IDD/DDD
A biologic approach

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Director of Clinical Research

Prevalence Of Lumbar Discogenic Pain Utilizing IASP Criteria

Study	Methodological Quality Scoring	Participants	Prevalence
Manchikanti et al, 2001 (378)	11/11	From a group of 120 patients with low back pain, 72 patients negative for facet joint pain underwent discography.	26% overall discogenic pain
Schwarzer et al, 1995 (380)	11/11	92 consecutive patients with chronic low back pain and no history of previous lumbar surgery referred for discography.	Internal disc disruption 39%
DePalma et al, 2011 (668)	11/11	Of the 156 patients, 71 underwent provocation discography. They also underwent other diagnostic blocks including facet joint nerve blocks and sacroiliac joint injections.	Internal disc disruption 42%

40%

The prevelance of discogenic pain decreases with age.

However, the prevalence of degenerative disc disease clearly increases with age.

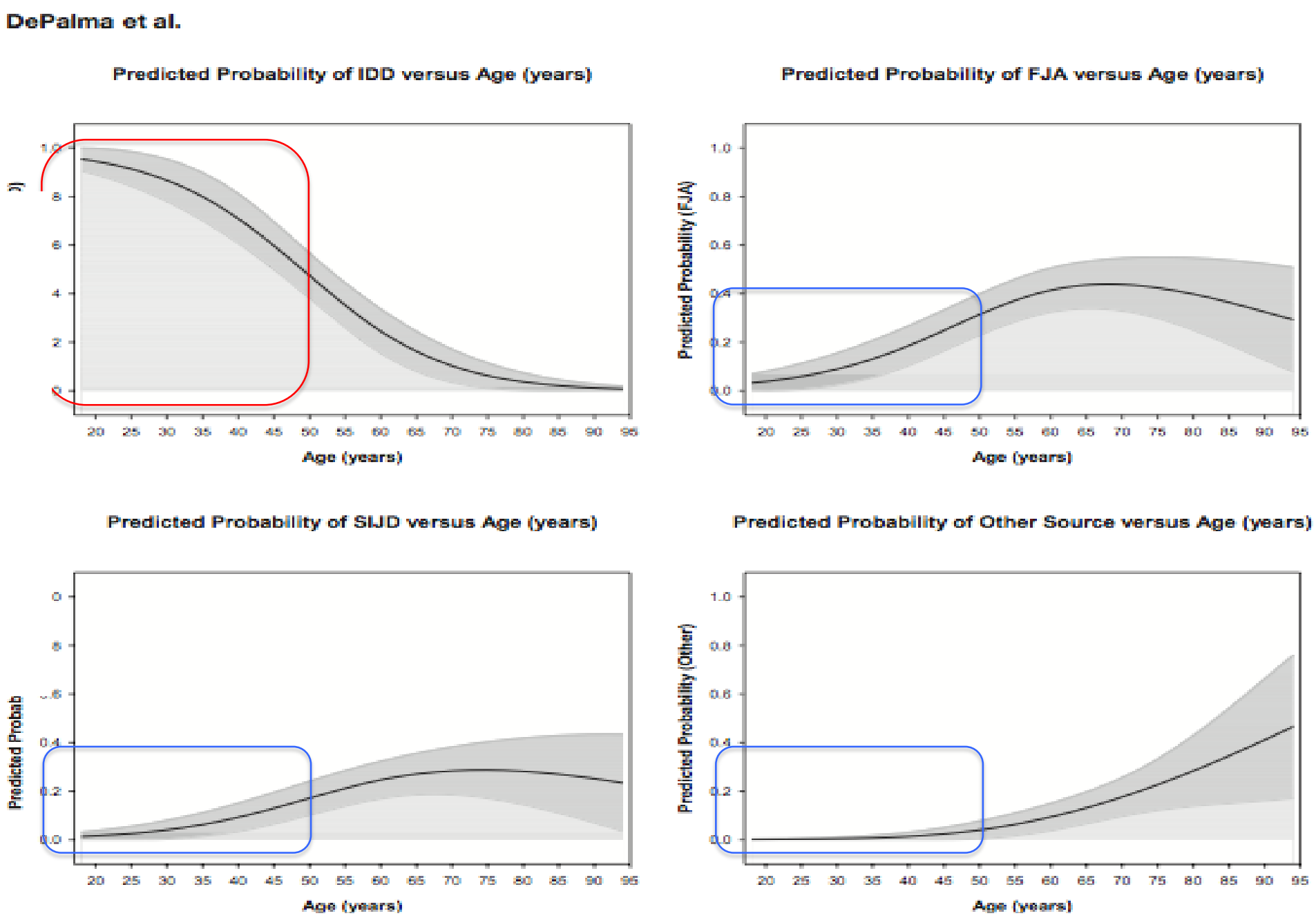


FIGURE 4: Predicted probabilities and 95% confidence intervals for internal disc disruption (IDD), facet joint pain (FJP), sacroiliac joint pain (SIJP), and other sources of low back pain (LBP) as a function of age.

Degenerative Disc Disease

Disc Age Related Change

It is ubiquitous, correlates only with age, not pain.

TEST	AUTHOR YEAR	PTS (n)	AGE RANGE (mean)	DISC HERNIATION	DISC BULGE	DISC DEGENERATION	CENTRAL CANAL STENOSIS	ANNULAR FISSURE
X-Ray	Hult 1954	1200	40-44 55-59			56% 95%		
X-Ray	Hellstrom 1990	143	14-25			20%		
Myelogram	Hitselberger 1968	300	(51)	31%				
CT	Wiesel 1984	51	(40)	20%			3.4%	
MRI	Weinreb 1989	86	(28)	9%	44%			
MRI	Boden 1990	53	< 60 ≥ 60	22% 36%	54% 79%	46% 93%	1% 21%	
MRI	Jensen 1990	98	(42)	28%	52%		7%	
MRI	Boos 1995	46	(36)	76%	51%	85%		
MRI	Stadnik 1998	36	(42)	33%	81%	56%		56%
MRI	Weishaupt 1998	60	(35)	60%	28%	72%		20%
MRI	Jarvik 2001	148	(54)	38%	64%	91%	10%	38%

Degenerative Disc Disease

- Degenerative Disc Disease is related to loss of proteoglycan and water content leading to inability of of the disc to resist compressive loading.

Internal Disc Disruption (IDD)

- In contrast, IDD is a specific entity: isolated, radial fissures
  - Nucleus pulposis ➡ Annulus fibrosis
- This is not age-related change
- IDD correlates with axial pain

Internal Disc Disruption: Etiology

IDD appears to be associated with endplate fracture

- Endplate fracture causes, overtime:
  - Reduction in water, proteoglycans
  - Delamination
  - Reduction in pressure within the nucleus

Internal Disc Disruption: Etiology

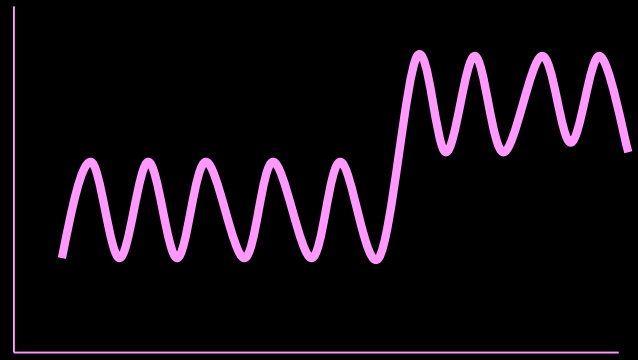
Endplate Fatigue Fracture

- Precipitates degradation of nuclear matrix
  - Inflammatory response
  - Nutritional / biochemical (pH) insults
- Nuclear dehydration
  - Unable to accept and disburse load
  - Load to transferred to posterior annulus

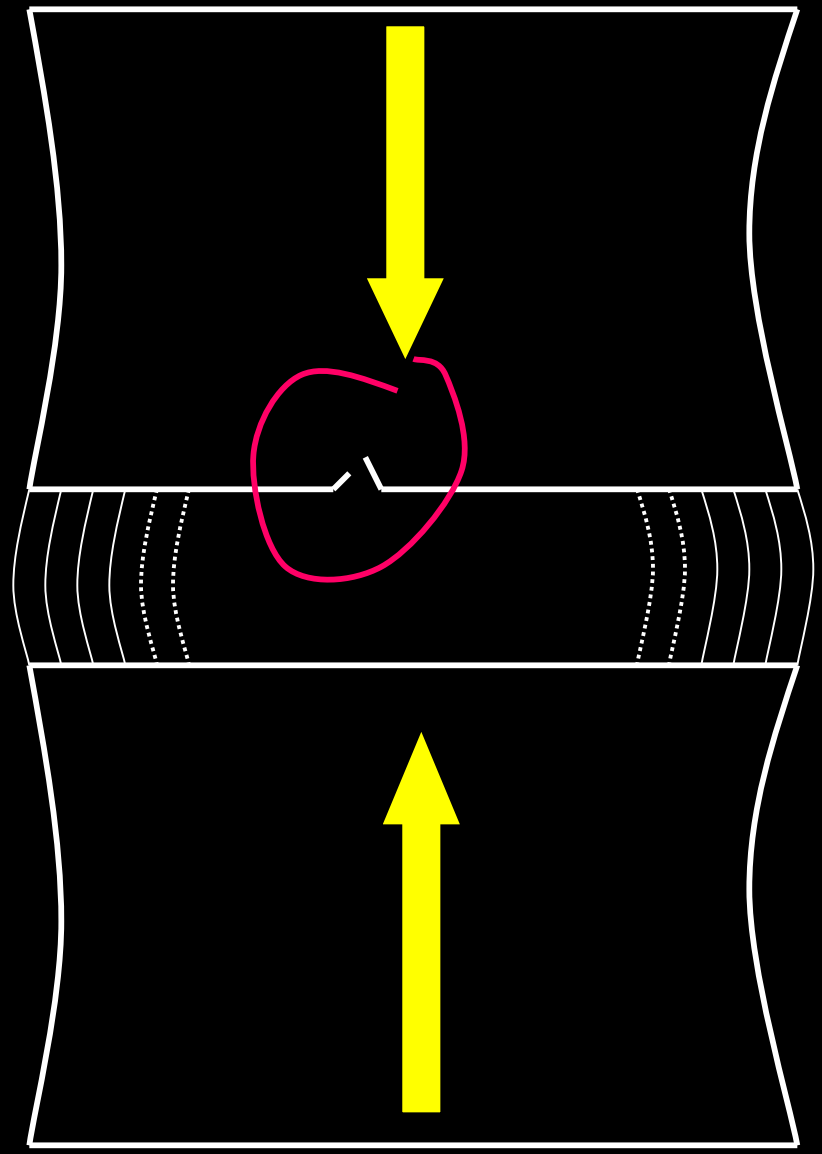
Internal Disc Disruption: Etiology

- **Evolution of radial fissures**
  - Excessive load on posterior annulus
  - Failure of internal bracing effect of pressurized nucleus
  - Inward buckling, tearing of annular fibers
- **Characteristics of radial fissures**
  - Most common posterolaterally
  - Single or few
  - Unique lesion of IDD

Cyclic stress applied



time



Internal Disc Disruption: Etiology

Fatigue failure of the subchondral endplate occurs with cyclic loading:

- @ 37-50% of Ultimate Tensile Strength (UTS); failure at 2,000 or 1,000 cycles
- @ 50-80% UTS; failure at 100 cycles

These are physiologic loads

Internal Disc Disruption: Etiology

The biomechanical effect of the endplate disruption can be detected & quantified:

STRESS PROFILOMETRY

Distribution

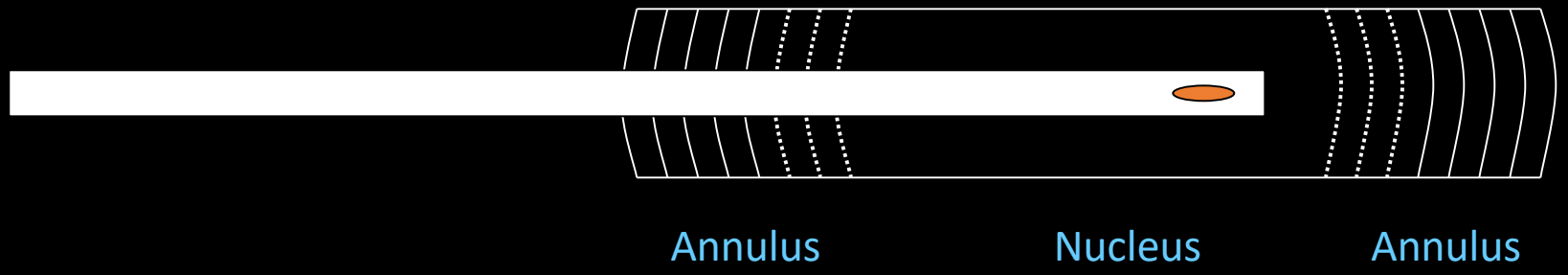
Magnitude

of stresses within and across the disc

Stress Profilometry

A pressure transducer is inserted across a diameter of the disc & slowly withdrawn while intradiscal pressures are measured.

Stress Profilometry



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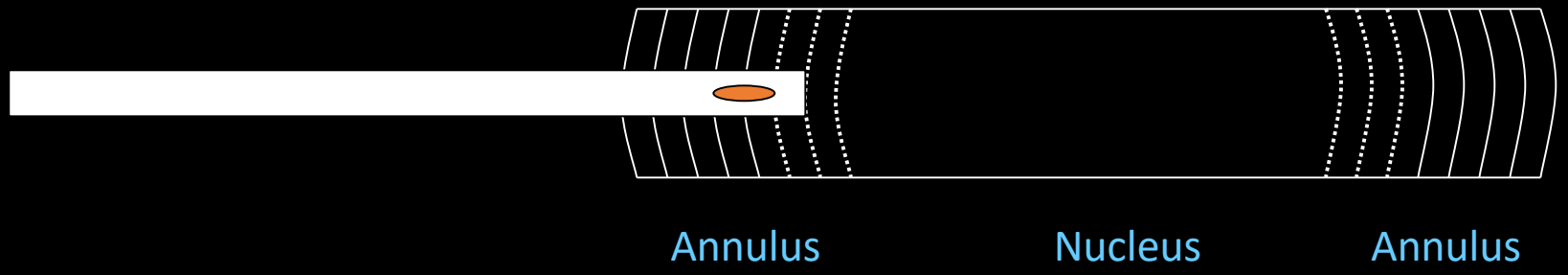
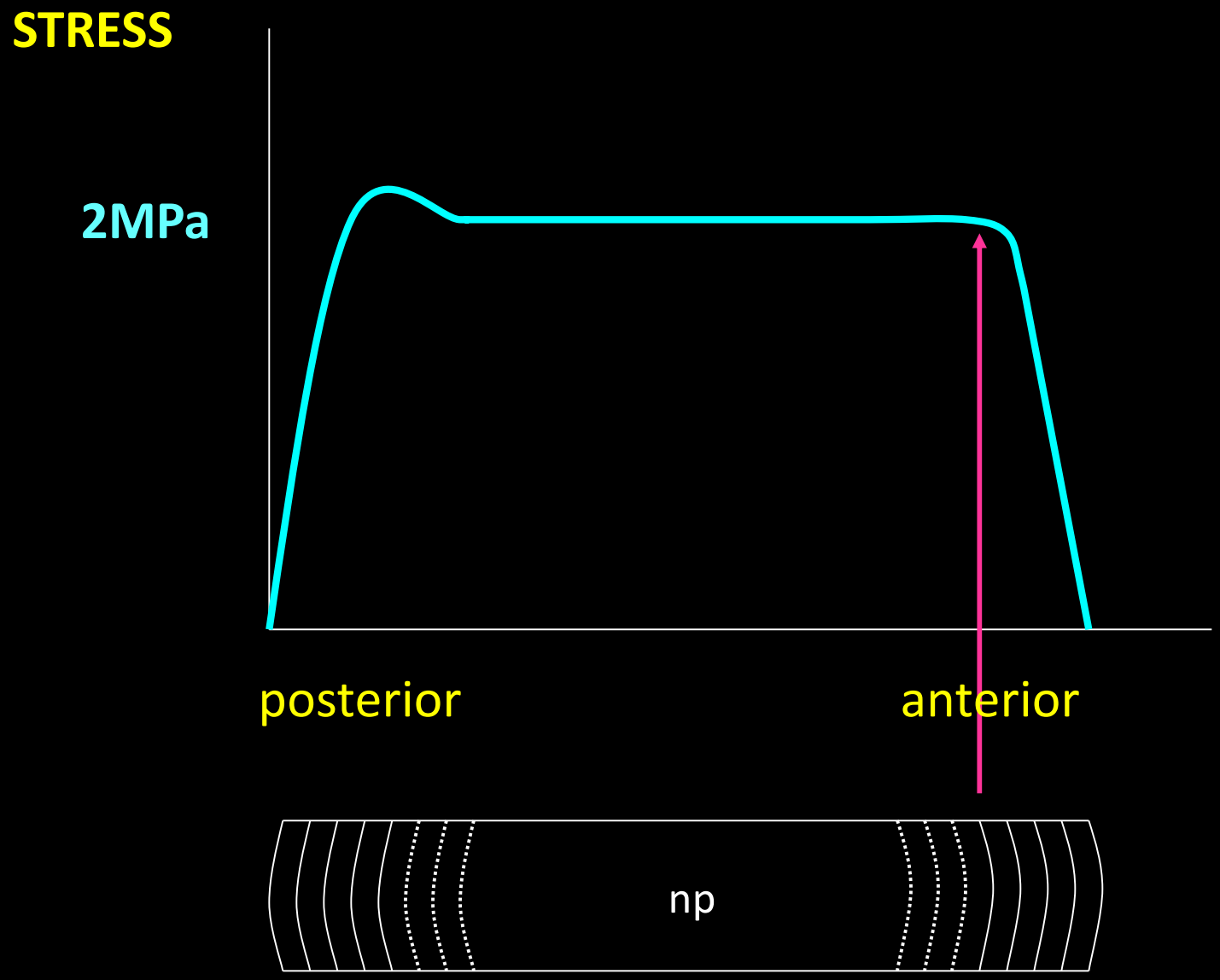
Stress Profilometry

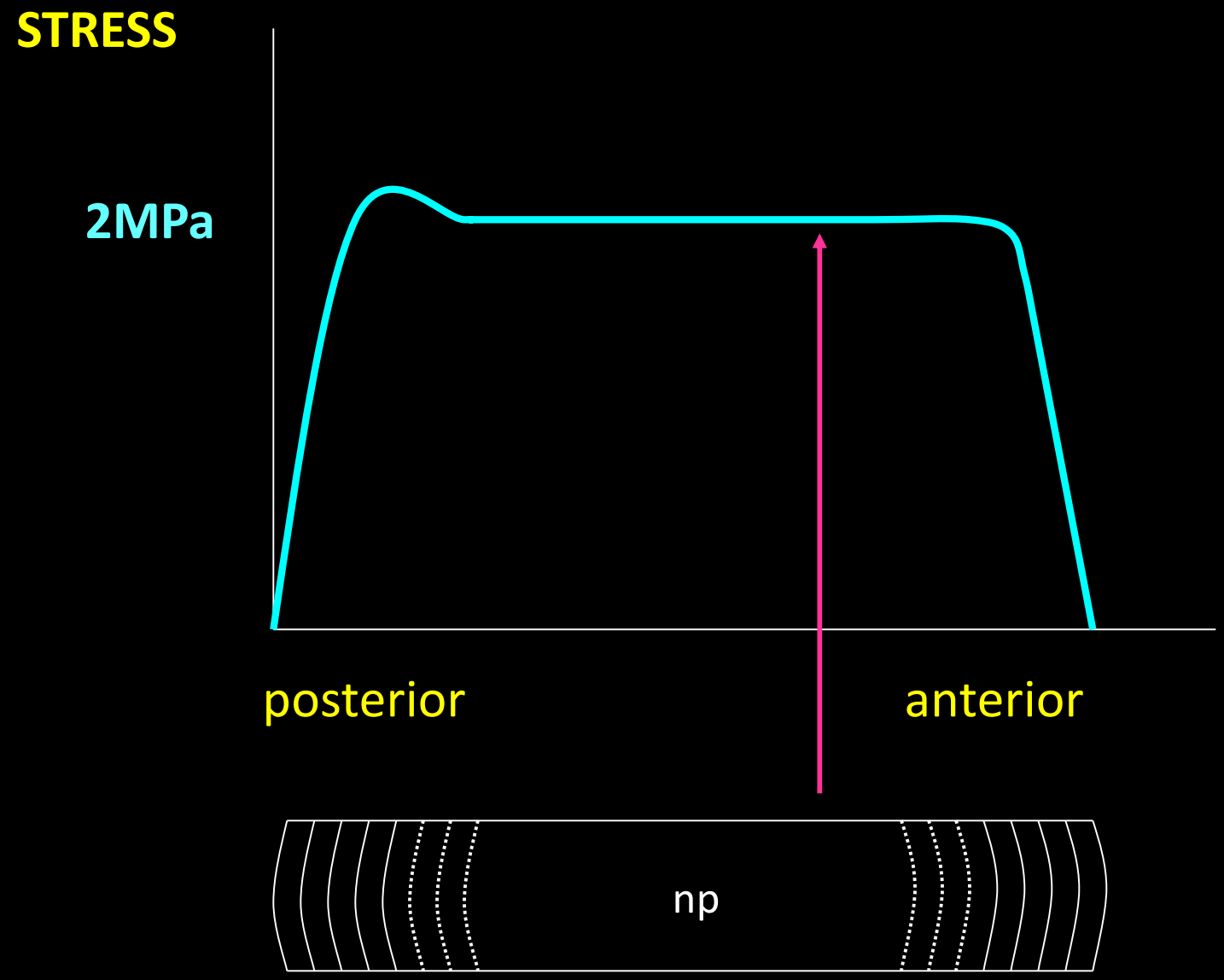


A pressure transducer is inserted across a diameter of the disc & slowly withdrawn while intradiscal pressures are measured.

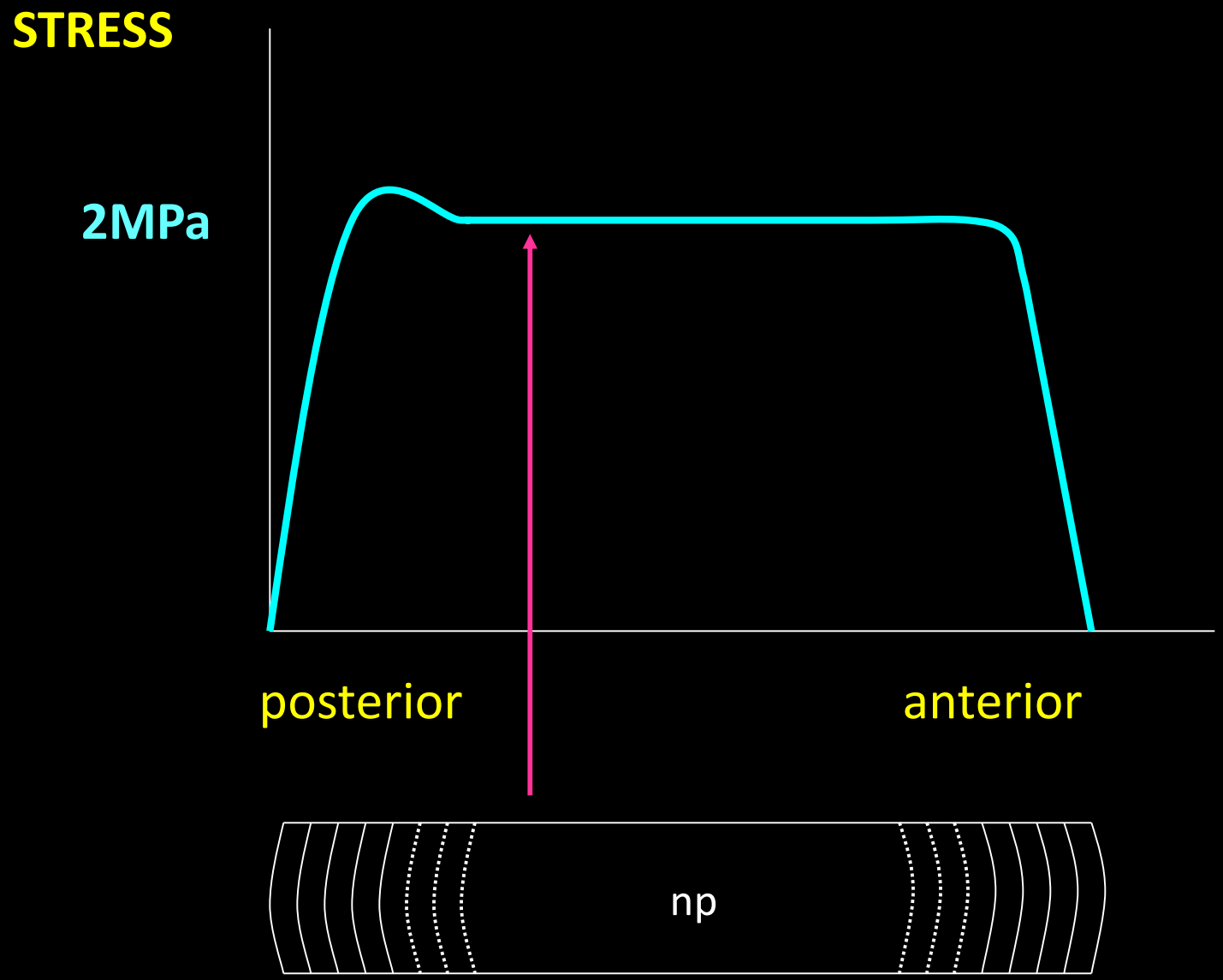
Stress Profilometry: Normal Disc



Stress Profilometry: Normal Disc



Stress Profilometry: Normal Disc



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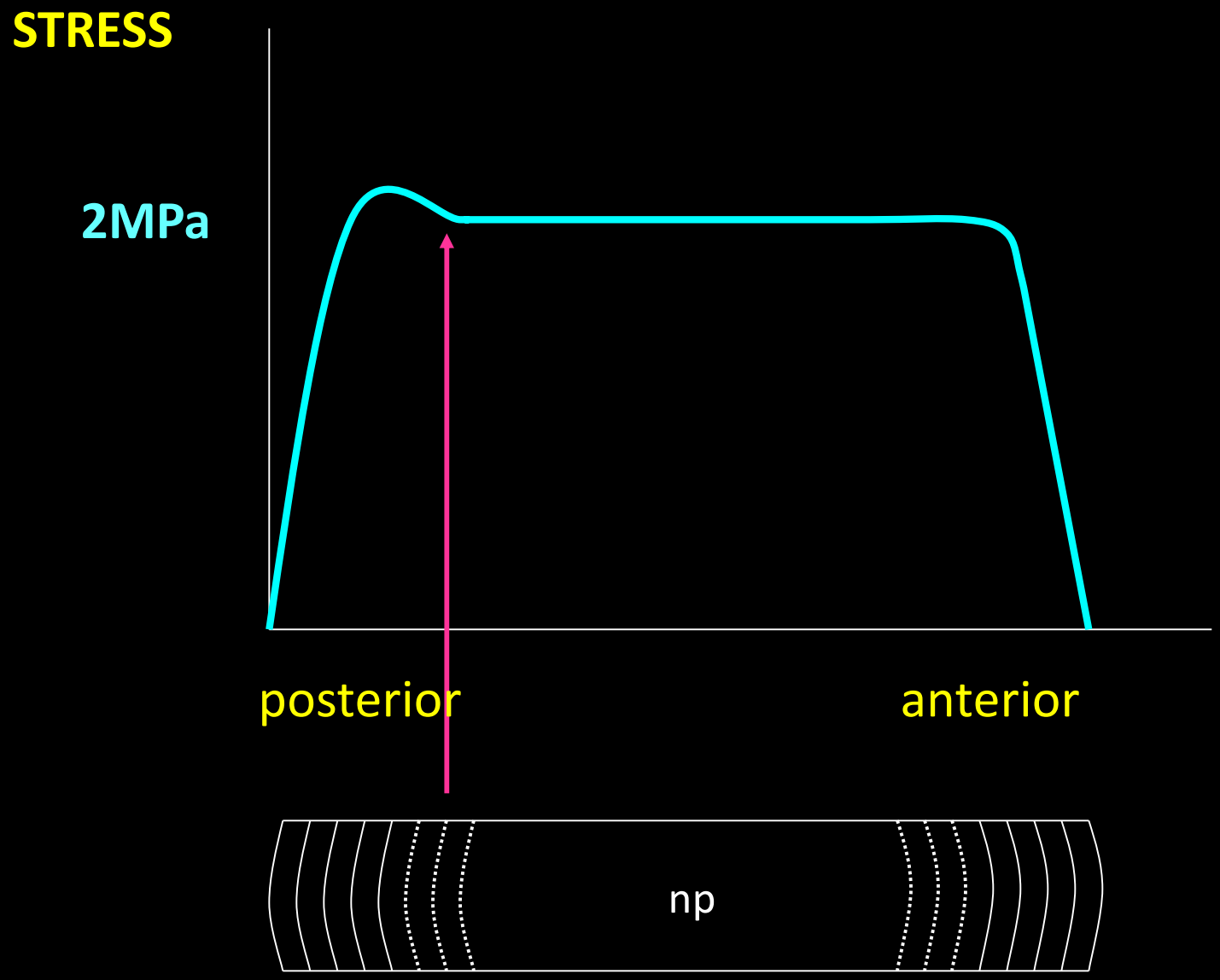
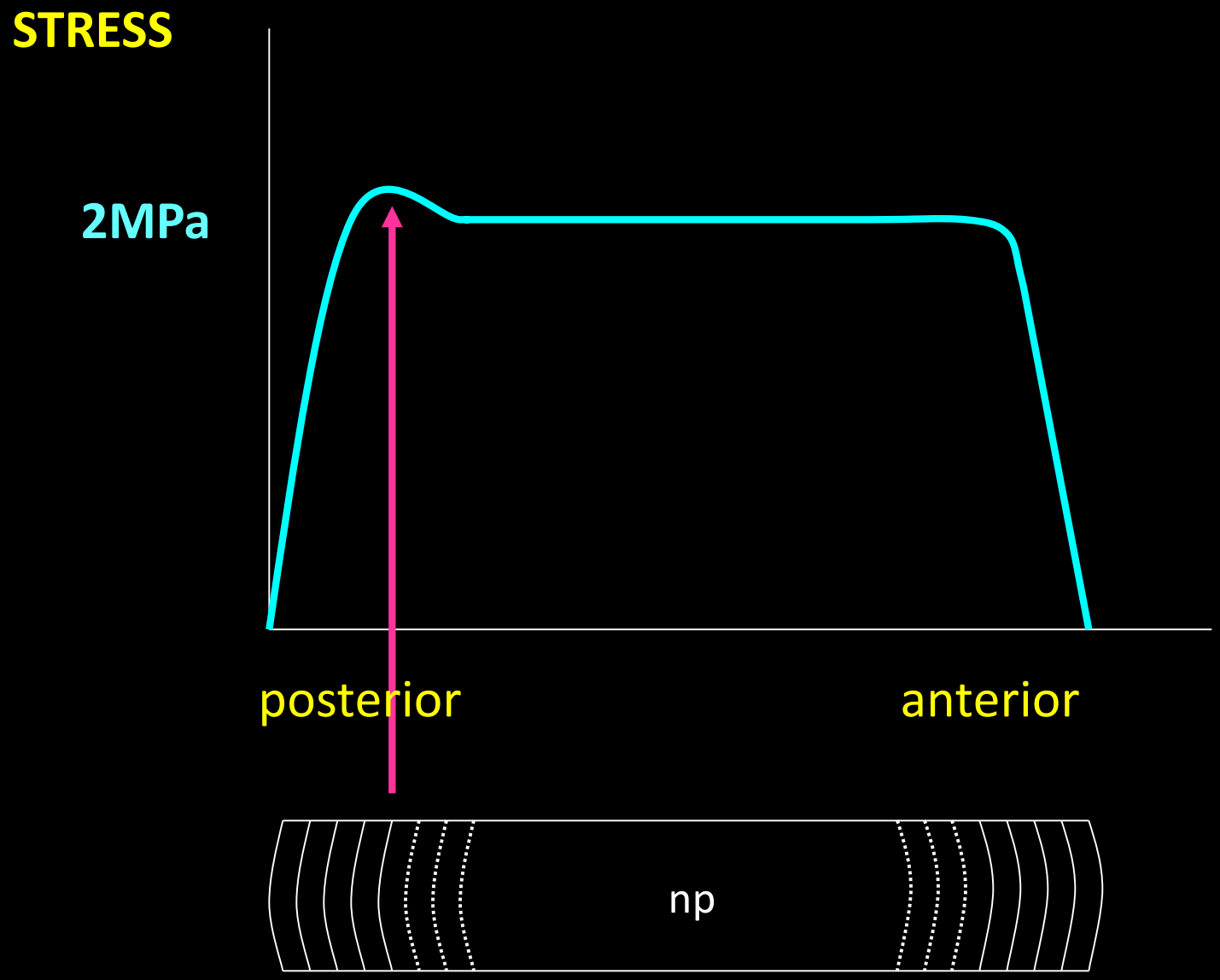
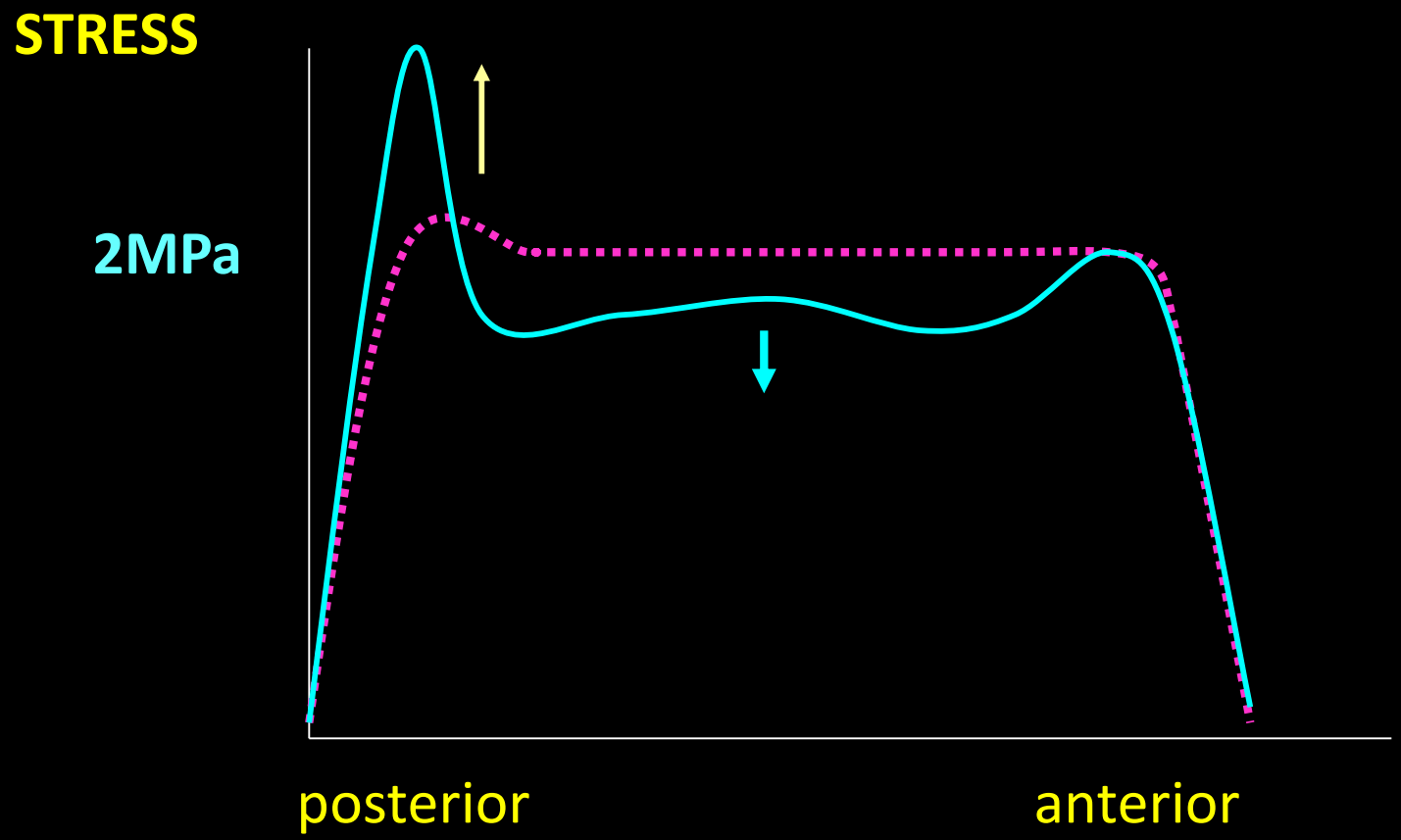


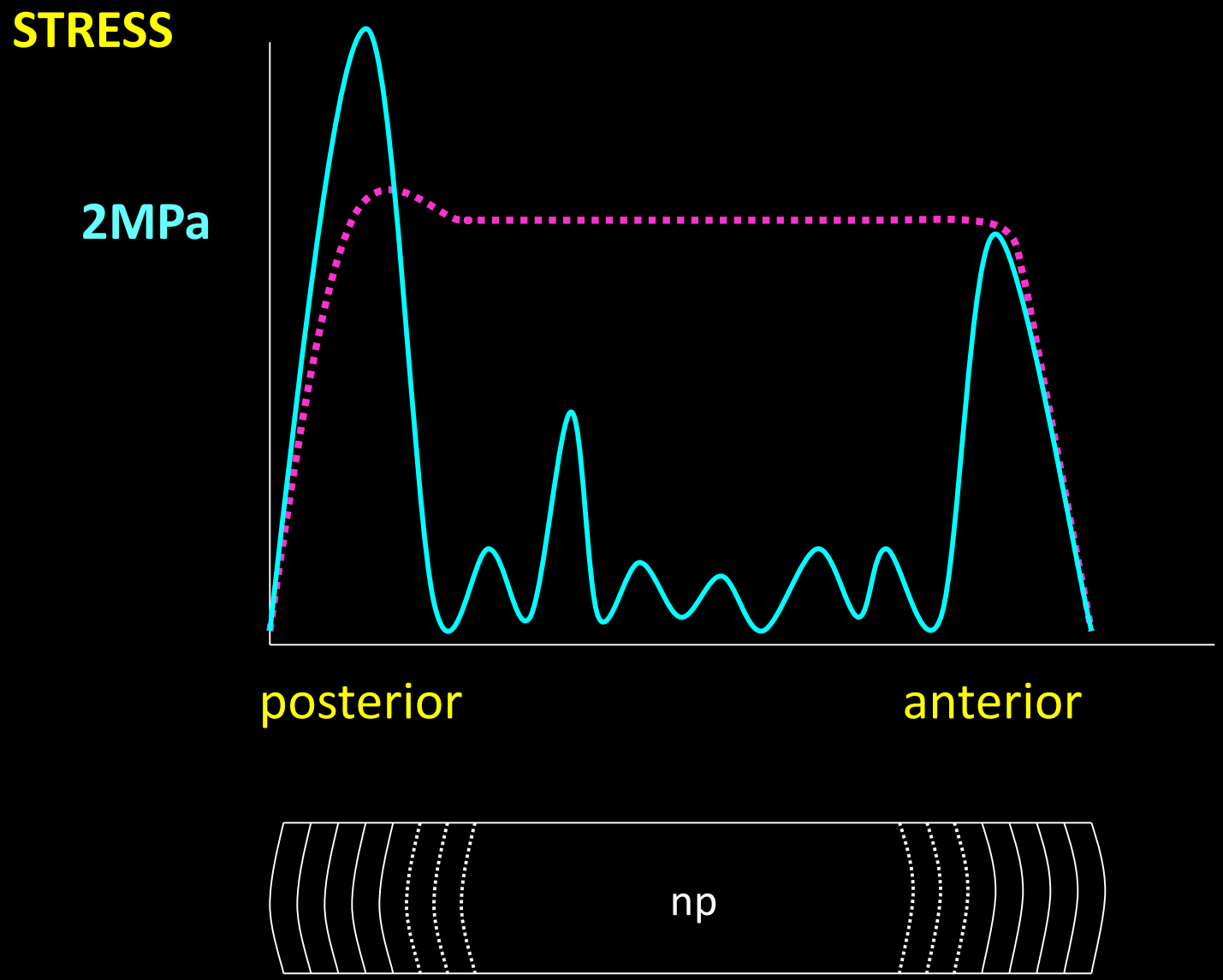
Stress Profilometry: Normal Disc



Stress Profilometry: Post Endplate Fracture



Stress Profilometry: Internal Disc Disruption



Internal Disc Disruption: Etiology

Endplate Fatigue Fracture

- Precipitates degradation of nuclear matrix
  Inflammatory response
  Nutritional / biochemical (pH) insults
- Nuclear dehydration
  Unable to accept and disburse load
  Load to transferred to posterior annulus

Internal Disc Disruption: Etiology

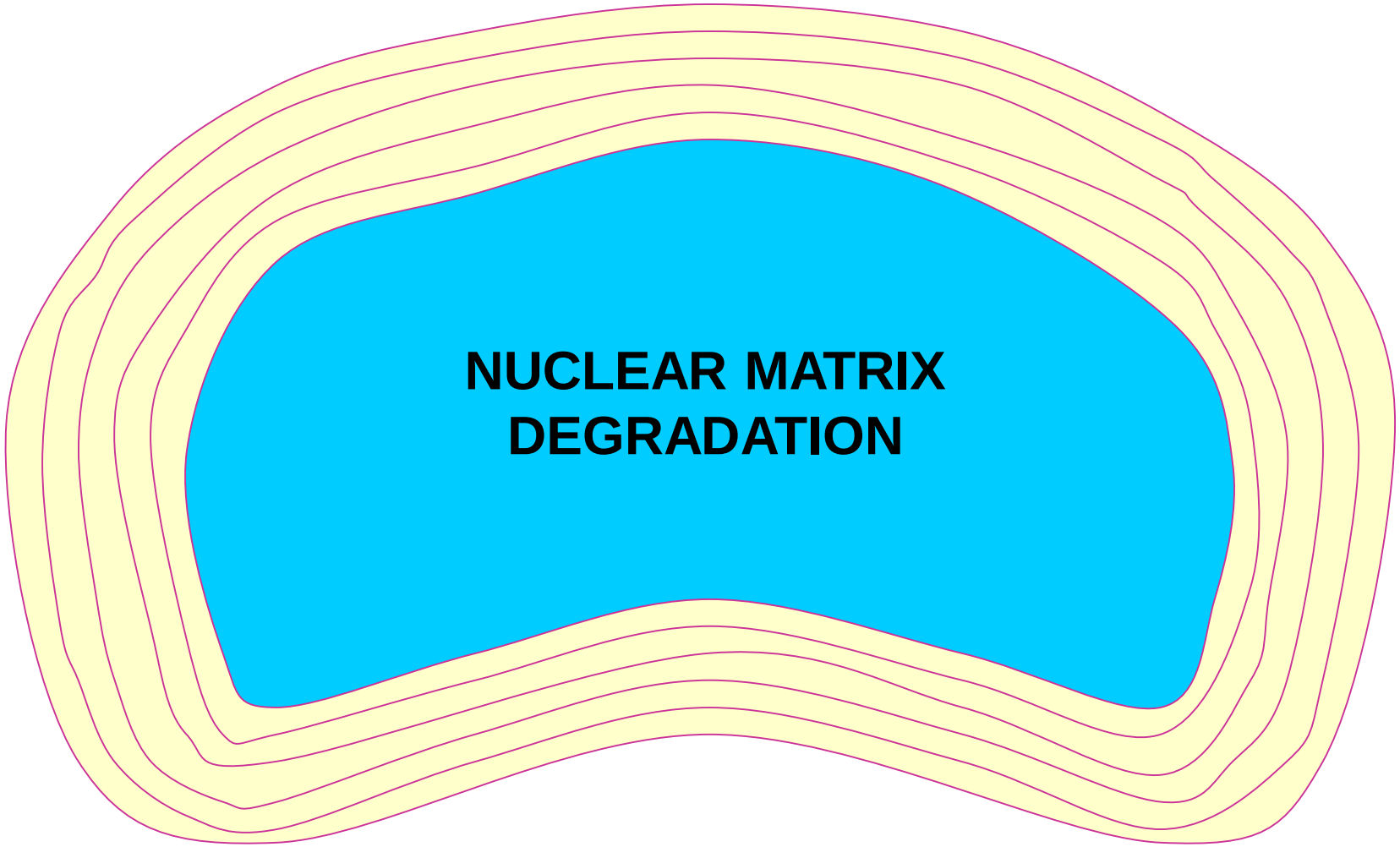
Evolution of radial fissures

- Excessive load on posterior annulus
- Failure of internal bracing effect of pressurized nucleus
- Inward buckling, tearing of annular fibers

Characteristics of radial fissures

- Most common posterolaterally
- Single or few
- Unique lesion of IDD

Internal Disc Disruption (IDD)



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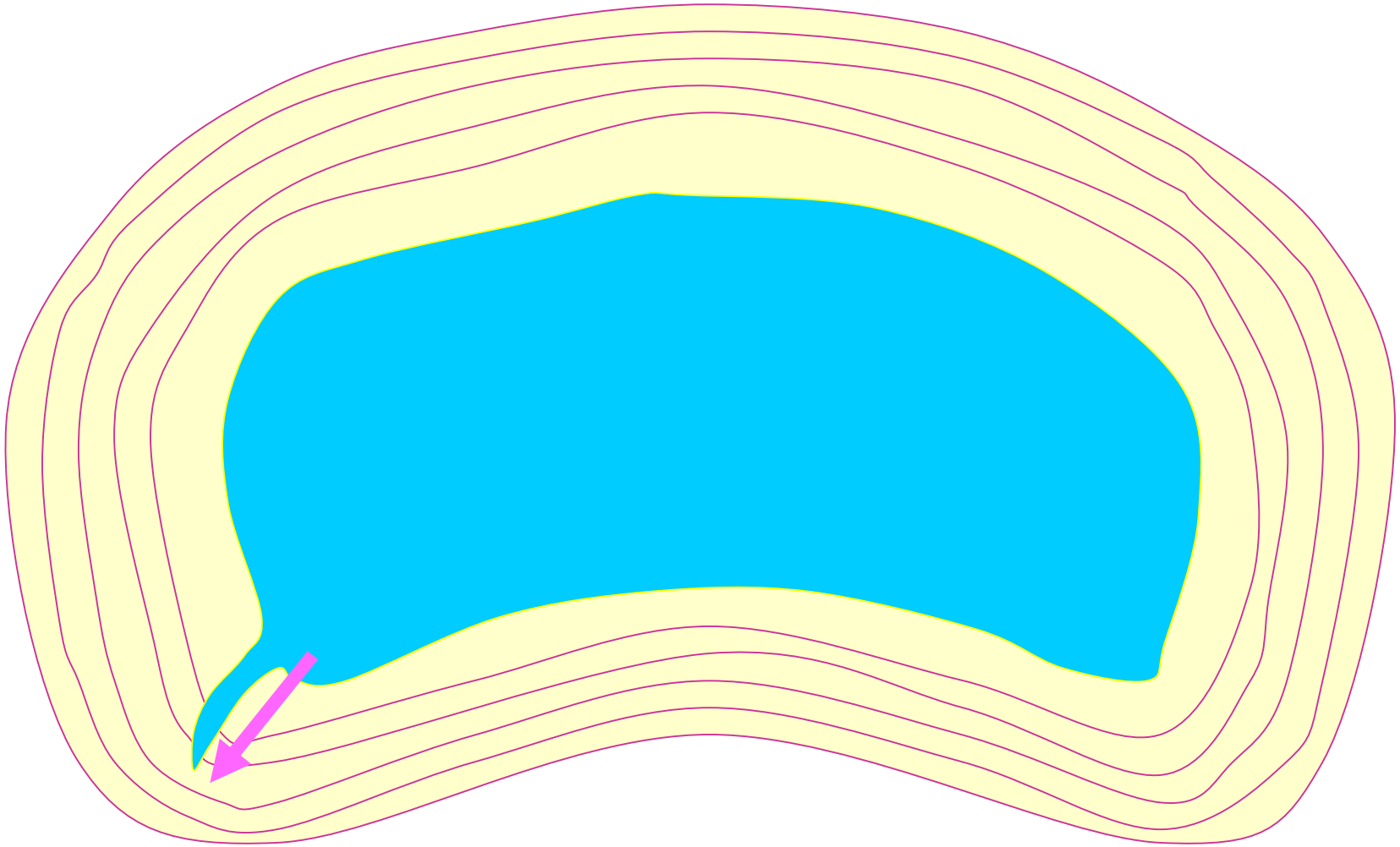
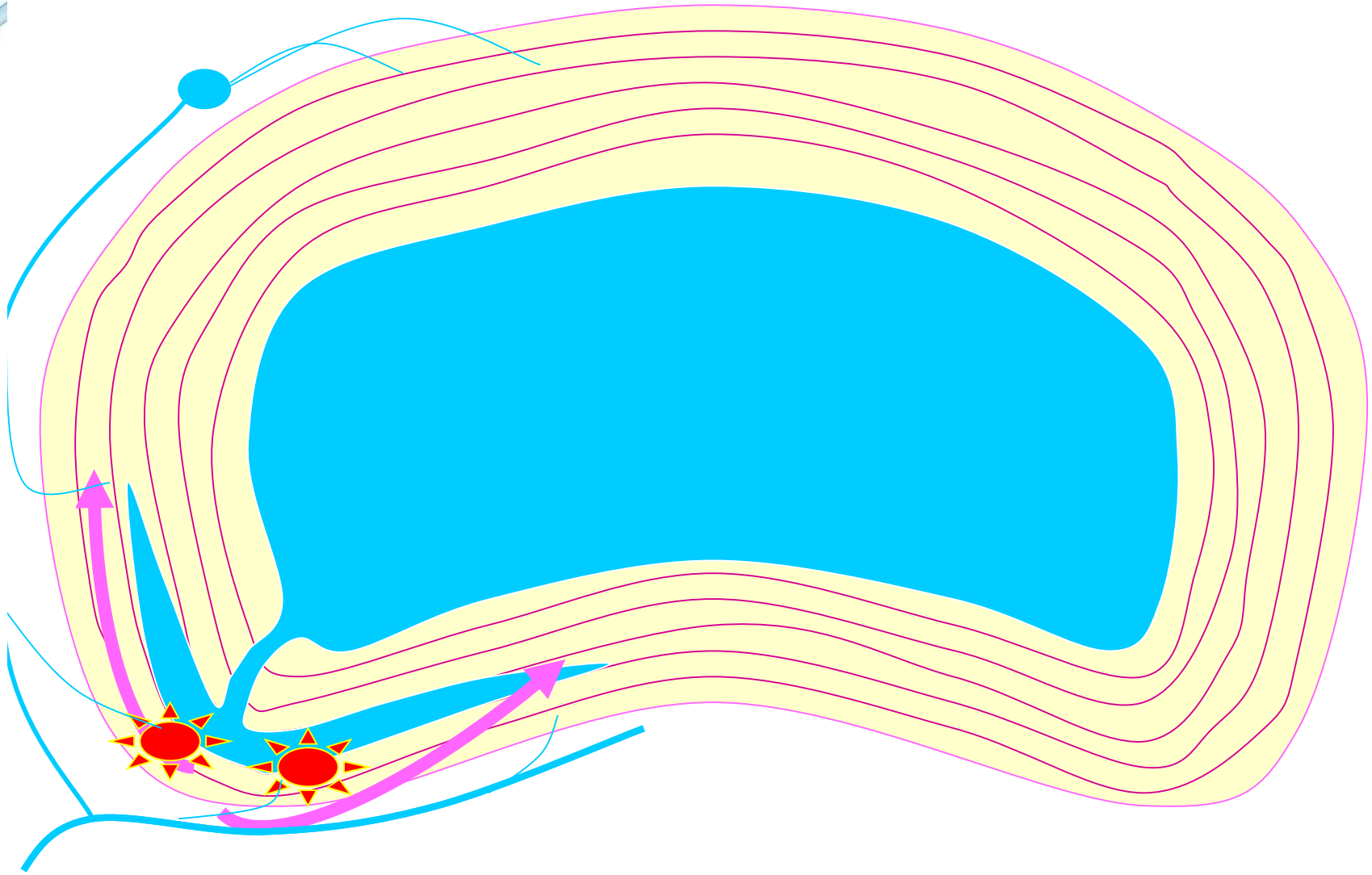


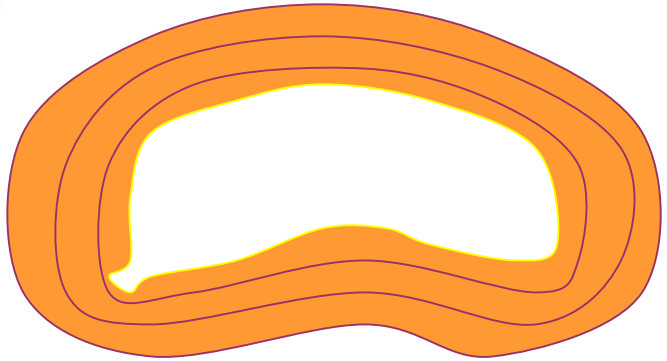
RADIAL FISSURE

Internal Disc Disruption (IDD)

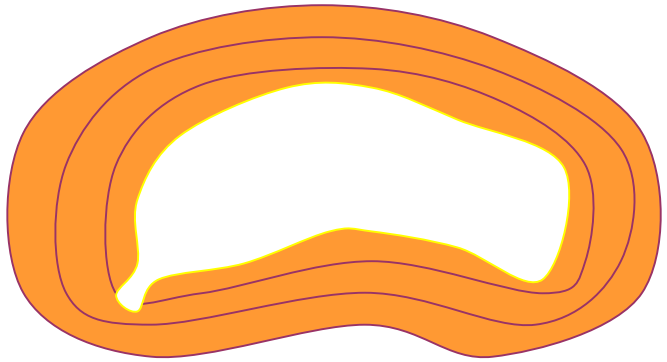


CIRCUMFERENTIAL FISSURE

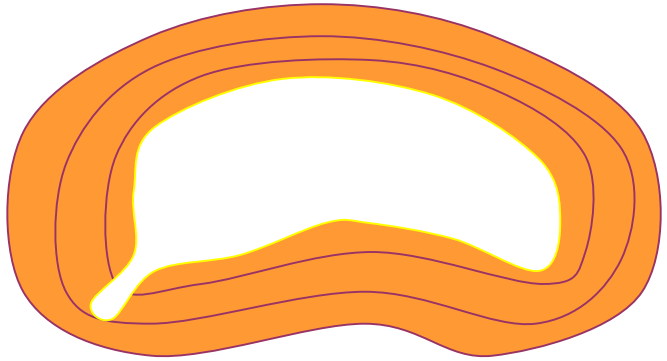
Internal Disc Disruption (IDD)



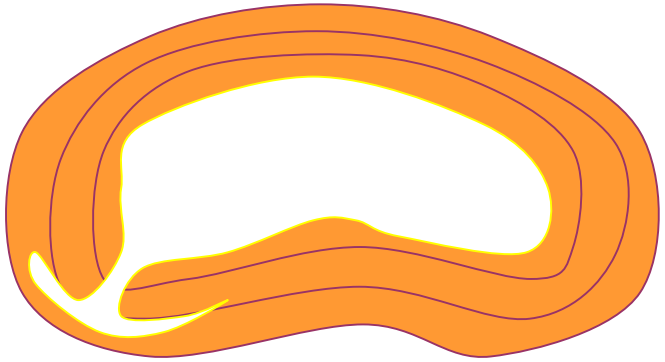
Grade I



Grade II



Grade III



Grade IV

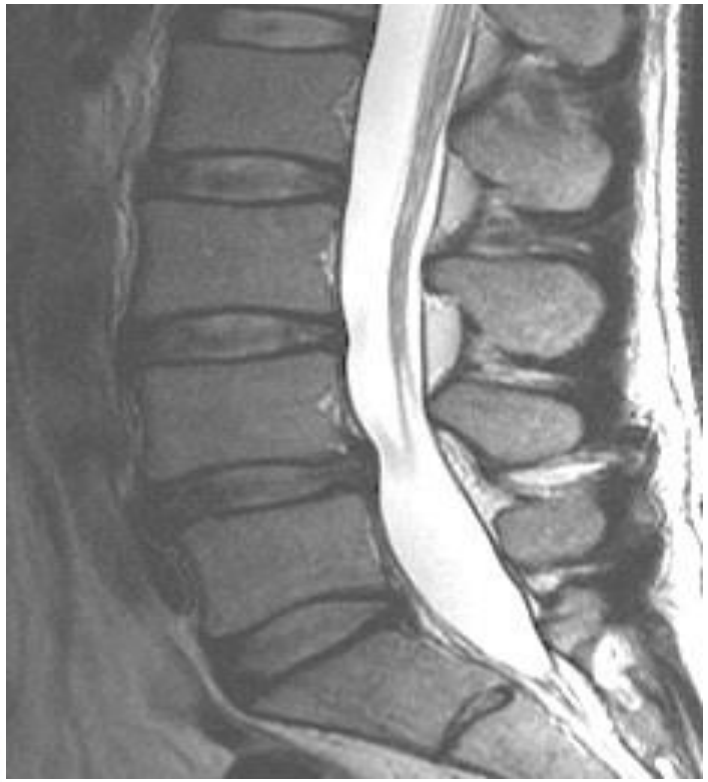
Internal Disc Disruption: Etiology

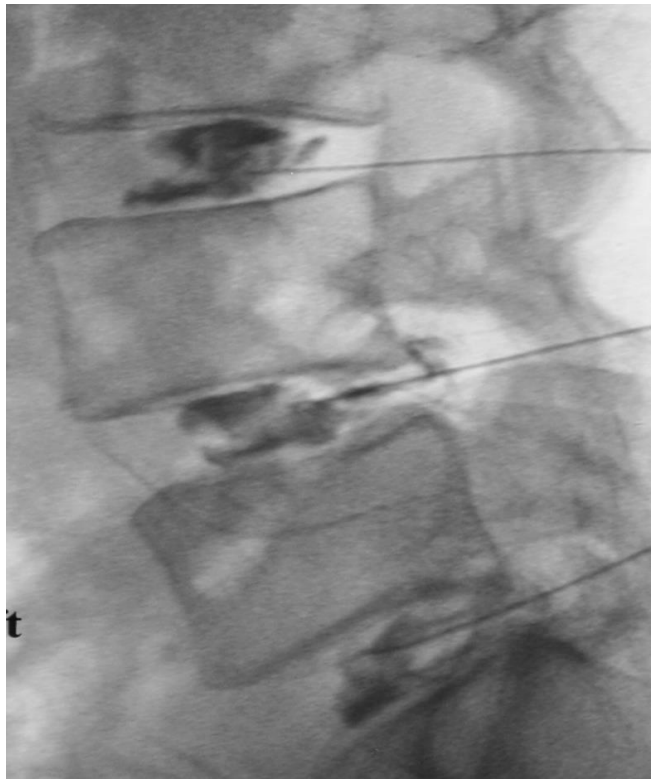
GENERATION OF PAIN

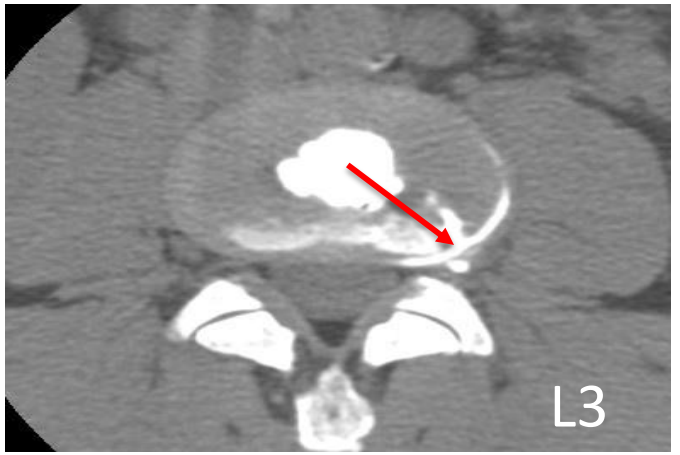
- Pain associated with grade III, IV fissures
  - Allows access of nuclear material to outer third of annulus, nociceptive appartus
  - Chemical stimulation (nitric oxide) of nociceptin

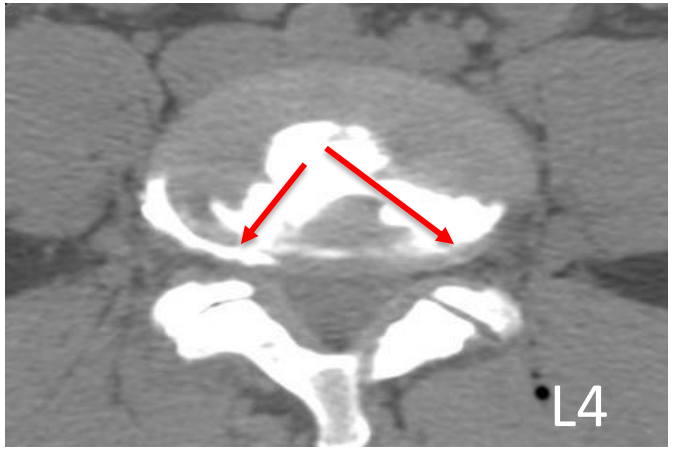
- Excess load on posterior annulus
  - Mechanical stimulation of nociceptin

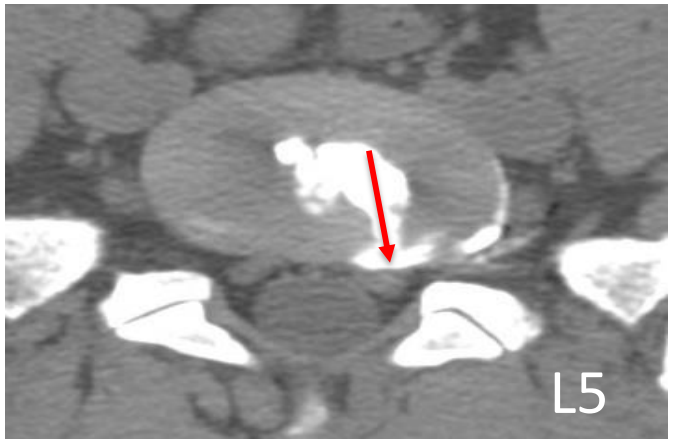
Internal Disc Disruption (IDD)
DISC STIMULATION











As important as it is to recognize these **macroscopic findings**, there are equally important changes occurring within the **microenviroment** of the disc.

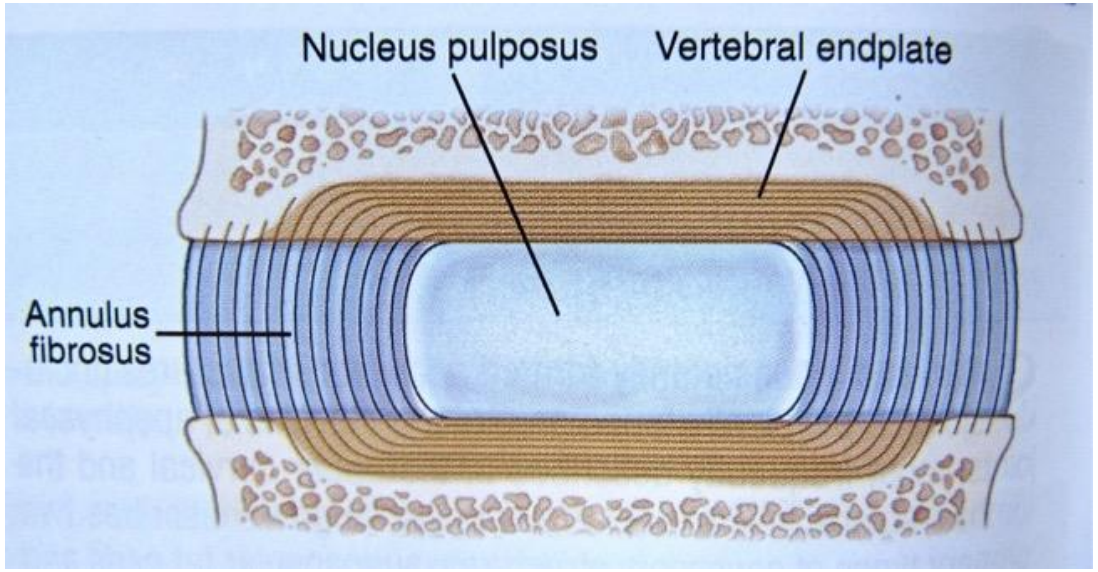
Disc Age Related Change or “Degeneration”

Consequence of Imbalance of Synthesis / Degradation

		NUCLEAR MATRIX	ANNULUS
Molecular	Altered PGs Dehydration	Cross-linking	Cross-linking
Microscopic	Cracks Tears	Fibrosis	Fibrosis
Macroscopic		Thinning Fragmentation	
Biomechanical		Depressurized	Stiffening
Imaging		Loss of T2 signal	

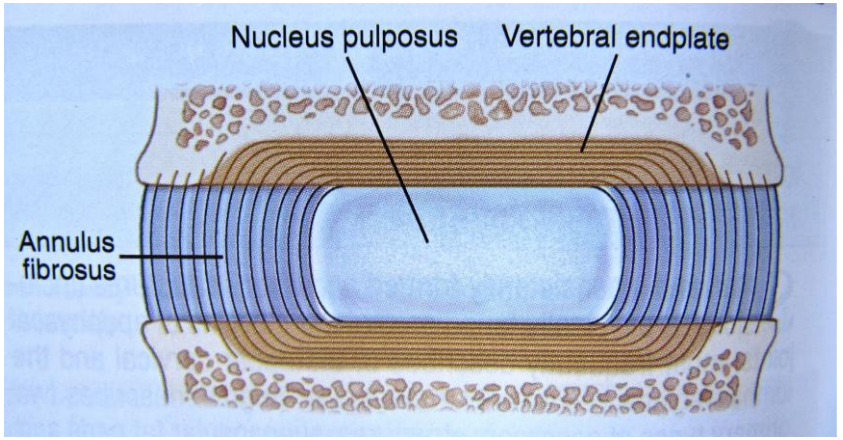
Disc Nucleus

- Nucleus Pulposus is a gel-like matrix containing proteoglycans and type II collagen. The negative charge of the glycosaminoglycans attracts and holds onto water.
- Hydration helps with maintenance of disc height and load-bearing capacity of the disc.
- Chondrocytes within the NP synthesize and maintain matrix.
- Degenerative Disc Disease is related to loss of proteoglycan and water content leading to inability of of the disc to resist compressive loading.



The Lumbar Discovertebral Complex

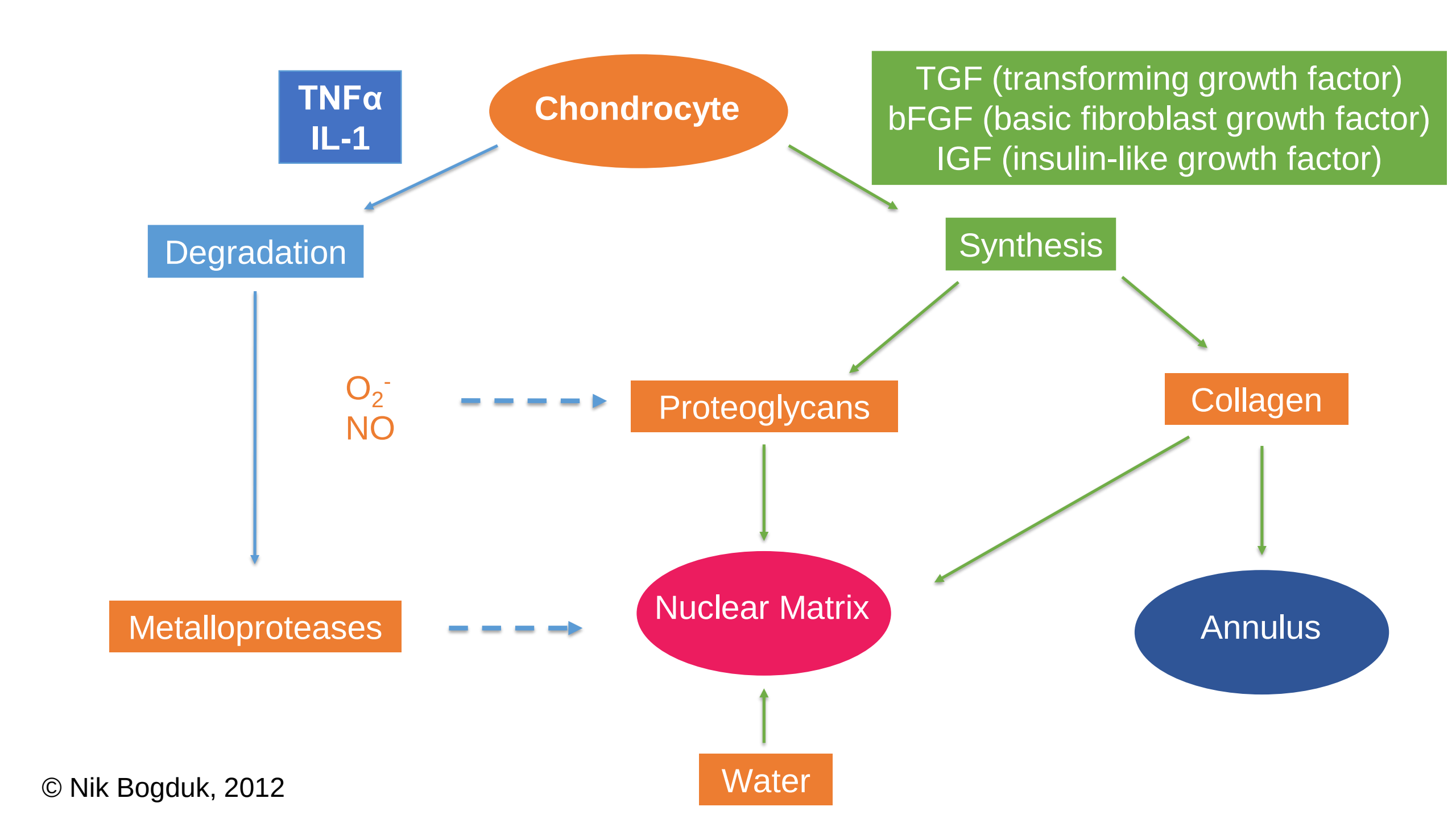
- Homeostasis: Chondrocytes control synthesis and degradation of the nuclear matrix:
  - Proteoglycans, collagen, H_20
- Hostile biochemical environment
  - No direct blood supply
  - Low O_2 tension
  - Anabolic metabolism pH (6.9-7.1)



- A variety of insults may upset this homeostatic balance
  - Metabolic disease (DM)
  - Genetic factors
  - Traumatic endplate injury
  - Nutritional (smoking, vascular disease)
  - Infectious

HOMEOSTASIS

The Balance of Synthesis and Degradation



Growth Factors

- **Up-regulate ECM proteins:**
  - Transforming growth factor (TGF-beta)
  - Insulin-like growth factor 1 (IGF-1)
  - Epidermal growth factor (EGF)
  - Platelet-derived growth factor
  - Bone morphogenetic proteins (BMP)
  - BMP-7 (OP-1), BMP-2, GDF-5
- **Increase Anabolic Activity**

- **Down-regulate inflammatory cytokines:**
  - Interleukin (IL-1, IL-6)
  - Tumor necrosis factor-alpha (TNF)
  - Matrix metalloproteinases (MMPs)
  - Nitric oxide (NO)
  - Prostaglandin E2 (PGE2)
- **Decrease Catabolic Activity**

It’s Been Said….

the disc

is where good therapies

go to

DIE

Disc Biologics

- Disc restorative solution
- Ozone
- Methylene blue
- Fibrin sealant
- IDET
- Biaculoplasty
- Nucleoplasty
- Isolated Growth Factors
- Disc Chondrocytes
- Mesenchymal Stem Cells
- Platelet Rich Plasma

Disc Degeneration

- Can biologics slow or even reverse the cascade of DDD?
- Will transplantation of cells into the disc improve the production of proteoglycan rich extraceullular matrix and lead to better hydration and biomechanical properties?

Animal Data

Meta-Analysis Of Animal Data

- 6 rct's in animals met criteria
- Looked at the association between disc stem cell transplant and subsequent change of disc height

Gene 564 (2015) 1–8

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Research paper

Efficacy of intervertebral disc regeneration with stem cells – A systematic review and meta-analysis of animal controlled trials

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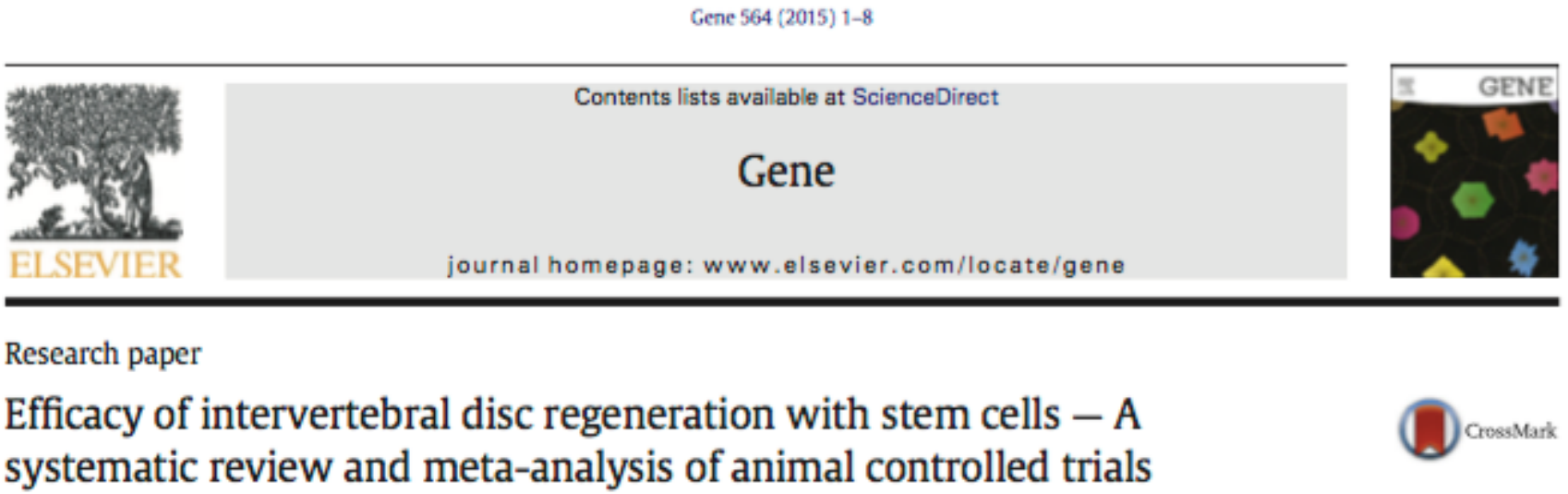
Meta-Analysis Of Animal Data

- Overall, IVD stem cell transplant was associated with 23.6% increase in disc height index (95% CI, 19.7-23.5; p<0.001)
- Of all the six studies, none showed decrease of disc height index in the transplant group compared with the controlled group.
- The increase in disc height index was statistically significant in all individual studies.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CrossMark

Meta-Analysis Of Animal Data

- The findings of this meta-analysis indicate that cell therapy may arrest or reverse the IVD degenerative process.

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Spine

Cell-Based Therapies for lumbar discogenic low back pain - a Systematic Review and Single Arm Meta-Analysis

Tao Wu1†, MD; Hai-xin Song2†, MD; Yan Dong3, MD; Jian-hua Li4*, MD

1 Department of Rehabilitation Medicine, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University
2 Department of Rehabilitation Medicine, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University
3 Department of Rehabilitation Medicine, Hangzhou Hospital of Zhejiang CAPF
4 Department of Rehabilitation Medicine, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University

Wu et al Study

- **Objective** To assess the efficacy of mesenchymal stem cells (MSC) or chondrocyte in patients with discogenic low back pain
- **Study Design** A systematic review and single arm meta-analysis of clinical trials.
- **Objective** To assess the efficacy of mesenchymal stem cells (MSC) or chondrocyte in patients with discogenic low back pain.
- **Methods:** A comprehensive literature search from database on PubMed, Ovid MEDLINE,Ovid EMBASE, EBSCO and Web of Science from database inception through on September 10th, 2015. We included clinical trials that evaluated stem cells or chondrocyte-based therapy in patients with disc-genic back pain. The primary outcomes of interest were pain score and Oswestry Disability Index (ODI). We performed random effects model meta-analyses to assess net changes in the same outcome variables.

Wu et al Study

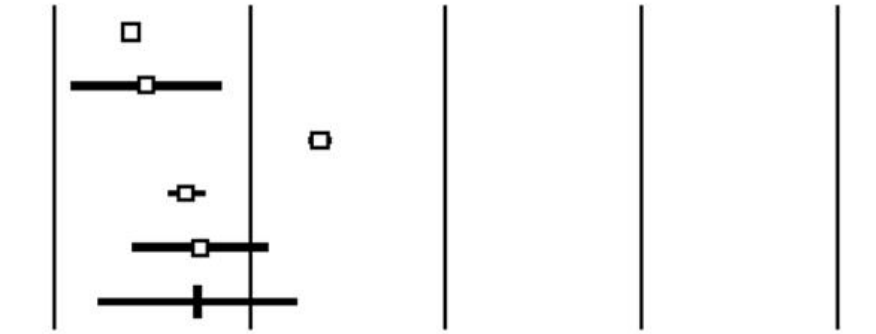
- **Results:** The initial search identified 1393 articles, of which 6 studies were eligible for this review. All studies were published from 2006 to 2015 and 74 patients were included.

Wu et al Study

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Kenneth Pettine 2015	-56.125	0.800	0.639	-57.692	-54.558	-70.188	0.000
Xiaodong Pang 2014	-53.333	6.770	45.833	-66.602	-40.064	-7.878	0.000
Domagoj Coric 2013	-22.333	1.030	1.061	-24.352	-20.314	-21.681	0.000
Lluis Orozco 2011	-46.200	1.659	2.752	-49.451	-42.949	-27.851	0.000
Hans Joerg Meisel 2006	-43.703	6.137	37.664	-55.731	-31.674	-7.121	0.000
	-44.158	9.000	81.008	-61.799	-26.518	-4.906	0.000

Statistics for each study

Difference in means and 95% CI



Heterogeneity Q-value	df(Q)	P-value	I-squared	Tau squared	Tau
675.9	4	0.000	99.4	388.4	19.7

Decreased pain score (NRS & VAS, 0-100) after treatment: The pooled mean difference in pain score from baseline to follow-up points was 44.2 points decreased (95%CI: -61.8 to −26.5, p<0.001, I^2=99.4%)

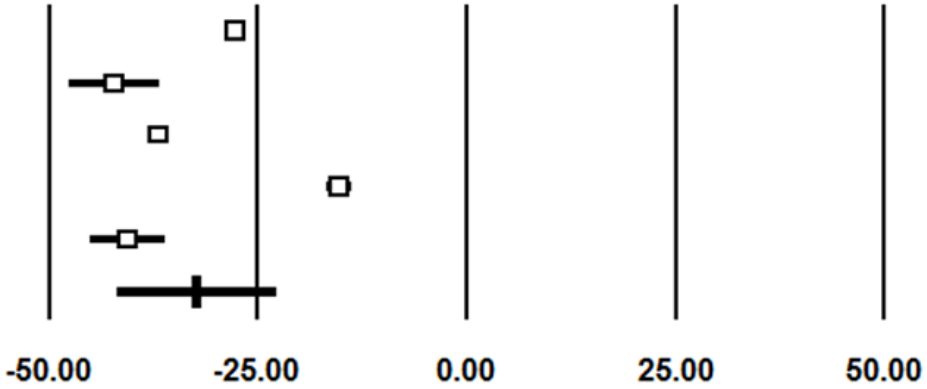
Decreased pain score after treatment

Wu et al Study

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Domagoj Coric 2013	-27.649	0.555	0.308	-28.737	-26.562	-49.849	0.000
Hans Joerg Meisel 2006	-42.083	2.665	7.104	-47.307	-36.859	-15.789	0.000
Kenneth Pettine 2015	-36.768	0.369	0.136	-37.491	-36.044	-99.606	0.000
Lluis Orozco 2011	-15.158	0.663	0.440	-16.457	-13.858	-22.861	0.000
Xiaodong Pang 2014	-40.444	2.205	4.861	-44.766	-36.123	-18.345	0.000
	-32.249	4.770	22.751	-41.597	-22.900	-6.761	0.000

Statistics for each study

Difference in means and 95% CI



Heterogeneity Q-value	df(Q)	P-value	I-squared	Tau squared	Tau
887.1	4	0.000	99.5	111.2	10.5

Decreased Oswestry Disability Index (ODI, 0-100) after treatment: The pooled mean difference in ODI from baseline to follow-up points was 32.2 points decreased (95%CI: -41.6 to −22.9, p<0.001, I^2=99.5%).

Oswestry Disability index decrease after treatment

Wu et al Study

- **Safety:**
  - There were no related adverse events reported in all of the included studies. There was no tumor formation observed in any clinical cases in stem cell transplantation during follow up period.

Key Points

Cell-Based Transplantation Therapy (Mesenchymal stem cells or chondrocytes) for patients who have discogenic low back pain is associated with improved pain relief and Oswestry Disability Index.

The optimal cell therapy protocol for discogenic low back pain remains unclear.

Clinical benefits of cell therapy for patients with disc-genic low back pain need further investigation and reevaluation to test the clinical efficacy.

Human Trials
Stem Cells and the Intervertebral Disc

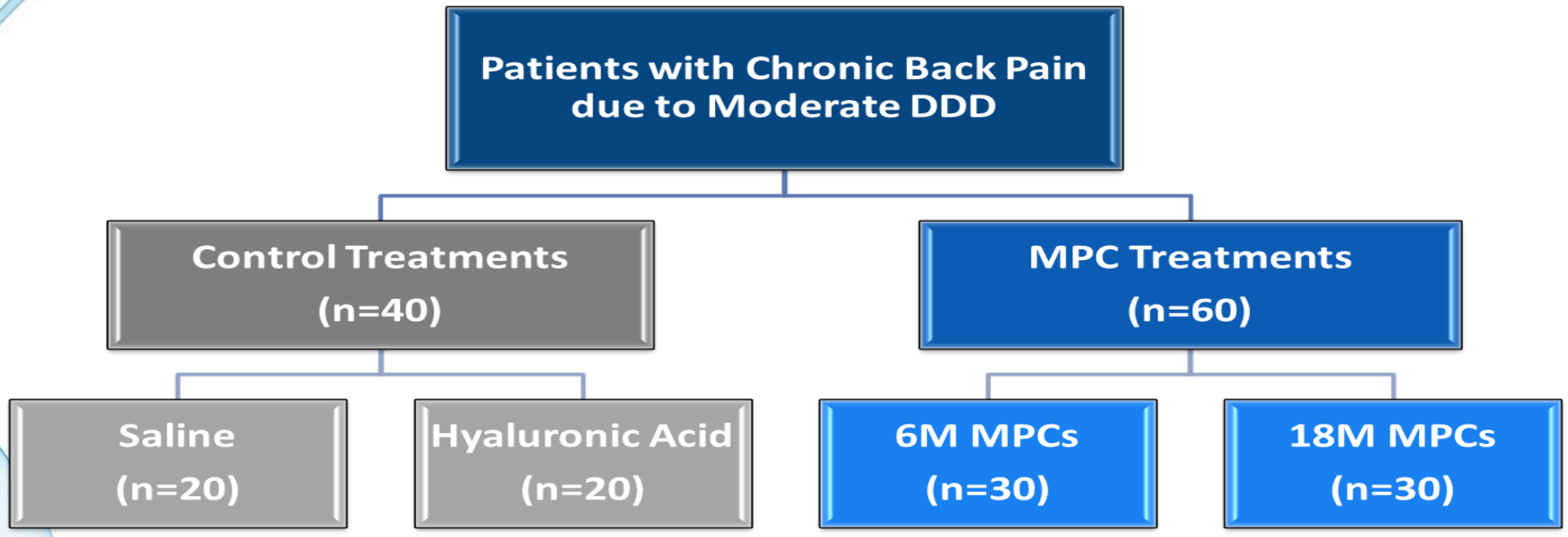
Allogeneic MSC's

Mesoblast

Safety and Preliminary Efficacy Study for Disc Repair (Mesoblast)

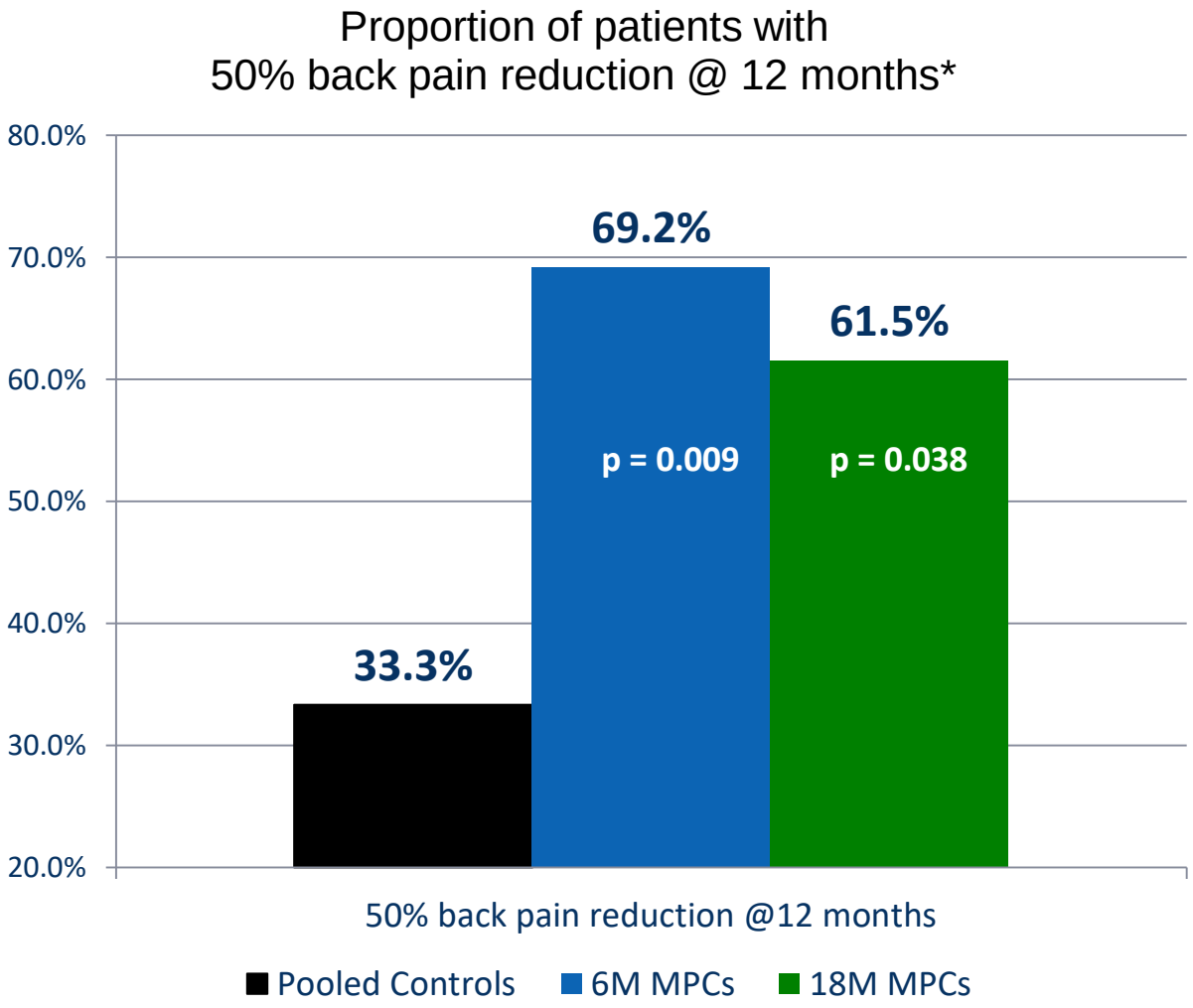
- MPC's for Lumbar Disc Disease in Adults
- Primary Objective: Safety @ 6 months
- Secondary Objective: Efficacy
- 100 Patients Worldwide
- Randomized to:
  - Normal Saline
  - Hyaluronic Acid (HA)
  - Low Dose (6 Million) MPC's in HA
  - High Dose (18 Million) MPC's in HA

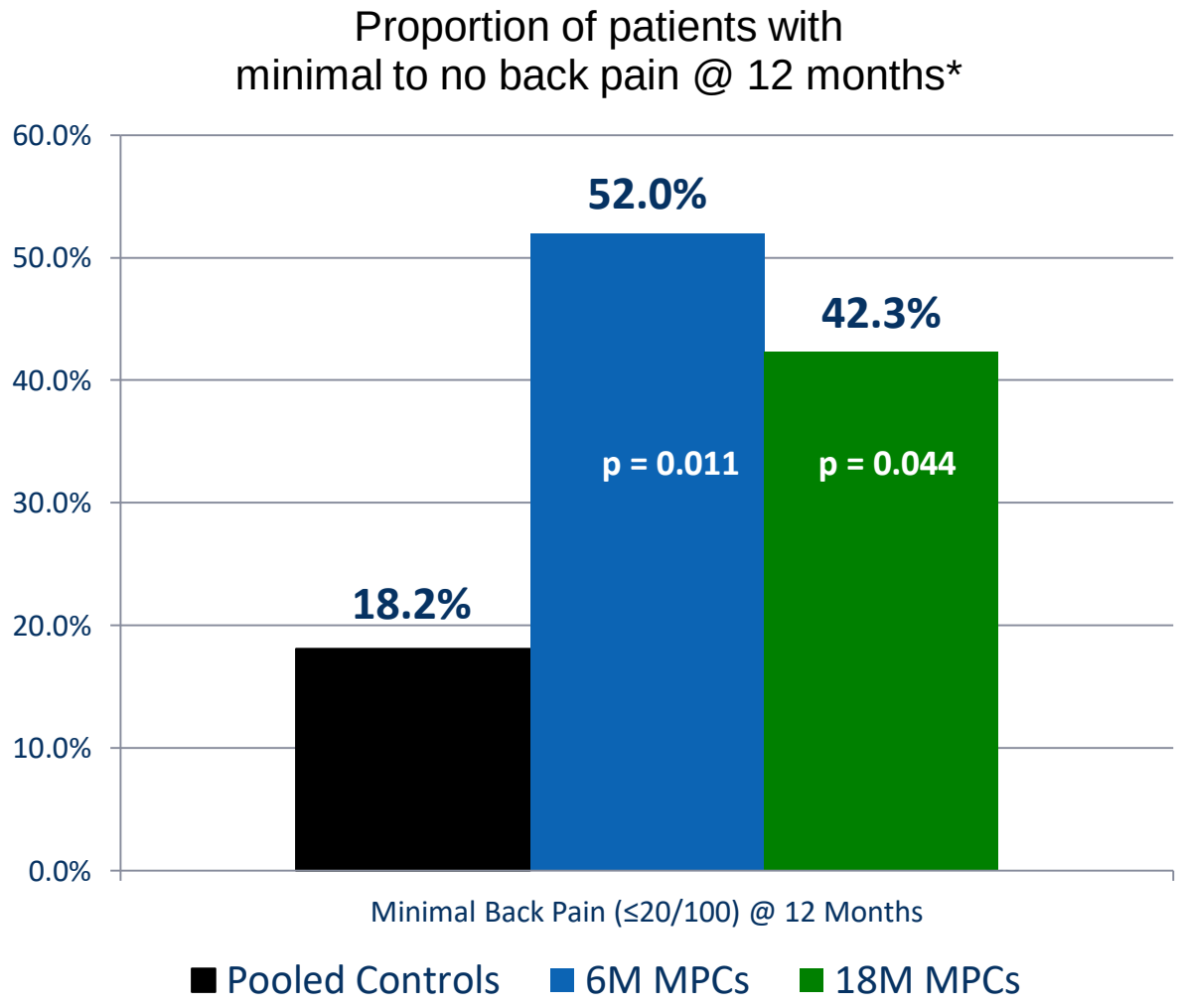
Study Design



- Prospective, multi-center, randomized, double-blind, controlled study
  - Patients and radiographic evaluators blinded to treatment
- **Follow-up:** 1, 3, 6, 12, 24 & 36 months

MPC groups have a greater proportion of patients with at least a 50% improvement in back pain or minimal/no residual back pain at 12 months relative to controls





* from post-hoc analysis

Take away points from Mesoblast Study

- Allogeneic MPCs were well tolerated
  - No issues related to use of an allogenic product were identified

Take away points from Mesoblast Study

- Both MPC doses showed improvement relative to controls for pain and functional improvement and reduced interventions
  - There appears to be a minimal number of cells needed to exert a physiologic response but more may not always be better.

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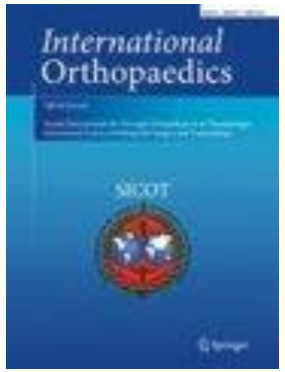
Autologous MSC's

BMC

Interventional Disc Repair by Autologous Mesenchymal Bone Marrow Cells: A Pilot Study

Lluis Orozco,[1] Robert Soler,[1] Carles Morera,[2] Mercedes Alberca,[3] Ana Sánchez,[3] and Javier García-Sancho[3,4]

- 10 pts with chronic LBP with Lumbar DDD
- Mesenchymal stem cells harvested from iliac crest, cultured (21-28 d), injected into nucleus pulposus
- 9:10 pts improved
- Analgesic effect approaching 71% efficacy
- No change in disc height



International Orthopaedics

Autologous Bone Marrow Concentrate Intradiscal Injection For The Treatment Of Degenerative Disc Disease With Three-Year Follow-Up.

Pettine KA, Suzuki RK, Sand TT, Murphy MB

Stem Cells, 2017

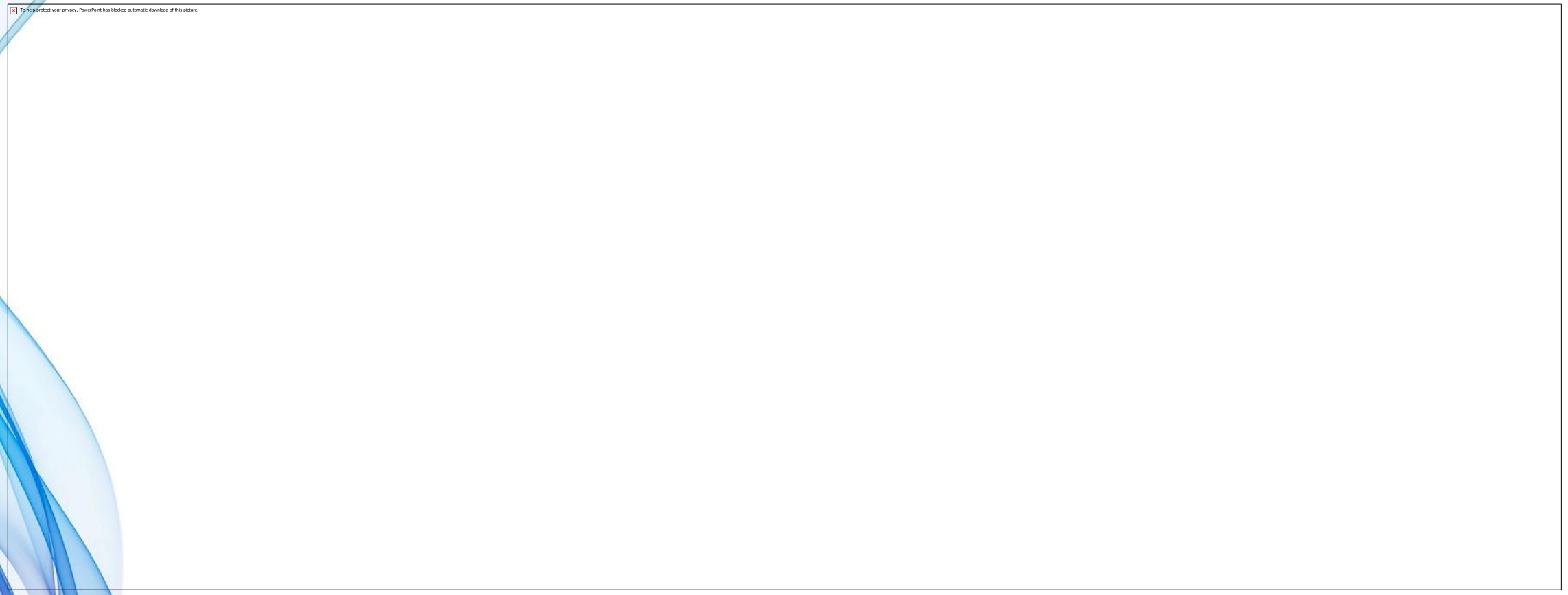
(3-yr results)

Clinical Study

- Failed conventional therapy >3 mo.
- Eligible for surgical relief
- IRB cleared protocol

		One-Level	Two-Levels
Number of Patients		13	13
Median Age		40 Range 25-51	37 Range 18-61
Average BMI		27.1	26.1
Cause of Injury	**Trauma**	7	5
	Unknown	6	8
Discs of Modified Pfirrmann Grade:	IV	2	1
	V	3	6
	VI	5	11
	VII	3	8

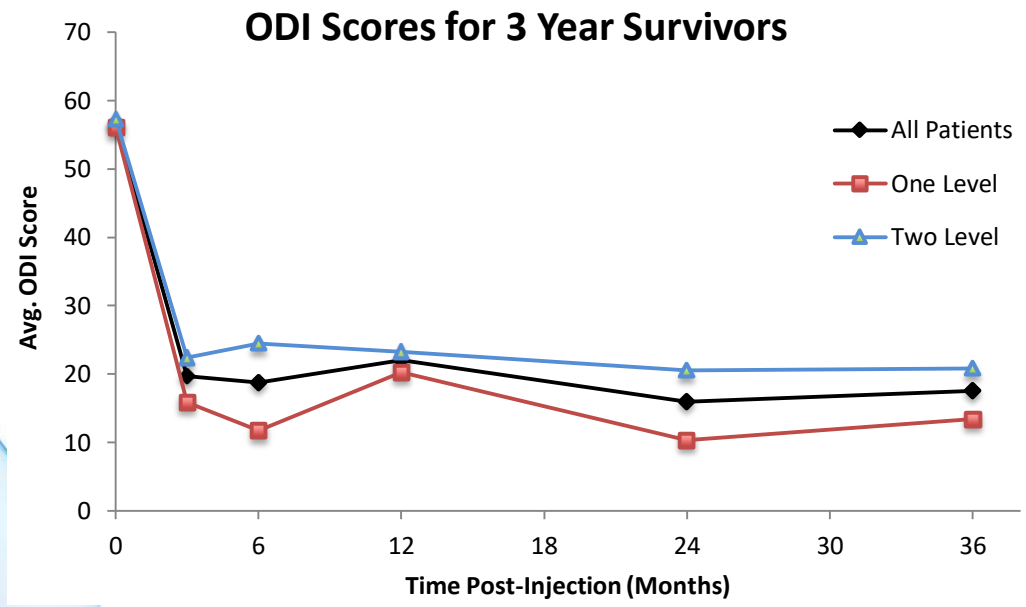
Modified Pfirrmann Grading System

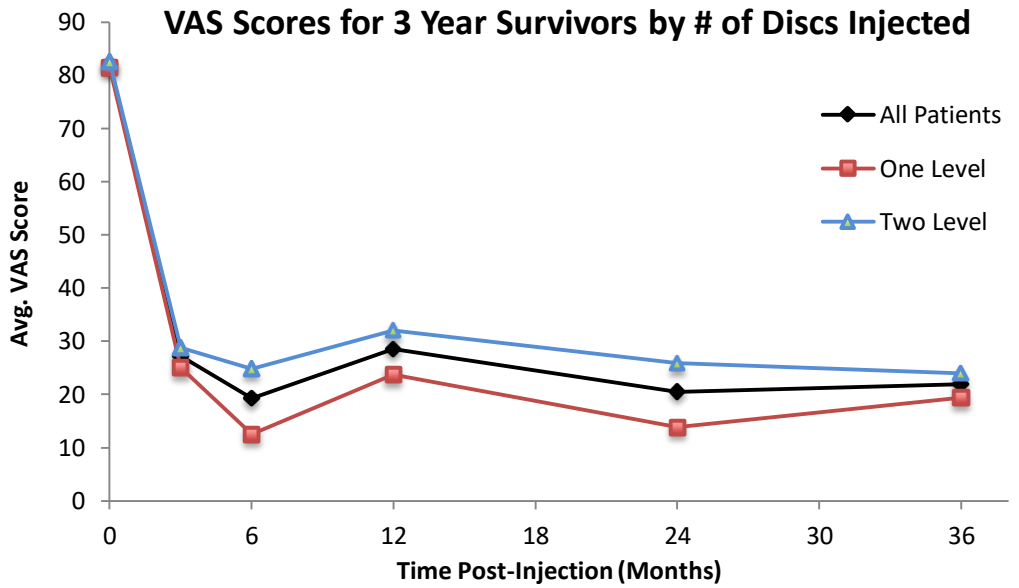


Pfirrmann Grading System

Grade	Structure	Distinction of nucleus and anulus	Signal intensity	Height of intervertebral disc
I	Homogeneous, bright white	Clear	Hyperintense, isointense to cerebrospinal fluid	Normal
II	Inhomogeneous with or without horizontal bands	Clear	Hyperintense, isointense to cerebrospinal fluid	Normal
III	Inhomogeneous, gray	Unclear	Intermediate	Normal to slightly decreased
IV	Inhomogeneous, gray to black	Lost	Intermediate to hypointense	Normal to moderately decreased
V	Inhomogeneous, black	Lost	Hypointense	Collapsed disc space

Pettine et al Study Results

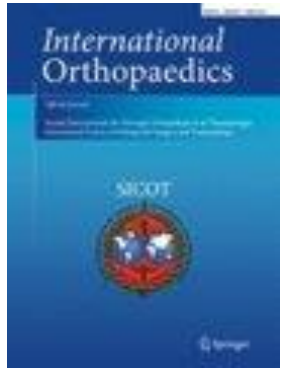


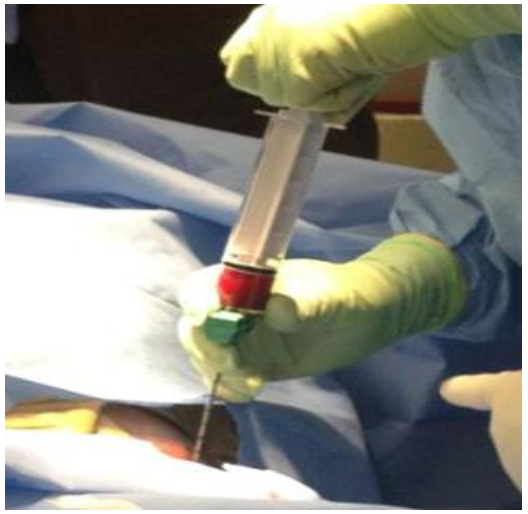


Disc Injection Therapy

3-year Survivor Cohort (n = 20)

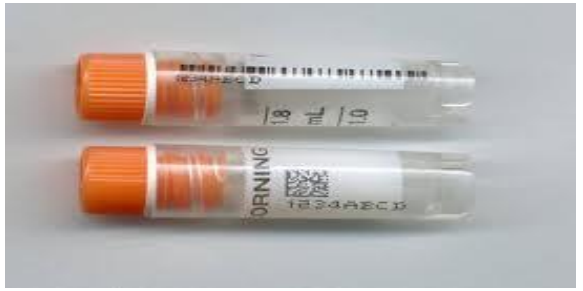
Disc Injection Therapy

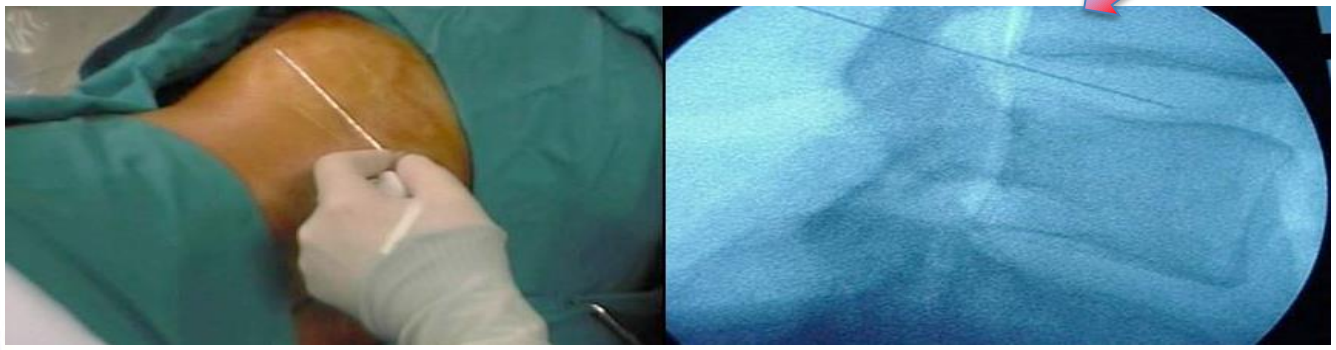




60cc BMA drawn from the posterior iliac crest

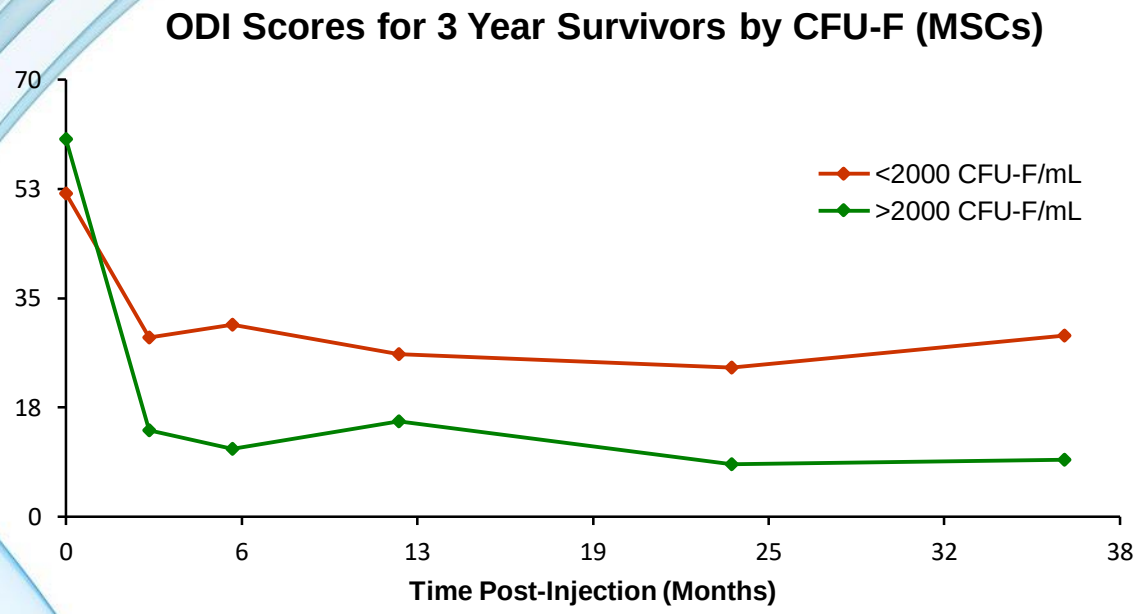
BMA centrifuged for 12 min. 6cc bone marrow concentrate (BMC) drawn

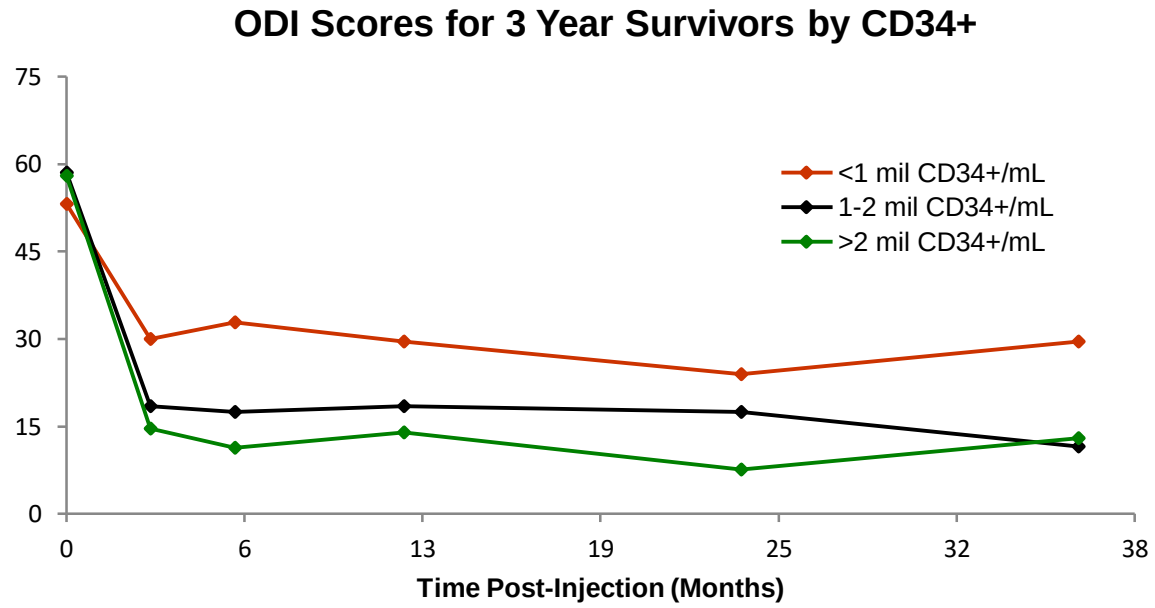




Total procedure time: 30-45 min.

Progenitor Cells & Disc Injections





% Improvement from Baseline 3 years post-BMC Injection (20 surviving of 26)

	All Patients	CFU-F <2000	CFU-F >2000	CD34+ <1 mil	CD34+ >2 mil	One Level	Two Levels	Age <30	Age 30-45	Age >45
% ODI Improvement	67%	41%	86%	38%	79%	71%	64%	64%	72%	56%
% VAS Improvement	73%	48%	90%	42%	83%	77%	70%	74%	75%	66%

8 of 20 patients w/ 1-yr MRI improved a Pfirrmann grade; 6/8 had >2000 MSCs/cc INT ORTHOP 2017 Pettine

Disc Injection Therapy

Patient Outcomes (September 2015)

- 8 patients showed a single grade level improvement in their Pfirrmann score at 1-yr (40% of enrolled patients)

- 3 1-level and 3 2-level patients progressed to surgical repair by 3-yr (77% avoided surgery through three years)

- 2 Patients received a 2nd injection two years ago; no additional 2nd injections have occurred

- 73% average reduction in pain and 67% average improvement in ODI at 3-yr for the surviving 20 patients

- >2000 CFU-F patients: 86% improvement in ODI/90% reduction in VAS; <2000 CFU-F: 41% ODI/48% VAS

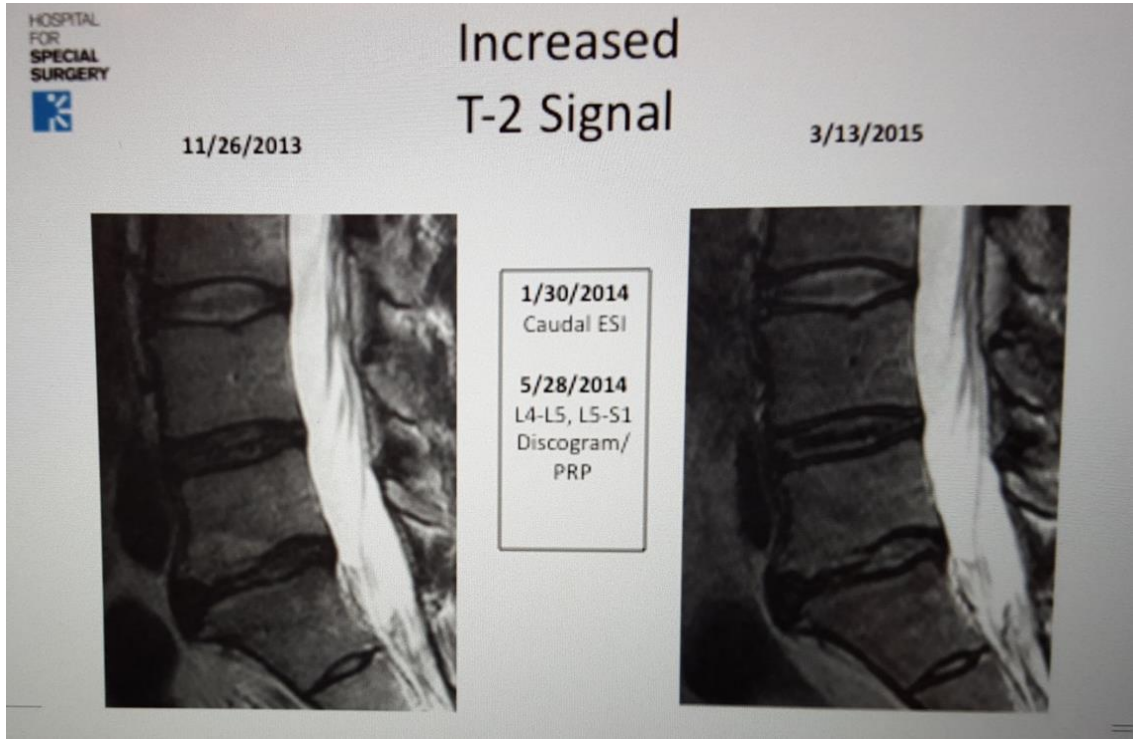
How does this compare to surgery?

- The overall improvement with an artificial disc was a 57% improvement in ODI and 63% improvement in VAS.
- The overall improvement with a lumbar fusion was 43.3% improvement in ODI and 52.7% improvement in VAS.
- This compares with a 71% improvement in ODI and 70% improvement in VAS in this BMC injection group
- The difference in hospital stay and cost in the surgery groups versus one hour in the outpatient BMC group is significant.
  - Celling/Sand PhD

LR-PRP Disc Double-Blind RCT

- 47 patients:
  - 29 Contrast Dye+LR-PRP
  - 18 Contrast Dye only
- NRS, SF-36, NASS scores improved.
- Statistically significant improvement in best NRS scores at 8 weeks.

MRI Pre- and Post L5-S1 PRP



Lutz GE. Increased Nuclear T2 Signal Intensity and Improved Function and Pain in a Patient One Year After an Intradiscal Platelet-Rich Plasma Injection. Pain Med 2017;18:1197-9. 10.1093/pm/pnw299

Lutz et al.

- Participants who received intradiscal PRP experienced statistically significantly ($p < 0.05$) greater improvements in pain, function, and satisfaction compared to those who received contrast agent alone over eight weeks.
- The overall success rate was 56% in the treatment group vs only 18% in the control group.
- The majority of participants who received intradiscal PRP experienced improvements in pain and function that were sustained for up to two years or more post-injection.
- Interestingly, those who received intradiscal PRP in two discs reported superior improvements across all outcome measures compared to those who only received PRP in one disc.
- There were no reported complications following injection among enrolled participants

LR-PRP Disc Double-Blind RCT

Pain Medicine

Intradiscal Platelet-Rich Plasma Injection for Chronic Discogenic Low Back Pain: Preliminary Results from a Prospective Trial.

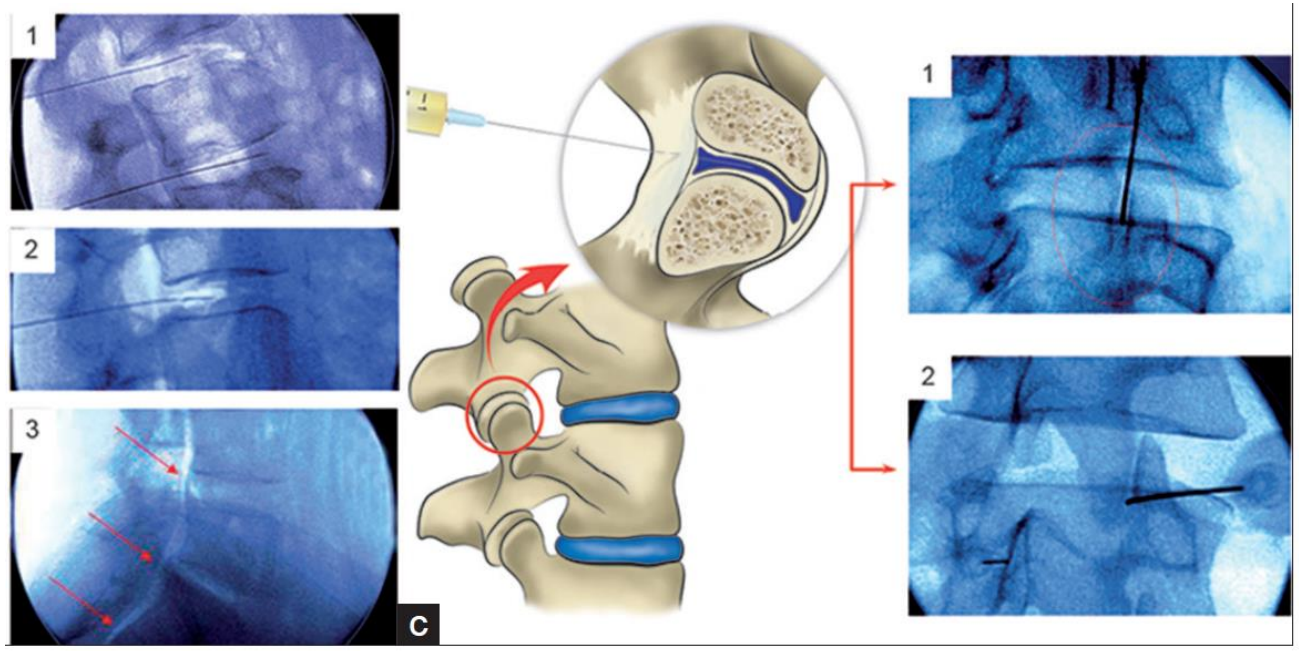
Levi D et al.

VAS > 50%, ODI > 30 achieved in:

- 14% (3/22) patients at 1 month
- 32%(7/22) patients at 2 months
- 47% (9/19) patients at 6 months

LP-PRP: Intradiscal, Intra-articular Facet, Epidural Space

- 86 patients, LBP>3M, prospective trial. PRP activated with CaCl.
- VAS Scores
  - Pre-Injection 8/10
  - 1 month 4/10
  - 2 months 2/10
  - 6 months 1/10



Kirchner F, Anitua E. *Intradiscal and intra-articular facet infiltrations with plasma rich in growth factors reduce pain in patients with chronic low back pain.* J Craniovert Jun Spine 2016; 7:250-6.

Study Details Noriega et al, 2017 Sample size = 24 Follow-up = 12 months RCT

Population 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

Cell/Solution Type Allogeneic bone marrow MSCs by intradiscal injection or a sham infiltration of paravertebral musculature with anesthetic

Cell or Solution Dose and Delivery Pathway The intervention group received allogeneic bone marrow MSCs by intradiscal injection of 25 X 10, 6 cells per segment under local anesthesia

Outcome Parameters VAS, ODI, MRI, SF-12

Results 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.
- 5 of the 12 outcomes in patients (40%) receiving MSCs were described as perfect treatment with 100% improvement.

Conclusion 28% improvement in all patients 40% of patients perfect result

- Positive result

Study Details Coric et al, 2013 Sample size =15 Follow-up=1 year Prospective cohort

Population15 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)

Cell/Solution Type Expanded allogeneic juvenile chondrocyte cells

Cell or Solution Dose and Delivery Pathway Mean 1.3mL (1–2 mL, 107/mL cells solution was injected in the center of the disc space

Outcome Parameters ODI and NRS scores, 36-item Short Form Health Survey and MRI

Results The mean ODI, NRS, and Short-form-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

Conclusion The results of this prospective cohort are promising with 77% of patients improving. Positive result

Study Details Orozco et al, 2011 Sample size =10 Follow-up=1 year Pilot phase 1 trial

Population 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)

Cell/Solution Type Autologous expanded bone marrow– derived mesenchymal stem cells

Cell or Solution Dose and Delivery Pathway 23±5X106 autologous expanded BMSCs was injected into the nucleus pulposus area

Outcome Parameters ODI and VAS scores and MRI

Results 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.

Conclusion 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. Positive result.

Study Details Kumar et al, 2017 Sample size = 10 Follow-up = 1 year Phase 1 study

Population 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

Cell/Solution Type Combined hyaluronic acid derivative and AT-MSCs Expanded 21 d

Cell or Solution Dose and Delivery Pathway A single intradiscal injection at a dose of 2 X 107 cells/disc (N=5) or 4 X 107 cells/disc (N=5)

Outcome Parameters VAS, ODI, Short-form 36, lumbar spine x-ray, MRI

Results 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

Conclusion 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

Study Details Mochida et al Sample size =9 Follow-up=3 years Prospective clinical study

Population 9 patients with Pfirrmann grade III disc degeneration and posterior lumbar intervertebral fusion. Patient age (yrs)=20-29 years

Cell/Solution Type Autologous cultured nucleus pulposus chondrocytes that cocultured with MSCs

Cell or Solution Dose and Delivery Pathway One million activated autologous NP cells were injected into the degenerated disc 7 d after fusion surgery

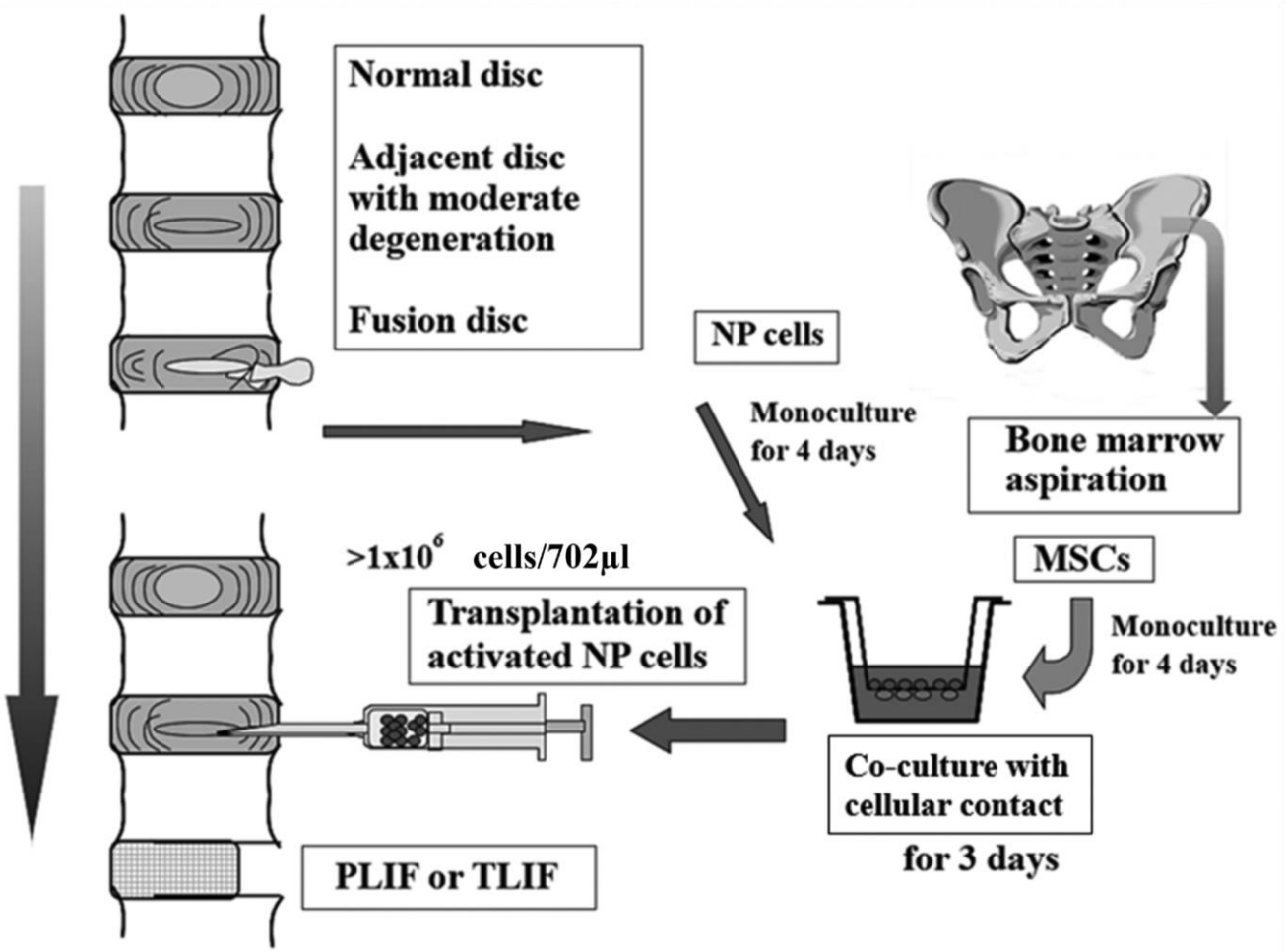
Outcome Parameters JOA scoring and MRI

Results 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 3-year follow-up period

Conclusion 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. Positive result

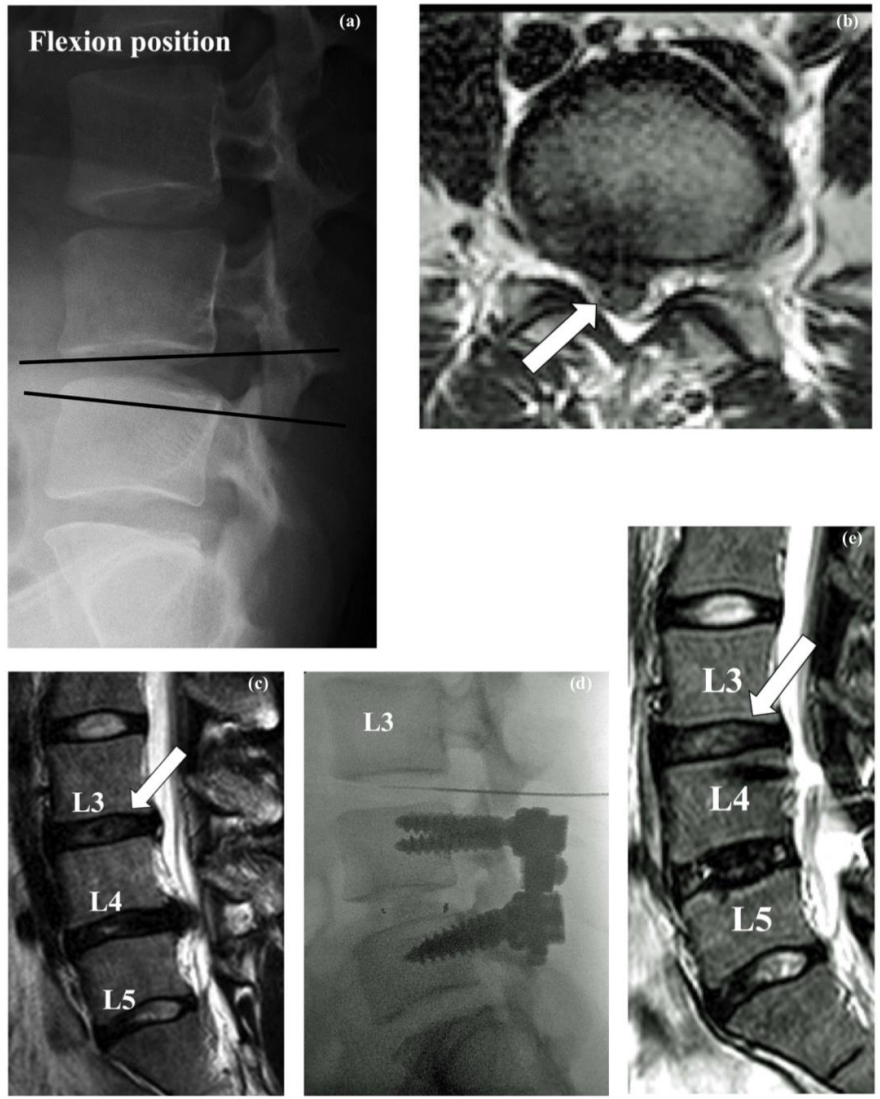
Mochida et al.

- At time of PLIF/TLIF bone marrow and nucleus cells obtained and cocultured



Mochida et al.

- Improvement at L34 after 3 years



Disc Injection Therapy

The Degenerative disc contains:

- Elevated levels of matrix metalloproteinases
- Elevated levels of IL-1

Bone marrow contains:

- alpha-2-Macroglobulin (inhibitor of MMP's)
- IL-1RAP (Interleukin-1 receptor accessory protein- reduces the pain associated with IL-1)

Disc Injection Therapy

Thus BMC is a multi-modal therapeutic agent

- It contains:
  - Biochemical Modifiers
  - MSC's, EPC's (endothelial progenitor cells), HSC's and other progenitor cells
- Takes control of the "pro-inflammatory" environment in the disc

MSC’s Intradiscal

- MSC’s have the capacity to repair degenerative discs
  - differentiation toward chondrocyte-like cells
  - producing proteoglycans and type II collagen
  - Supportive animal and human data

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Mesenchymal stem cells in regenerative medicine: Focus on articular cartilage and intervertebral disc regeneration

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Biological therapy
Cellular therapy
Articular cartilage
Osteoarthritis (OA)
Umbilical cord
Wharton's Jelly stem cell (WJSC)
Adipose-derived stem cell (AD-MSC)

ABSTRACT

Musculoskeletal disorders represent a major cause of disability and morbidity globally and result in enormous costs for health and social care systems. Development of cell-based therapies is rapidly proliferating in a number of disease areas, including musculoskeletal disorders. Novel biological therapies that can effectively treat joint and spine degeneration are high priorities in regenerative medicine. Mesenchymal stem cells (MSCs) isolated from bone marrow (BM-MSCs), adipose tissue (AD-MSCs) and umbilical cord (UC-MSCs) show considerable promise for use in cartilage and intervertebral disc (IVD) repair. This review article focuses on stem cell-based therapeutics for cartilage and IVD repair in the context of the rising global burden of musculoskeletal disorders. We discuss the biology MSCs and chondroprogenitor cells and specifically focus on umbilical cord/Wharton's jelly derived MSCs and examine their potential for regenerative applications. We also summarize key components of the molecular machinery and signaling pathways responsible for the control of chondrogenesis and explore biomimetic scaffolds and biomaterials for articular cartilage and IVD regeneration. This review explores the exciting opportunities afforded by MSCs and discusses the challenges associated with cartilage and IVD repair and regeneration. There are still many technical challenges associated with isolating, expanding, differentiating, and pre-conditioning MSCs for subsequent implantation into degenerate joints and the spine. However, the prospect of combining biomaterials and cell-based therapies that incorporate chondrocytes, chondroprogenitors and MSCs leads to the optimistic view that interdisciplinary approaches will lead to significant breakthroughs in regenerating musculoskeletal tissues, such as the joint and the spine in the near future.

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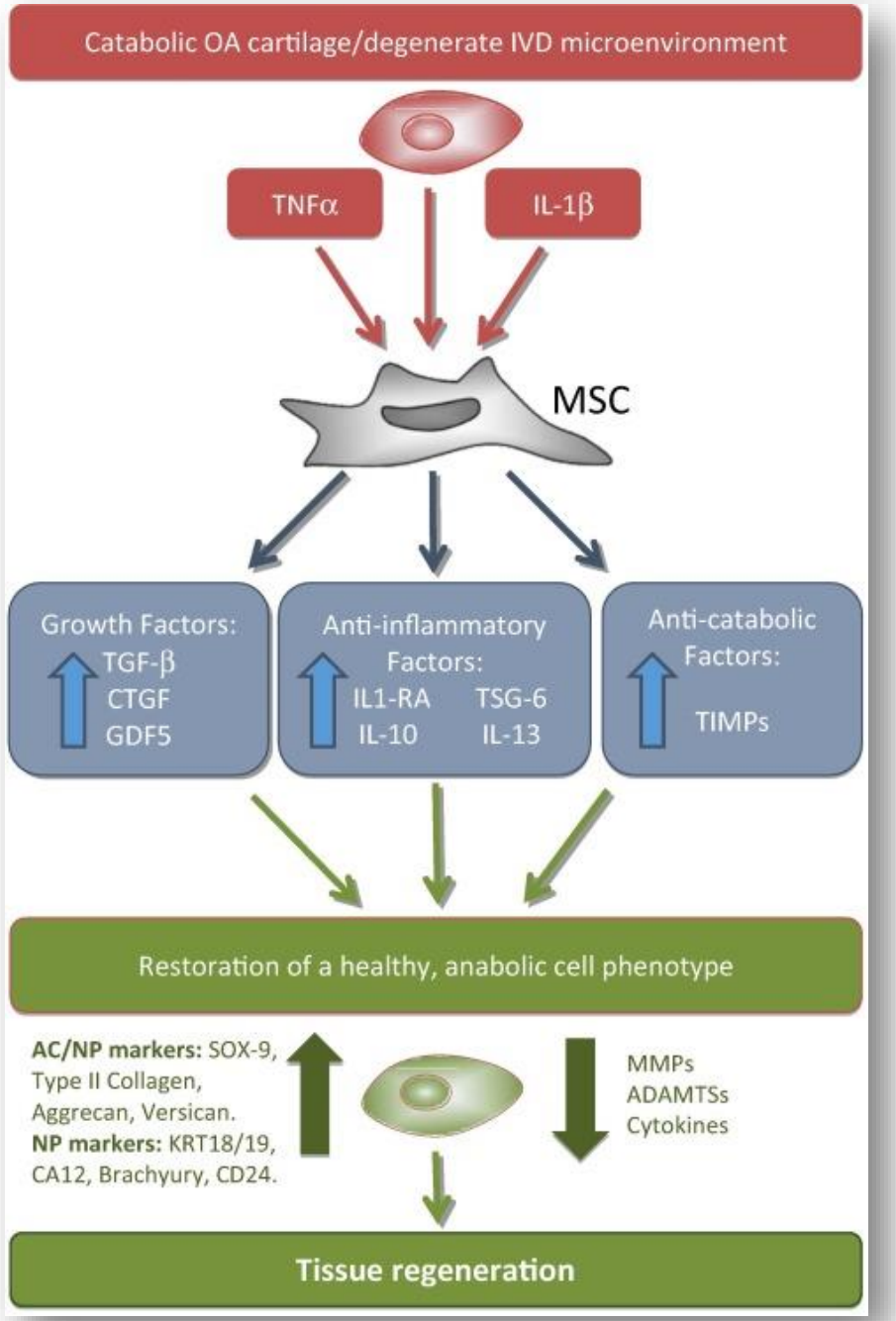


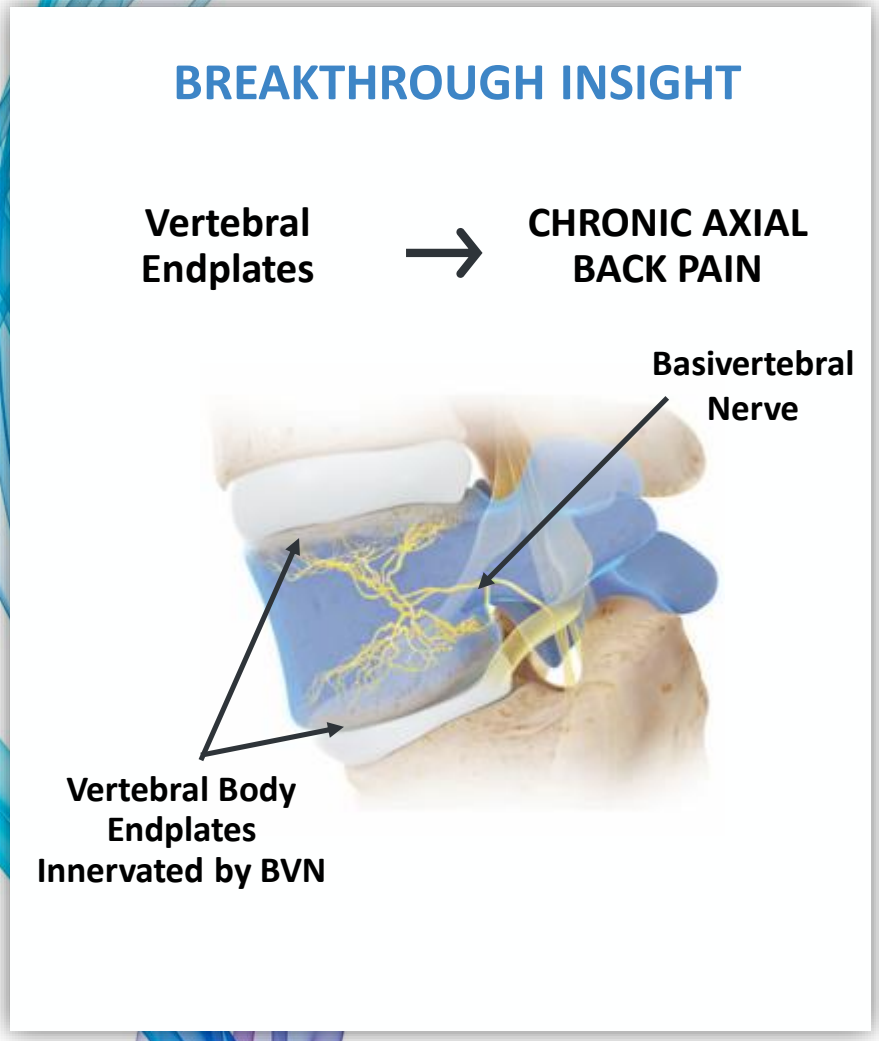
PRP in discogenic pain

Table 7. *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 (277) 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 (276) 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 (274) Lumbar discogenic pain Prospective case series n=20	Chronic PRP, single injection, 2mL injected up to 3 disc levels	18 months	At 18 months, 15 patients remained for survey compared to 18 patients surveyed at 6 months: >50% relief in VAS in 93% of patients at 18 months (n=14/15) and in 94% of patients (n=17/18) at 6 months (2). Improvement in SF-36 scores in 93% of patients at 18 months (n=14/15) compared to 100% (n=18/18) at 6 months.
Akeda et al, 2017 (279) 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 (275) 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 (278) 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 low back pain 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

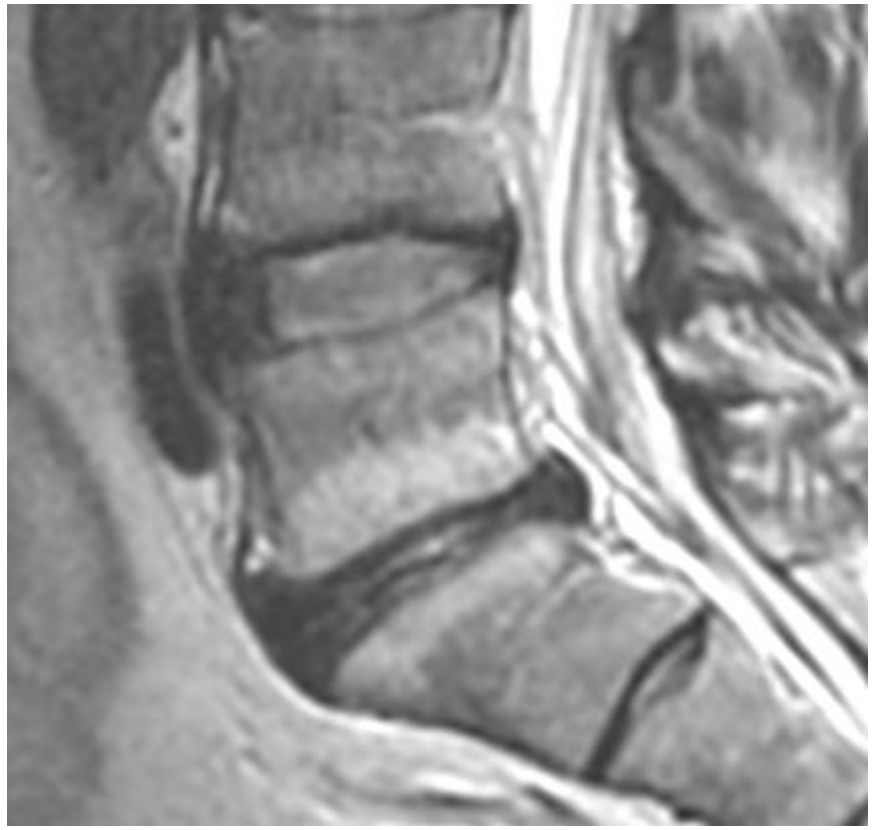
Vertebrogenic Pain - A Paradigm Shift away from the Disc



- **We have been treating the disc for the last 30 years. There is increasing evidence that along with the disc, the vertebral endplates are also an important source of pain.**

Clinical Evidence Linking Modic Changes to LBP

- MC Highly specific for CLBP
  - If you have Modic changes, you have a 88% probability of having LBP
- LBP patients with MC report a greater frequency and duration of LBP episodes
- LBP severity correlates with MC lesion size[6]
- MC independent risk factor for prolonged, severe and disabling LBP



All of you remember Modic changes- endplate changes described by Mike Modic in 1988. They are highly specific (88%) for LBP. Not very Sensitive (35%).

Subchondral Vertebral Body Injections of Autologous Bone Marrow Concentrate

Study done by Philippe Hernigou

Patient Response

The final degree of pain relief will vary from patient to patient, but generally 30% of the patients will experience noticeable pain reduction within 5-10 days, followed by 70% of patients within 3 weeks, reaching 80-90% of patients within 4-6 weeks. The level of pain medication used by the patients is recorded and can serve as an indication of pain relief. Ultimately, the return to normal daily activities also can be used in determining therapeutic benefit.

It is best to wait 3 months before attempting a follow-up treatment for a patient reporting little or no pain relief. A follow-up MRI should not be obtained until 6 months after treatment to reduce the level of treatment artifacts.

The End

Thank you for your time.

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