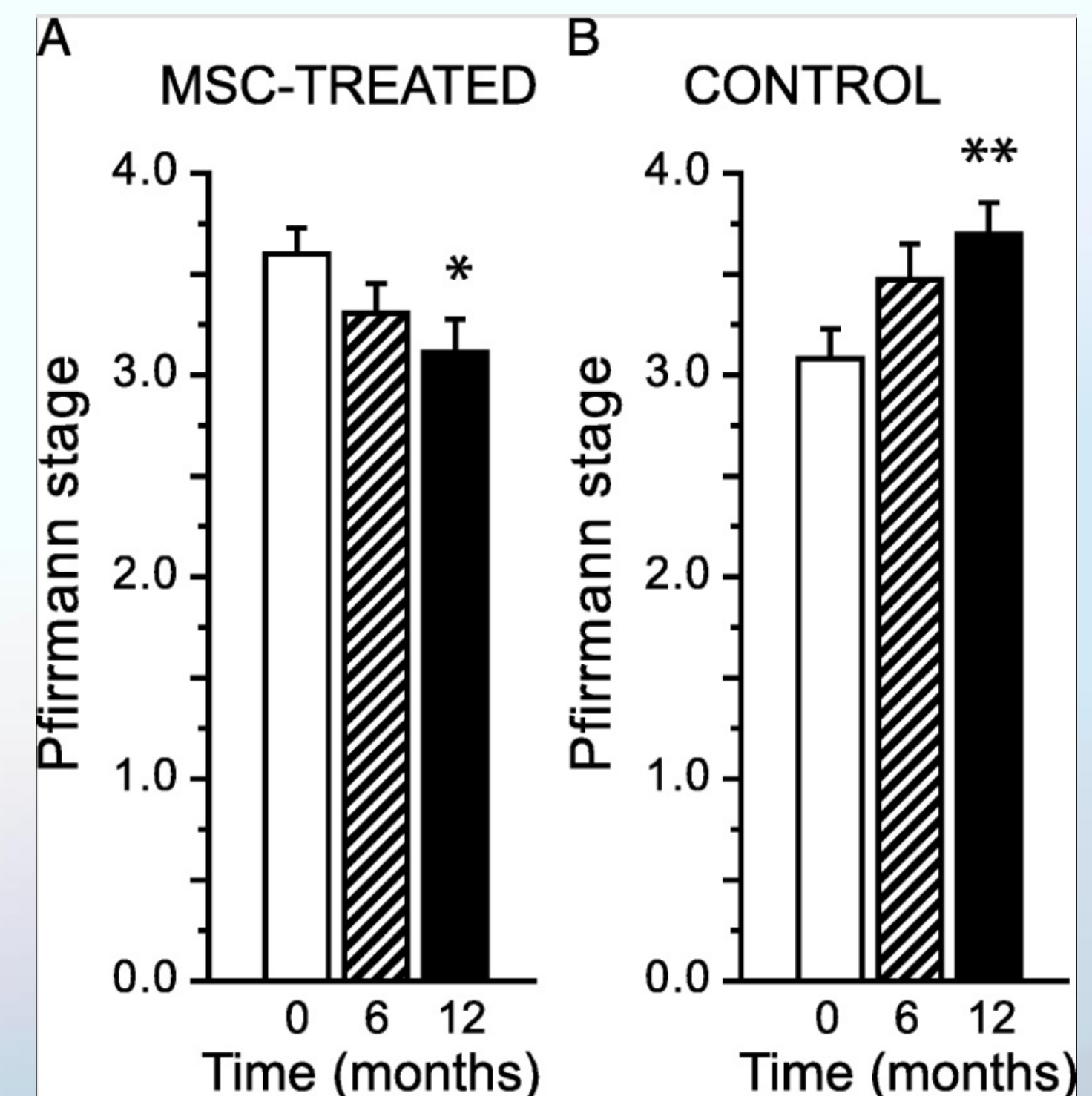
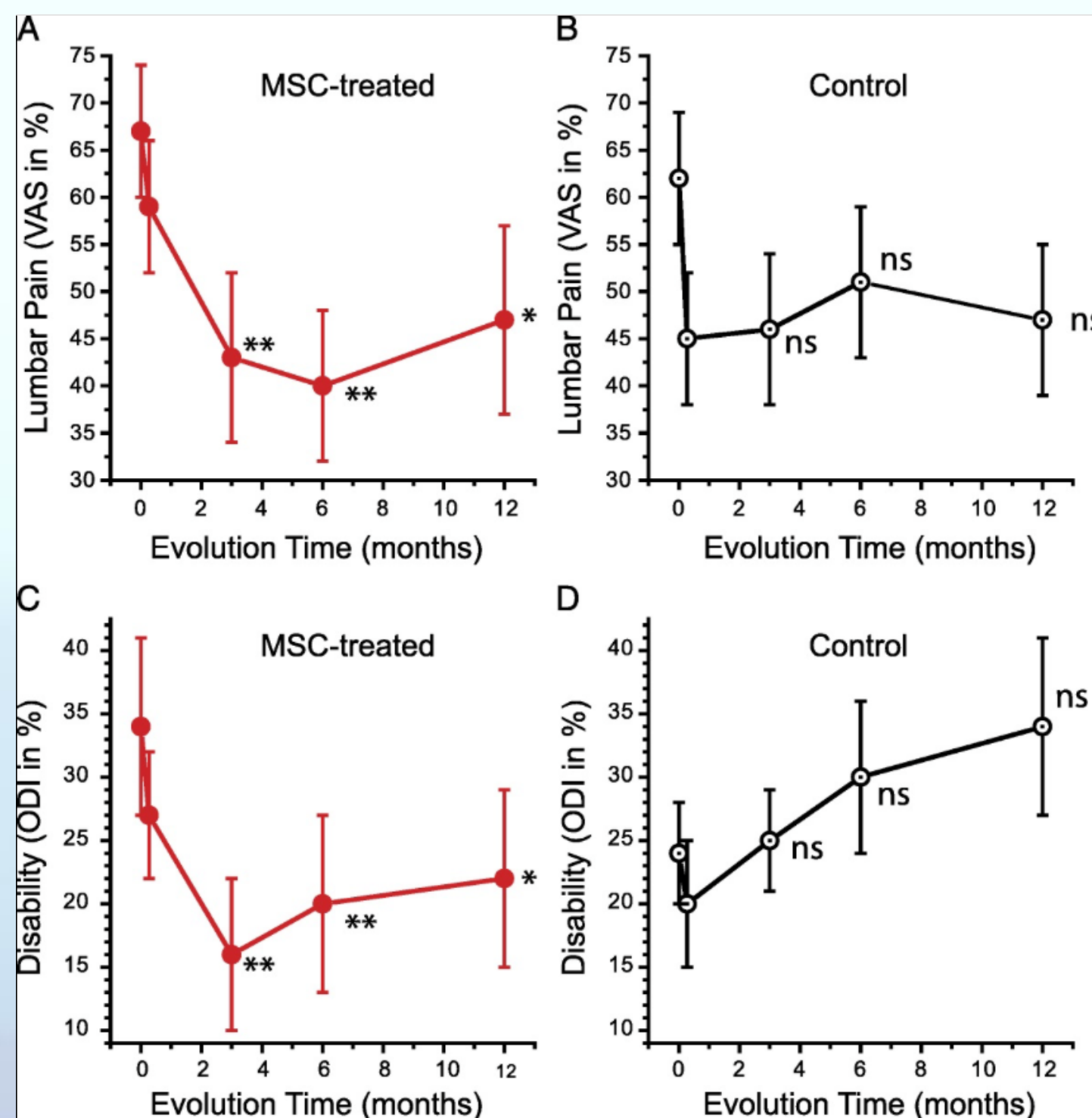
Degenerative Disc Disease: Intra-discal injections

- Noriega 2017: “Inter-vertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial”
- “Clinical outcomes were followed up for 1 year and included evaluation of pain, disability, and quality of life. Disc quality was followed up by magnetic resonance imaging.”
- Results:
 - "Compared with the basal level of pain and disability, improvement was statistically significant at all time points except at 8 days.”

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

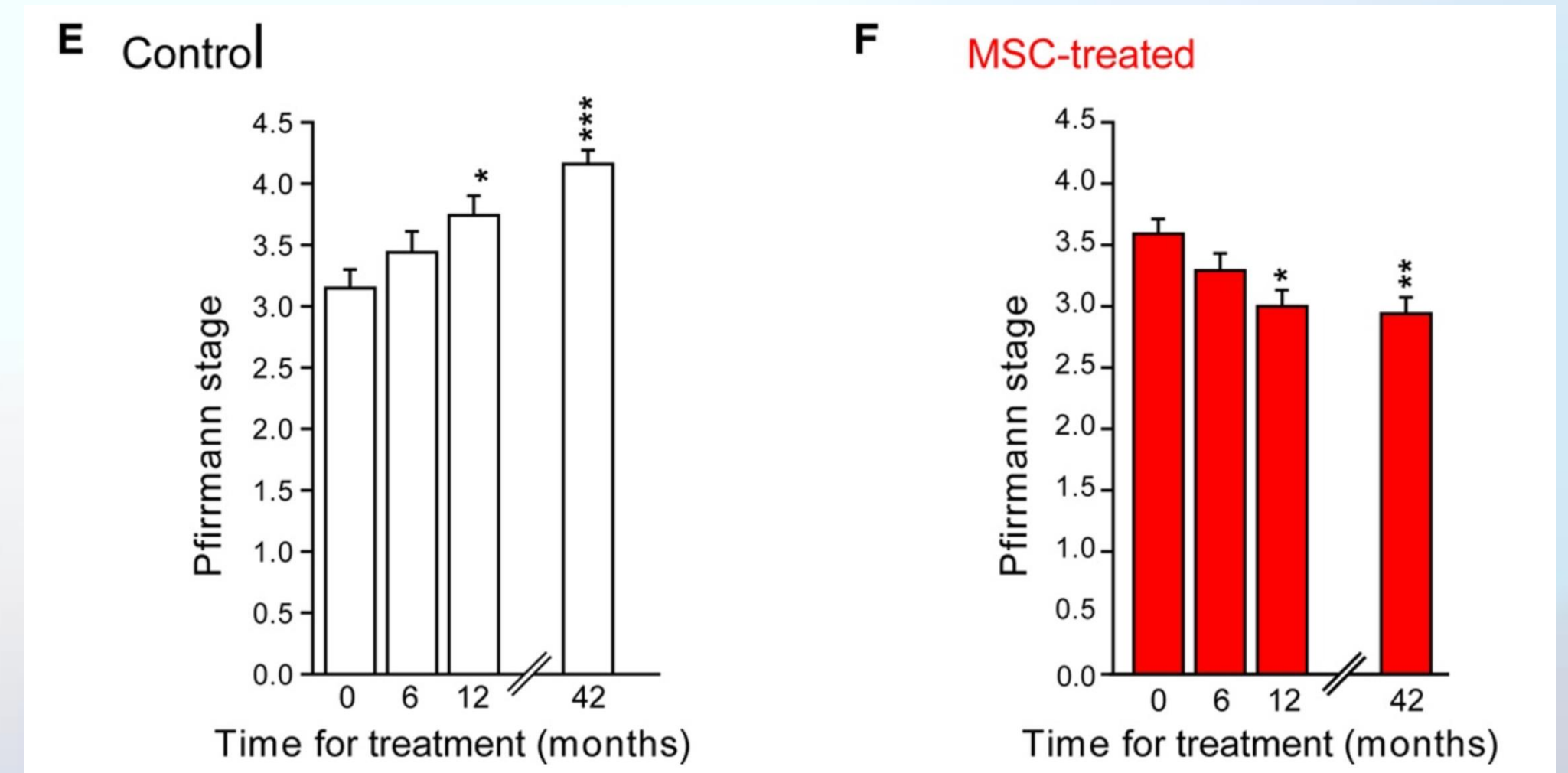
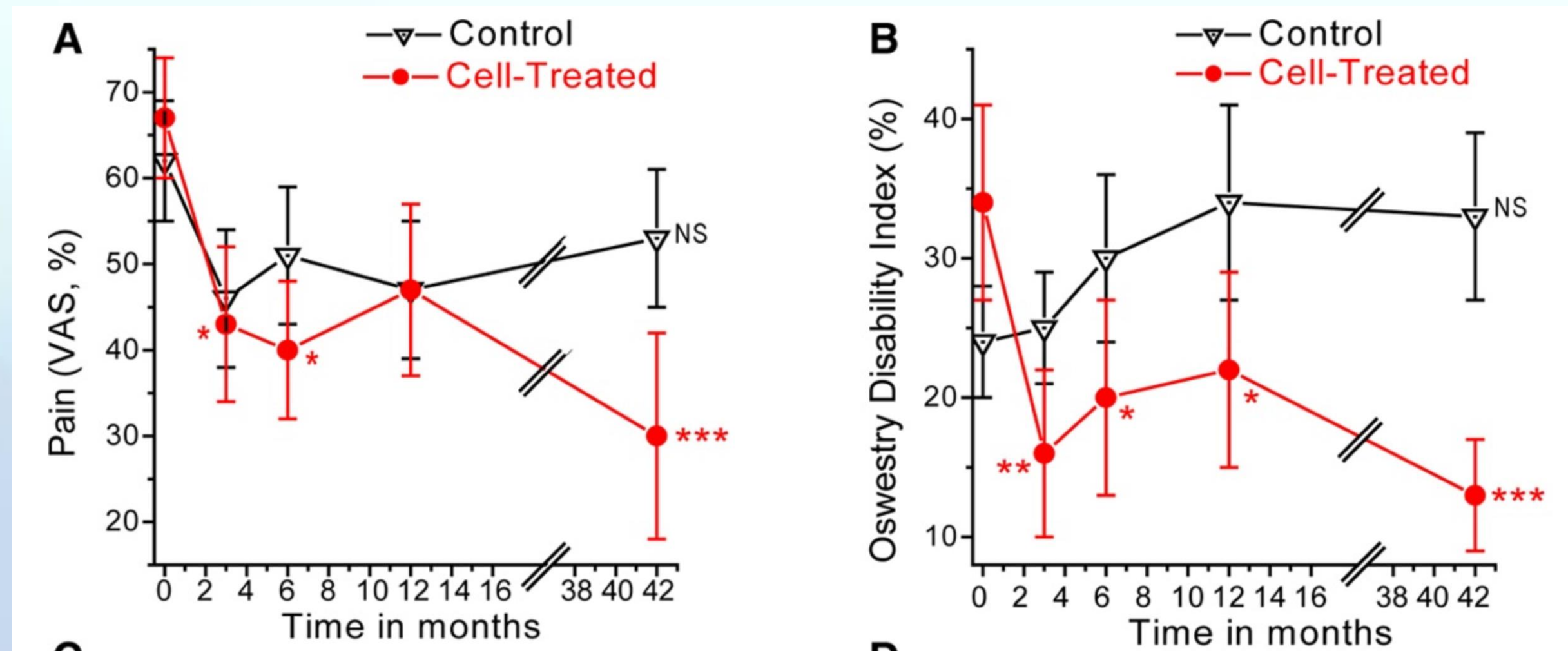
- Noriega 2017: “Inter-vertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial”



Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Noriega 2021: “Treatment of Degenerative Disc Disease With Allogeneic Mesenchymal Stem Cells: Long-term Follow-up Results”
- Follow up at 3.5 years:



Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Additional Studies:
 - **Pang et al. 2014**, Case series, 2 patients with chronic LBP
 - Umbilical cord derived MSC injected into the disc
 - Improvement in VAS and ODI at 2 years
 - **Pettine et al. 2017**, Case series, 26 patients DDD, candidates for surgical intervention
 - Autologous BM-MSC (120 million nucleated cells), intra-discal injections (ART bone marrow concentration system (Celling Biosciences, Austin, TX, USA))
 - Improvements in VAD, ODI, only 6 progressed to surgery in 3 year follow up, MRI improvements seen.
 - No adverse events.

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- Ongoing studies
- Phase I/II, small single center
- Vadala 2025: Autologous Bone Marrow Aspirate (BMAC)
 - Preliminary reports note safety (No major AE)
 - Significant reduction in Pfirrmann score
 - Cells were isolated and cultured to 15 million cells

Year (pub/press)	Study / sponsor (first author where available)	Design (phase)
2022 → ongoing (Phase 2 start 2022)	BRTX-100 (BioRestorative Therapies) — BRTX clinical program (NCT04042844)	Phase 2 (randomized, double-blind, controlled)
2024 (published July 2024)	DiscGenics — IDCT / rebonuputemcel (combined Phase I/II first-in-human)	Phase I/II first-in-human, open-label (published results)
2023 – 2025 (clinical reports / registry)	Single-center / multicenter in-office intradiscal MSC injections (various centers; e.g., Sanitas / private clinic cohort reported)	Case series / registry / observational (some single-arm)
2024–2025	RELIEF (Maal et al.) — phase I	Phase I safety & feasibility
2025 (preliminary reports / briefings)	Phase IIB / randomized intradiscal BM-MSC trial (Vadalà et al.)	Phase IIB randomized, double-blind (prelim report 2025)
2023–2025 (reviews & syntheses summarizing clinical studies)	Multiple systematic reviews / narrative reviews (e.g., Frontiers 2023, 2024 reviews)	Reviews summarizing human trials

Regenerative approaches to LDH

Degenerative Disc Disease: Intra-discal injections

- MSC final statements
 - Good safety profile
 - Promising data showing improvements in functional scores, pain, and objective changes on imaging studies
 - Further research is needed to identify optimal dose and type of “MSC”
- “Based on the available evidence regarding the use of medicinal signaling/ mesenchymal stem cell (MSCs) with a high-quality RCT, multiple moderate-quality observational studies, a single-arm meta-analysis, and 2 systematic reviews, the qualitative evidence has been assessed as Level III (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.” ASIPP 2019

Pain generators of the low back

Facet (zygapophyseal joint) arthropathy

- Diarthrodial synovial joint
- Joint capsule with synovial membrane that produces synovial fluid
- Cartilage surrounds the ends of the adjoining bones to allow for a smooth surface for movement.
- Can consider treatment of synovial joints analogous (extrapolate from knees, hips, etc).
- Between 15-30% of LBP has an origin of ZP joint(s)

Regenerative approaches to FJA

Facet joint arthropathy (FJA)

- Conservative treatment options are similar to DDD
- Procedurally, injections into the facet joint have been utilized including corticosteroids. In addition, radio frequency ablation/medial branch blocks are additionally longer term treatment options to reduce pain (diagnostic and therapeutic).
- PRP
- UCSC/ADSC/BMSC

Regenerative approaches to FJA

Facet joint arthropathy (FJA): PRP

- PRP for facet mediated LBP: A comprehensive review
- **Patel A. et al., 2022 — Review / clinical series summary**
- Results: Concluded PRP is a promising alternative with reports of short- and longer-term pain/function improvements, but emphasized small sample sizes and need for RCTs.

Table 1. Clinical studies utilizing platelet-rich plasma in facet-mediated pain states.

Study Details	Methods	Results	Conclusions
-Kirchner and Anitua, 2016 -Sample size=86 -Follow-up = 6 months -Observational retrospective pilot study	86 patients who simultaneously underwent one intradiscal, an intra-articular facet, and a transforaminal epidural injection of PRGF under fluoroscopy -Outcomes assessed with VAS	VAS decreased significantly at 1,3 and 6 months post-treatment. (P<0.05) 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 • Low-quality observational study. • Numerous confounding factors due to multiple interventions at once.
-Wu et al, 2016 -Sample size=19 -Follow-up=3 months -Prospective clinical evaluation	19 patients given intra-articular injections of PRP -Outcomes were assessed with VAS, ODI, and RMDQ	• 79% of the patients reported improvement with good or excellent at 3 month follow-up post-intervention • ODI and RMDQ were also significantly improved.	• Positive results in a study with a small number of patients • relatively short follow-up of 3 months
-Wu et al, 2017 -Sample size=46 -Follow-up=6 months -Prospective randomized trial	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 • 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, degree of improvement was greater for PRP than for steroid group. • Highest improvement rate with over 50% pain relief in 81% was found at 3 and 6 months after treatment, in contrast to highest success rate in 85% of the patients in the steroid group after one month	• Positive study • There was significant improvement in both groups in short-term. However, improvement was long lasting for 6 months in PRP group • Limited with a small number of patients

Regenerative approaches to FJA

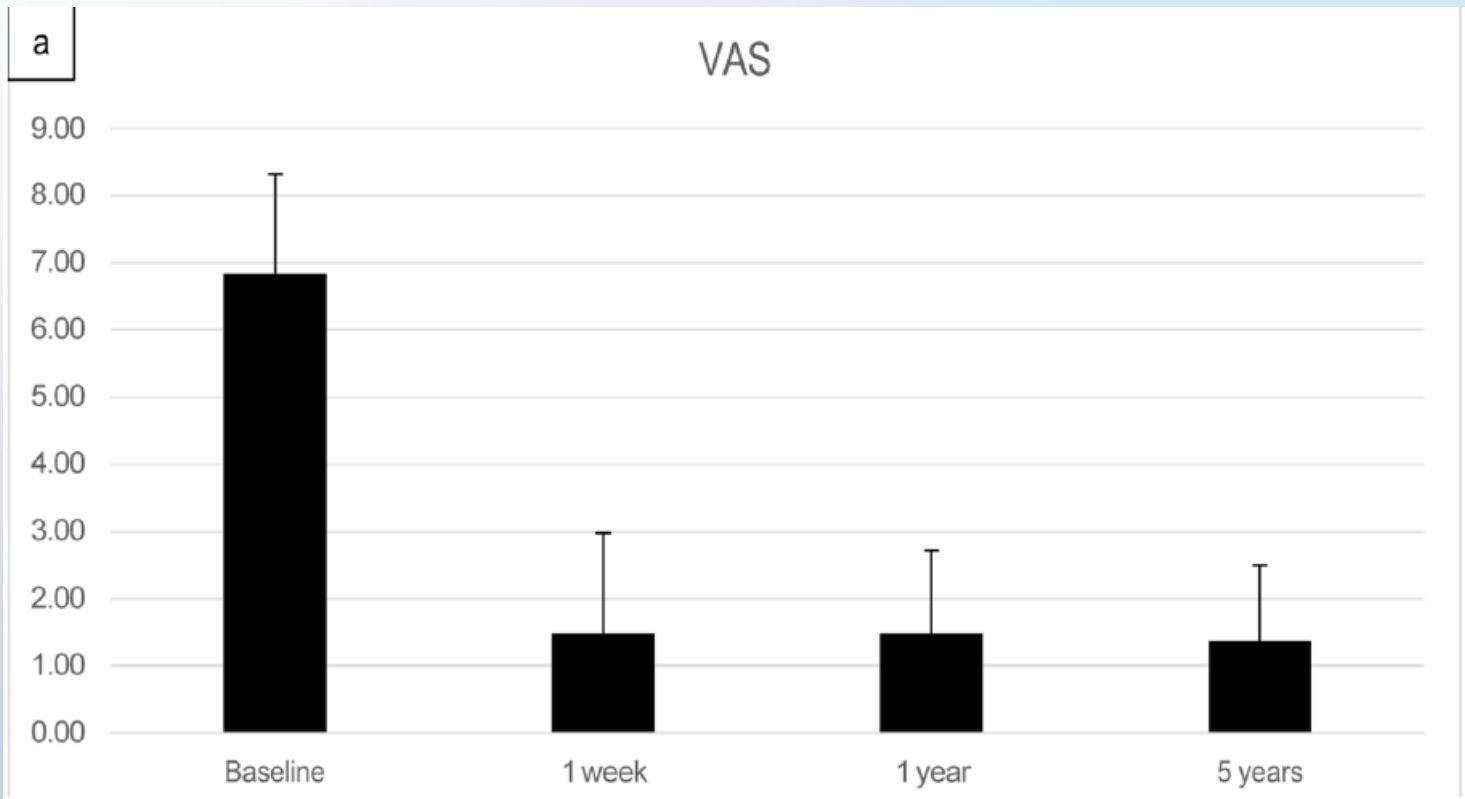
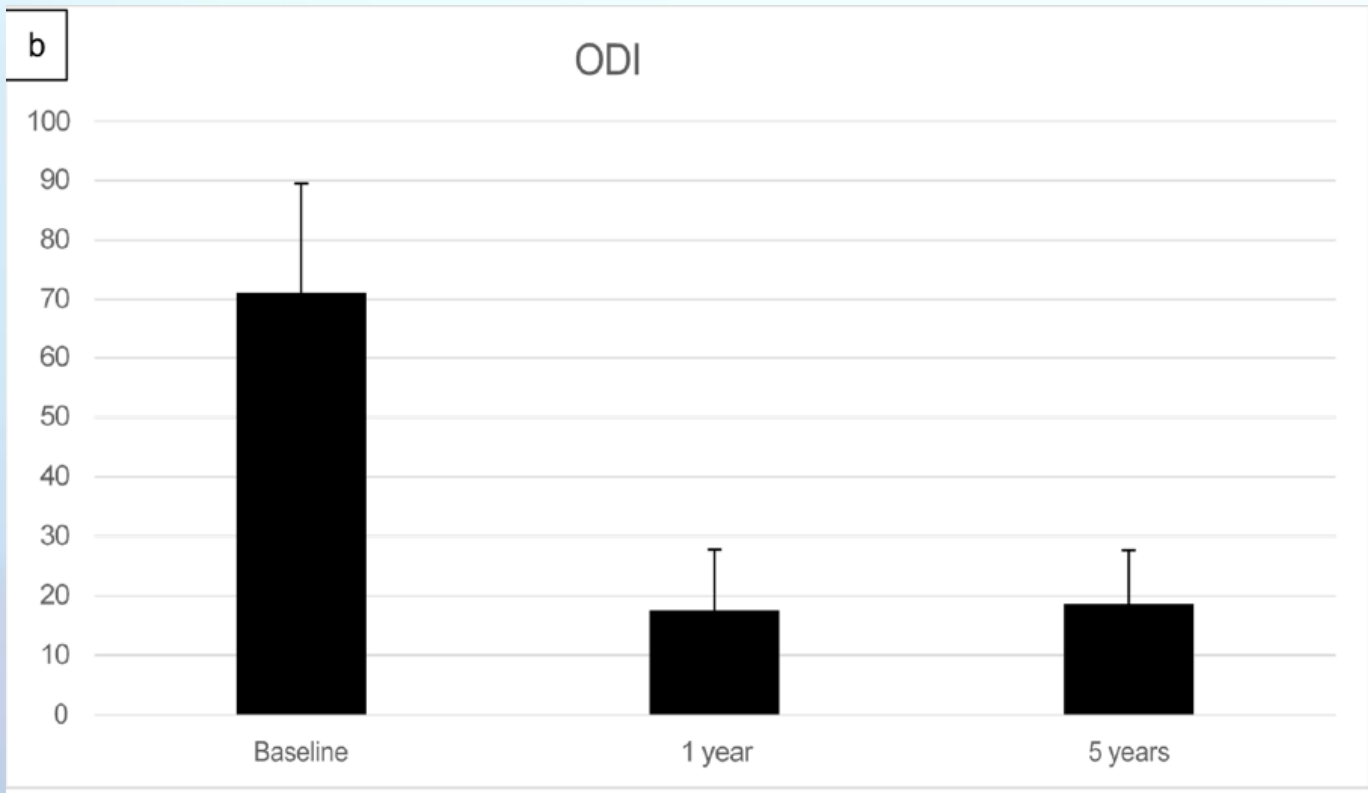
Facet joint arthropathy (FJA): PRP vs corticosteroid

- Several studies have demonstrated the superior efficacy of PRP compared to corticosteroid:
 - **Cauchon AM et al., 2024 — Prospective comparative study**
 - Results: PRP was reported as safe and superior to corticosteroids at 3 and 6 months for pain, function, and patient satisfaction.
 - PRP prep: Arthrex Angel device (leukocyte poor PRP)
 - **Singh C. et al., 2023 — Comparative cohort / prospective report**
 - Results: Both PRP and steroid groups improved; some analyses reported PRP yielded longer duration of benefit at 6 months.
 - PRP prep: 2 spin manual method
 - **Kotb S., et al., 2022 - Prospective comparative study**
 - Results: MRI findings of a reduction in synovitis of the associated facet joints compared to steroid injections.
 - PRP prep: 2 spin method (manual)

Regenerative approaches to FJA

Facet joint arthropathy (FJA): Bone marrow EV, adipose

Wilson, J. et al., Safety of bone marrow derived MSC extracellular vesicle injection for lumbar facet joint pain (pilot study)	2024	Open-label pilot / safety study	20	Extracellular vesicles (EVs) derived from BM-MSCs	Lumbar facet joint space	0.5 mL per joint	3 mos	Significant improvements in severity, interference, and Oswestry Disability Index (~65-72%)	No major adverse events reported
Rothoerl, R, et al., Safety and Efficacy of Autologous Stem Cell Treatment for Facetogenic Chronic Back Pain	2023	Case series	37	Adipose-tissue derived regenerative cells (ADRC)	Facet joint syndrome of the lumbar spine	1mL	1 week 1 year 5 years	Reduction in VAS and ODI at all time points, maintained at 5 year.	No major adverse events, one hematoma at liposuction site.



Regenerative approaches to FJA

Facet joint arthropathy (FJA): Extracellular vesicles (EV), exosomes

Wilson, J. et al., Safety of bone marrow derived MSC extracellular vesicle injection for lumbar facet joint pain (pilot study)	2024	Open-label pilot / safety study	20	Extracellular vesicles (EVs) derived from BM-MSCs	Lumbar facet joint space	0.5 mL per joint	3 mos	Significant improvements in severity, interference, and Oswestry Disability Index (~65-72%)	No major adverse events reported
Phillips et al., One month safety study of ExoFlo injection for the treatment of lumbar or cervical radiculopathy in the epidural space	2021	Case series	5/5	Bone marrow derived MSC extracellular vesicle isolate	Epidural space injection for L/C radic due to LDH	2ml	24hr, 3d, 1wk, 3wk, 1mo	Reduction in VAS and ODI at all time points, maintained at 5 year.	No major adverse events.

Exosomes for the Management of Low Back Pain: A Review of Current Clinical Evidence

Ashim Gupta [1](#), [2](#), [3](#), [4](#)

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“In conclusion, the above-mentioned prospective studies demonstrated that the administration of extracellular vesicles, or exosomes, in the epidural or facet joint space is safe and potentially efficacious in low back pain patients.”

Pain generators of the low back

Lumbo-sacral radiculopathy (LSR)

- Radiculopathy/radiculitis - irritation or compression of a nerve, typically in the spine resulting in an array of symptoms, oftentimes including numbness, tingling, burning, or electric shock type sensation down into a limb.
- Most commonly caused by a herniated disc. Can also be seen with spondylosis of the spine. Spondylosis is defined as degenerative changes of the spine which often includes a trifecta of disc herniation or bulge, facet joint enlargement, and ligament flavum hypertrophy.
- Treatment options include conservative therapy, oral pain or anti-inflammatory medications, and injection therapy.
 - Injection therapy includes epidural injections designed to bathe the nerve and reduce inflammation, oftentimes with corticosteroids.

Regenerative approaches to LSR

Lumbo-sacral radiculopathy: Platelet rich plasma (PRP)

Is platelet-rich plasma better than steroids as epidural drug of choice in lumbar disc disease with radiculopathy? Meta-analysis of randomized controlled trials

[Sathish Muthu](#)^{1,2,3}, [Vibhu Krishnan Viswanathan](#)^{1,4}, [Prakash Gangadaran](#)^{5,6,7,*}

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PMCID: PMC11832311 PMID: [39968415](#)

5 studies included, all RCTs comparing PRP versus CS

Regenerative approaches to LSR

Lumbo-sacral radiculopathy: PRP vs CS

1	A Gupta 2024 N=50	2ml PRP with 0.5ml 0.5% Bupivacaine	40mg Triamcinolone with 0.5ml 0.5% Bupivacaine	Fluoroscopy-guided transforaminal epidural route	mODI, VAS, SF-12
2	A Saraf 2023 N=60	3 ml of autologous PRP	2 ml of methylprednisolone acetate (40 mg/ml) with 1 ml 1% lignocaine	Fluoroscopy-guided transforaminal epidural route	mODI, VAS, SLRT, Failures
3	A Wongjarup ong 2019 N=60	2 mL of PRP followed by NS 0.5 ml	2ml of 1% lidocaine with 40 mg triamcinolone	Fluoroscopy-guided transforaminal epidural route	mODI, VAS, Adverse Event, Failures
4	R Ruiz- Lopez 2020 N=30	16.5 mL of LR-PRP	20 ml with 60 mg of triamcinolone acetonide	Fluoroscopy-guided caudal epidural route	VAS, SF-36
5	Z Xu 2021 N=124	3 ml autologous PRP	2 ml betamethasone + 0.5 ml 0.9% saline + 0.5 ml 2% lidocaine	USG-guided transforaminal epidural route	mODI, VAS, SF-36, F- wave rate & latency

Regenerative approaches to LSR

Lumbo-sacral radiculopathy: PRP vs CS

- “The **safety profile** of the epidural PRP is also similar to ESI. Nevertheless, large-scale, multi-centric RCTs involving larger sample population, and longer follow-up are necessary to further validate our observations.”
- PRP is demonstrating superior efficacy compared to corticosteroid epidural injection therapy for long term improvement of radicular pain related to LDH.

Regenerative approaches to LSR

Lumbo-sacral radiculopathy: Stem cells

- There are limited studies evaluating the efficacy of epidural stem cell injections for the treatment of radicular low back pain.
- A study by Christopher Centeno et al. 2017 looking at LDH **with radicular features**.
 - Retrospective chart review of 33 patients with DDD and clinical features of radiculopathy who had failed conservative and interventional therapy
 - **Intra-discal injection** of autologous, culture-expanded MSCs with platelet lysate (PL)
 - Outcomes:
 - Percent improvement, Single Assessment Numerical Evaluation (SANE)
 - Pain score, NPS (numeric pain score)
 - Function, FRI (functional rating index)

Regenerative approaches to LSR

Lumbo-sacral radiculopathy: Stem cells

- Results:
 - SANE: 30/33 baseline
 - At 40 months, 50% of the patients reporting >50% improvement and 90% of patients demonstrating some (>0%) improvement.
 - NPS: 25/33 baseline
 - Between months 1-24 post treatment, average NPS scores ranged from 3.3-3.6. Between year 2 to year 6, average NPD scores ranged from 1.9-2.3.
 - Functional Rating Index: 16/33
 - Average pre-treatment score was 60.5, post-treatment scores ranged from 31-44

Regenerative Approaches to Low Back Pain (LBP)

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