Biologic Treatments for Discs: Fact or Fiction

Marko Bodor MD

Physical Medicine and Rehabilitation,
Spine and Sports Medicine
Napa, California

Assistant Professor
Departments of Neurological Surgery
University of California San Francisco
Physical Medicine and Rehabilitation
University of California Davis



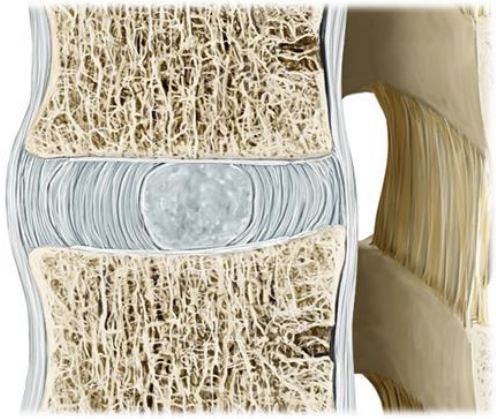

Disclosures

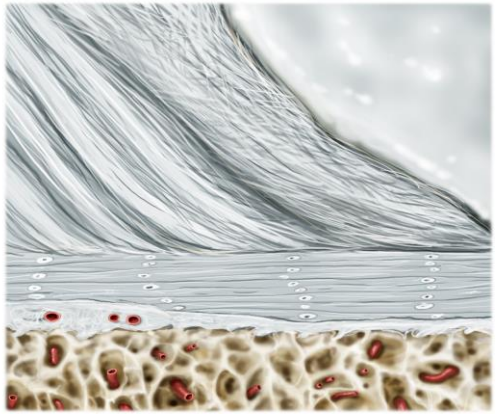
- Napa Medical Research Foundation, a 501(c)3 non-profit – Research Support
- Sonex Health (carpal tunnel release device)– Advisor and Key Opinion Leader

Prevalence of Spine Pain in the US Population

- Neck – up to 10%, of which 15-40% discogenic
- Thoracic – up to 15%, of which (?)% discogenic
- Lumbar – up to 20% of which 25-40% discogenic

Normal Disc Anatomy

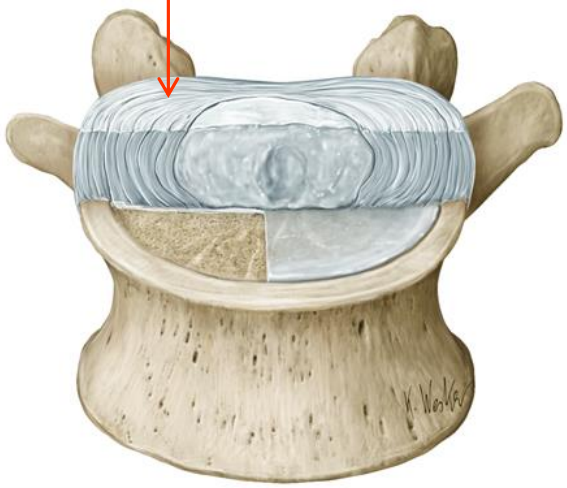


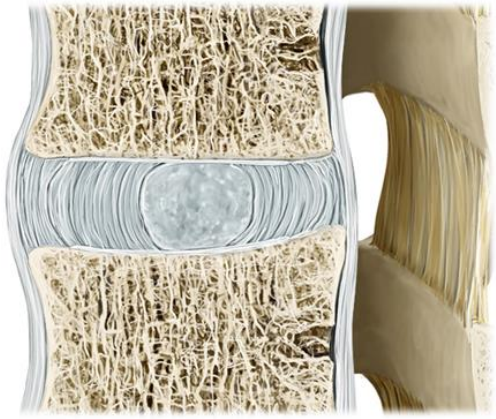


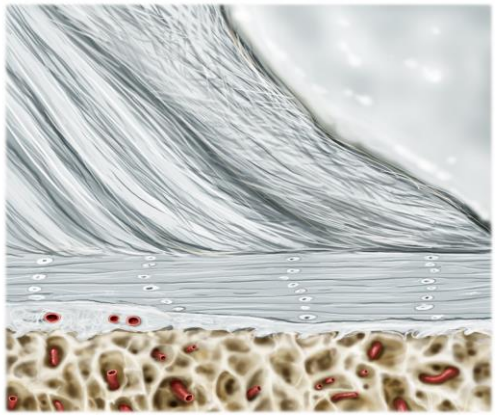
Illustrations by Karl Wesker. From Thieme Atlas of Anatomy, Georg Thieme Verlag, 2010 Stuttgart.

Normal Disc Anatomy

15-25 mostly type I collagen lamellae, 9000 AF cells/mm^3



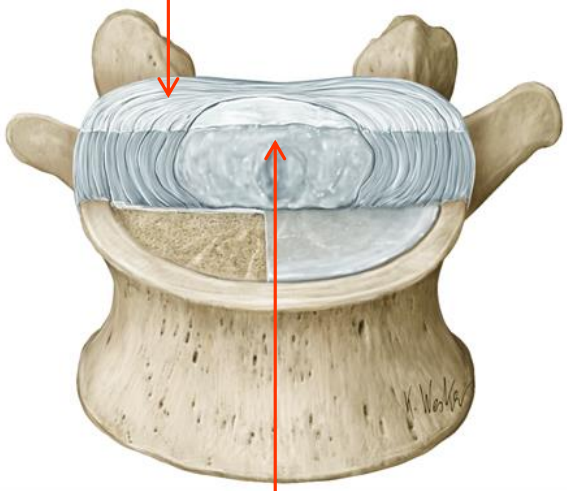




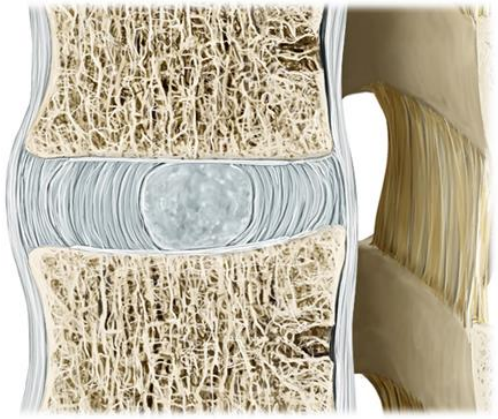
Illustrations by Karl Wesker. From Thieme Atlas of Anatomy, Georg Thieme Verlag, 2010 Stuttgart.

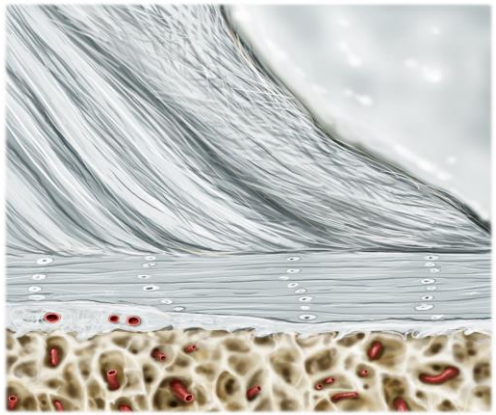
Normal Disc Anatomy

15-25 mostly type I collagen lamellae, 9000 AF cells/mm^3



Type II collagen, elastin, proteoglycans (GAGs and hyaluronic acid), 4000 NP cells/mm^3

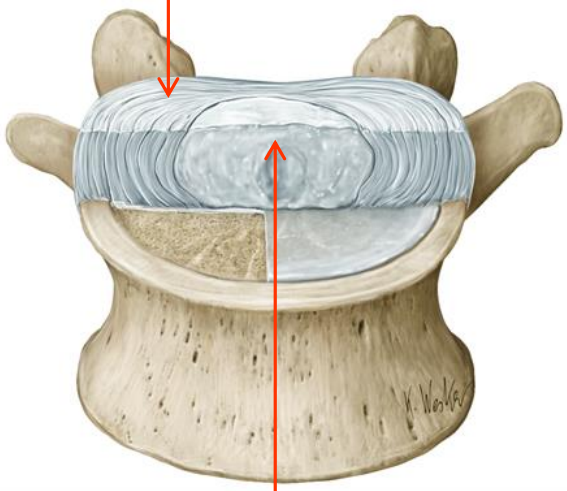


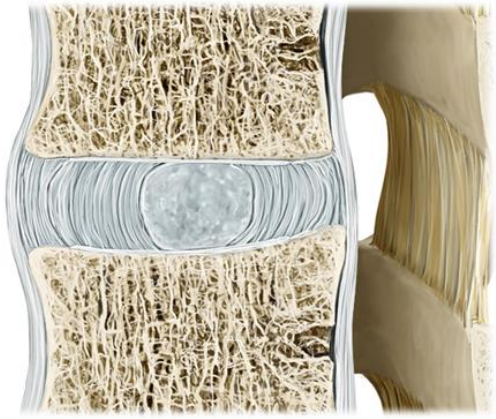


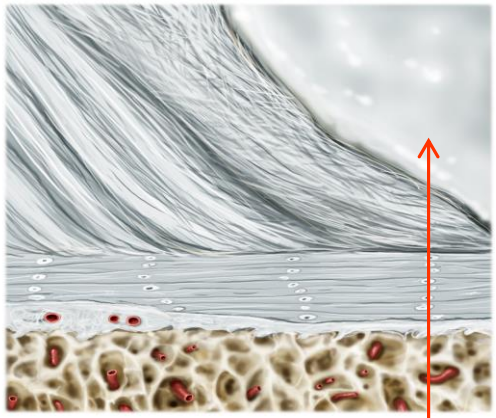
Illustrations by Karl Wesker. From Thieme Atlas of Anatomy, Georg Thieme Verlag, 2010 Stuttgart.

Normal Disc Anatomy

15-25 mostly type I collagen lamellae, 9000 AF cells/mm^3







Type II collagen, elastin, proteoglycans (GAGs and hyaluronic acid), 4000 NP cells/mm^3

NP cells with notochordal cell markers CK-8, -18, -19 and Galectin-3 are seen in 100% of young and 20-30% of middle-aged and older discs.

Factors Associated with Disc Degeneration

Genetic Factors (30-60%)

- Collagen IX and XI
- Interleukin-1
- Aggrecan
- Vitamin D receptor
- Matrix Metalloproteinase-3
- Cartilage intermediate layer protein (CILP)
- SNP rs4802666, MYH14 gene, encodes for non-muscle myosin

Environmental Factors (40-70%)

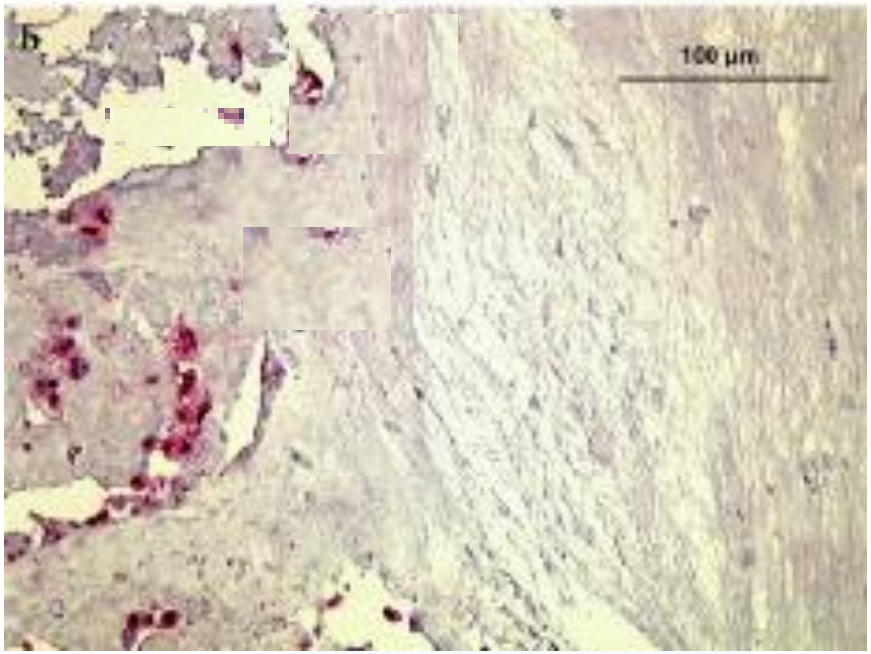
- Acute Trauma
- Nicotine
- Fructose/Sucrose (Obesity)
- Heavy Lifting
- Frequent Bending
- Frequent Twisting
- Infection (?)
- NSAIDs (?)

Histology of Normal Intervertebral Discs



Weiler C, Nerlich AG, Schaaf R, Bachmeier BE, Wuertz K, Boos N. Immunohistochemical identification of notochordal markers in cells in the aging human lumbar intervertebral disc. Eur Spine J 2010.

Histology of Normal Intervertebral Discs



Weiler C, Nerlich AG, Schaaf R, Bachmeier BE, Wuertz K, Boos N. Immunohistochemical identification of notochordal markers in cells in the aging human lumbar intervertebral disc. *Eur Spine J.* 2010.

Structure and Function of Blood Cells and Platelets

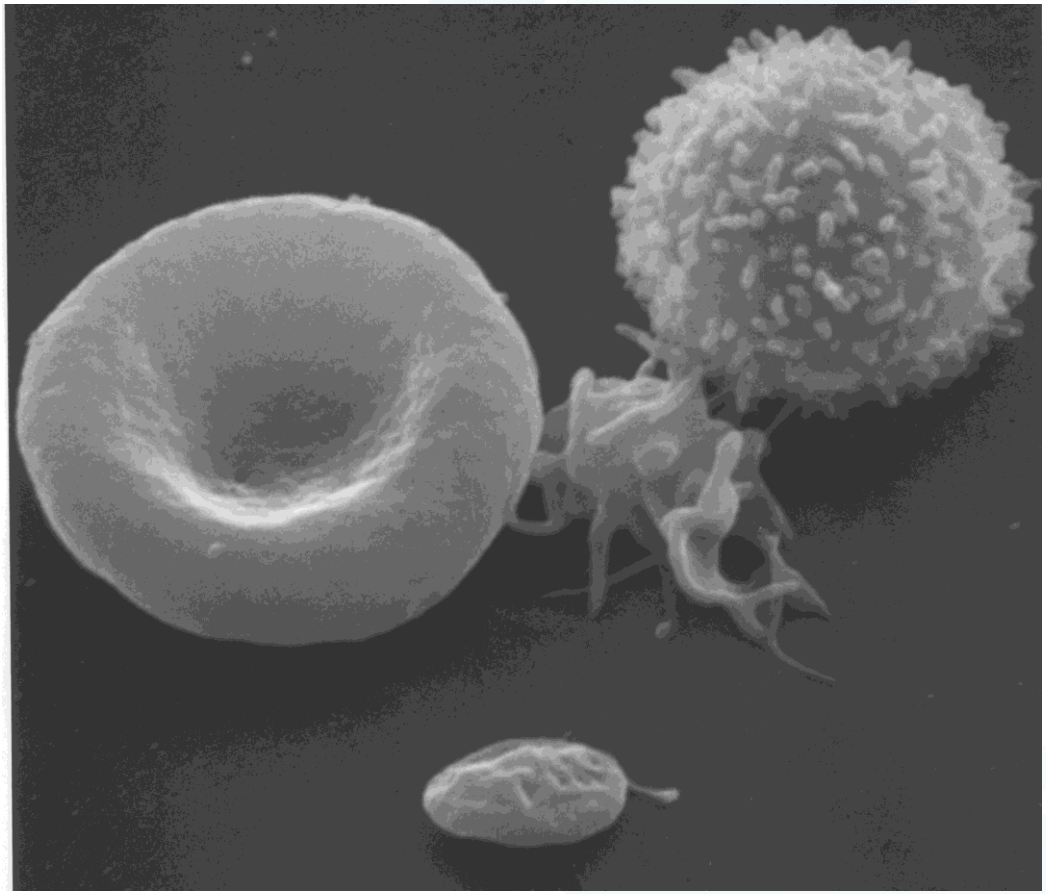
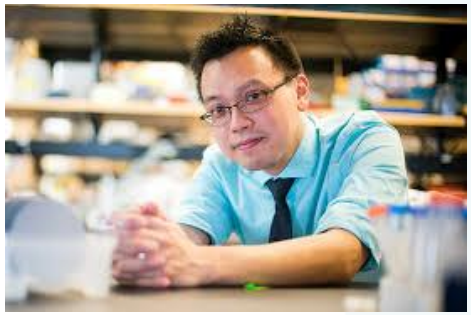
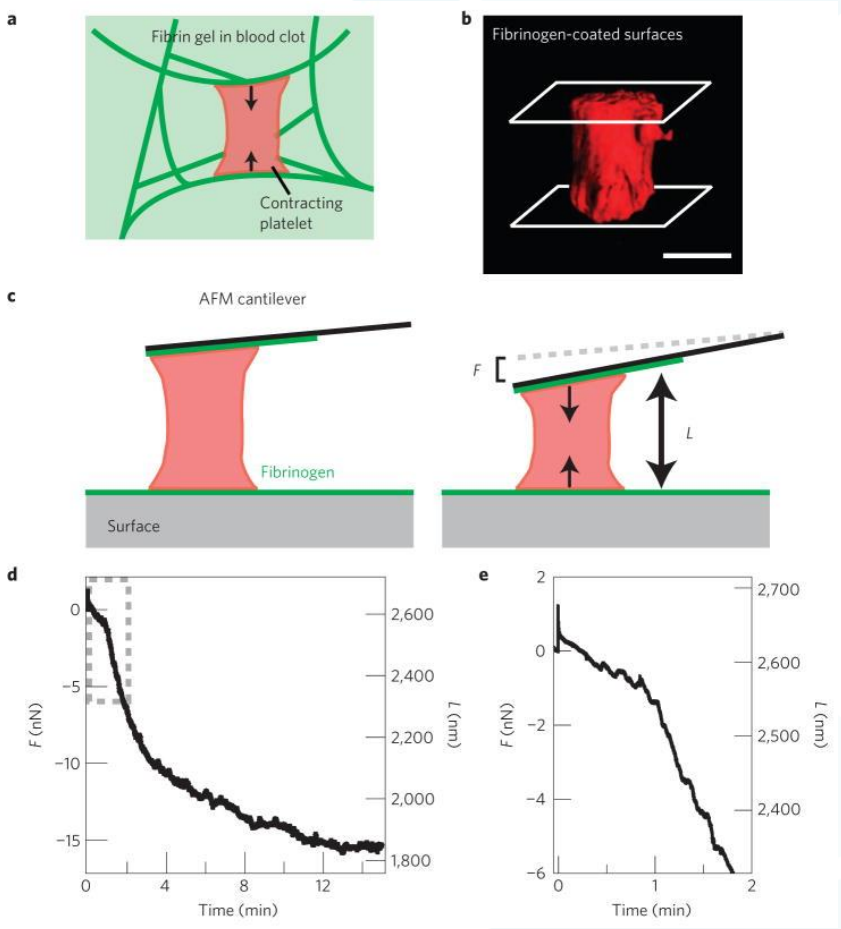


Image courtesy of National Cancer Institute

Platelets and Nanotechnology

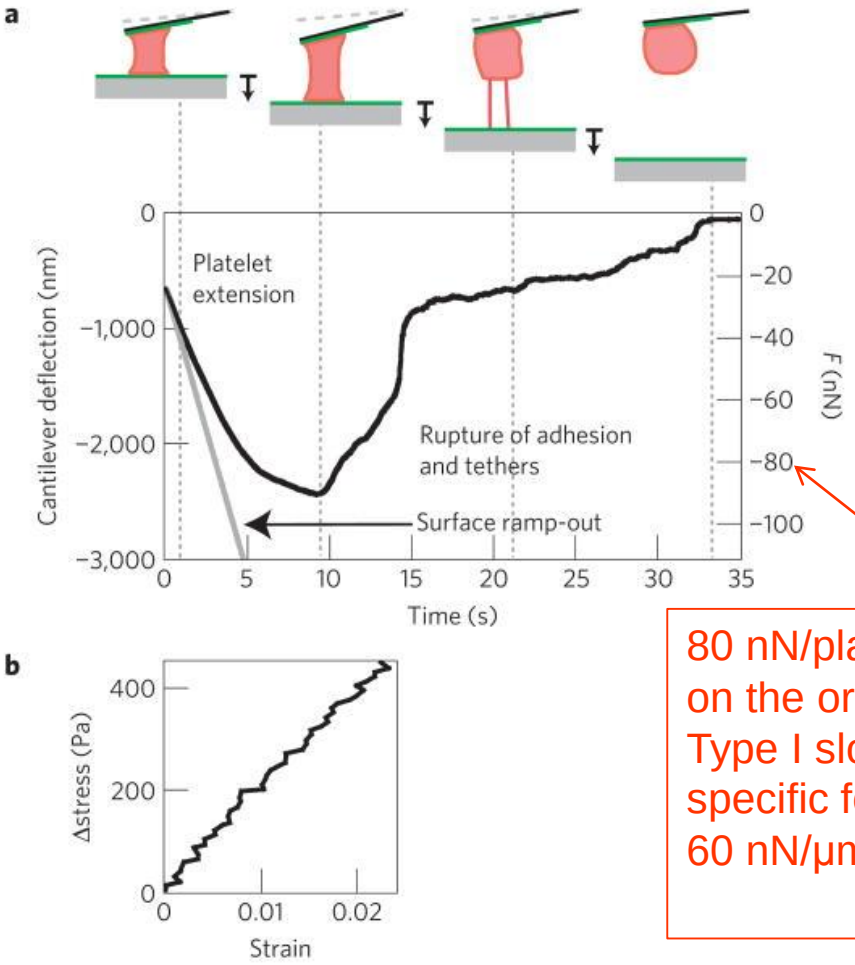


Platelet Mechanics and Contraction



Lam et al. Mechanics and contraction dynamics of single platelets and implications for clot stiffening. *Nat Mater.* 10(1):61-6. 2011.

Platelet Holding Force

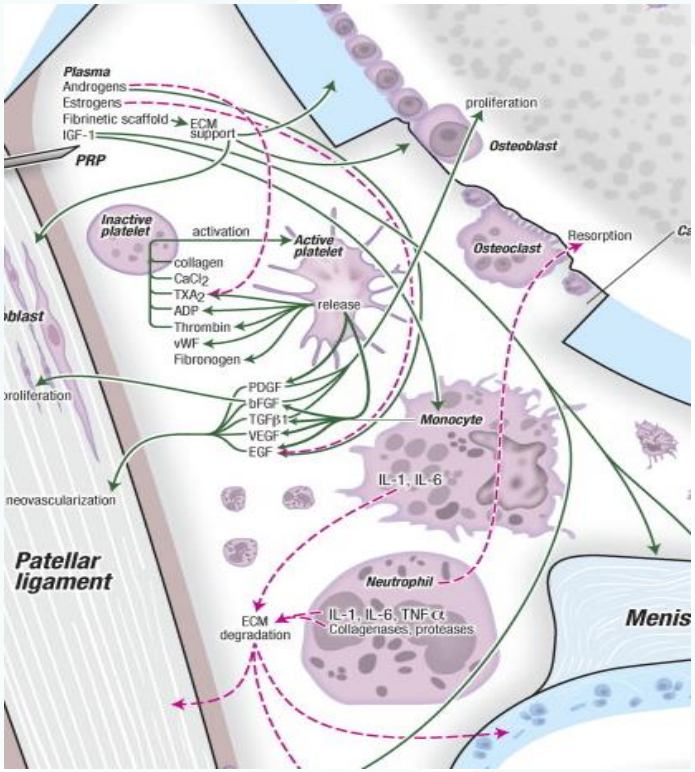


80 nN/platelet ≈ 20 nN/μm^2, on the order of magnitude of Type I slow-twitch muscle fiber specific force ≈ 0.6 kg/cm^2 = 60 nN/μm^2.

Lam et al. Mechanics and contraction dynamics of single platelets and implications for clot stiffening. Nat Mater 10(1):61-6. 2011.

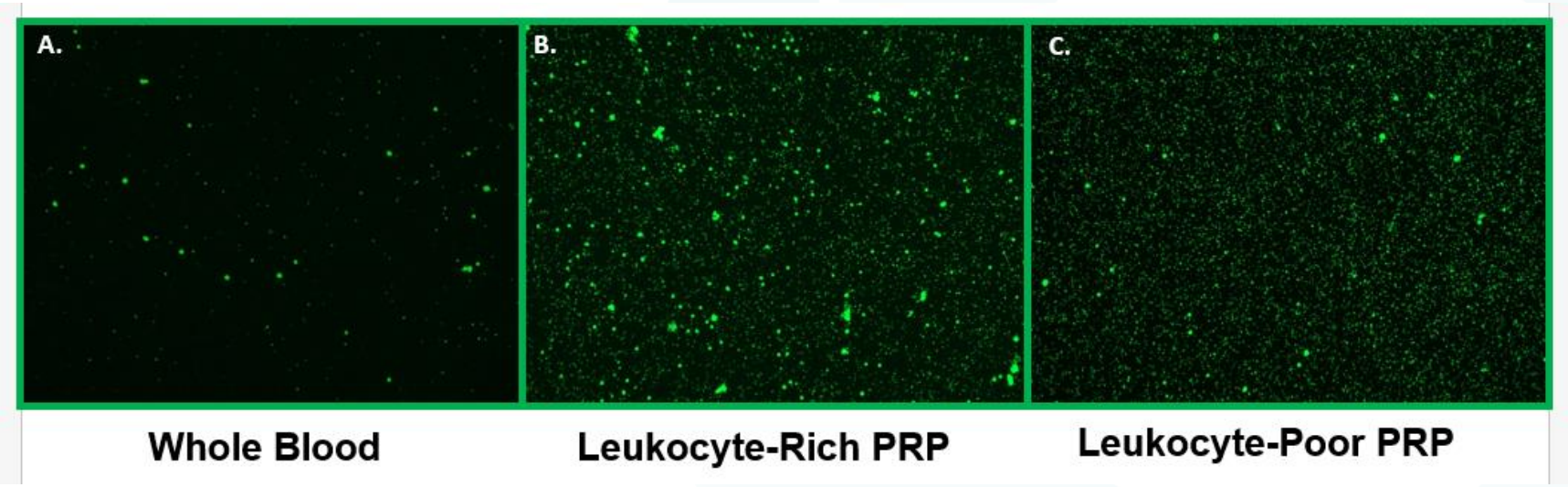
Platelets Secrete Growth Factors

- Platelet Derived Growth Factor (PDGF)
- Vascular Endothelial Growth Factor (VEGF)
- Transforming Growth Factor β (TGFβ)
- Epidermal Growth Factor (EGF)
- And many more GFs



Boswell SG et al. Platelet-rich plasma: a milieu of bioactive factors. *Arthroscopy.* 2012*;* 28:429-439.

Platelet Concentrates/Platelet Rich Plasma



Calcein Fluorescein Dye Microscopy

PRP for Knee Osteoarthritis

6 Level I studies using Leukocyte Poor PRP.

Riboh JC et al. Effect of Leukocyte Concentration on the Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis. *Am J Sports Med.* 2016 Mar;44(3):792-800.

PRP for Tendinopathy

8 Level I studies using Leukocyte Rich PRP.

1 Level I study using Leukocyte Poor PRP.

Fitzpatrick J, Bulsara M & Zheng MH. The Effectiveness of Platelet-Rich Plasma in the Treatment of Tendinopathy. *Am J Sports Med.* 2017; 45:226-233.

PRP for Tendinopathy

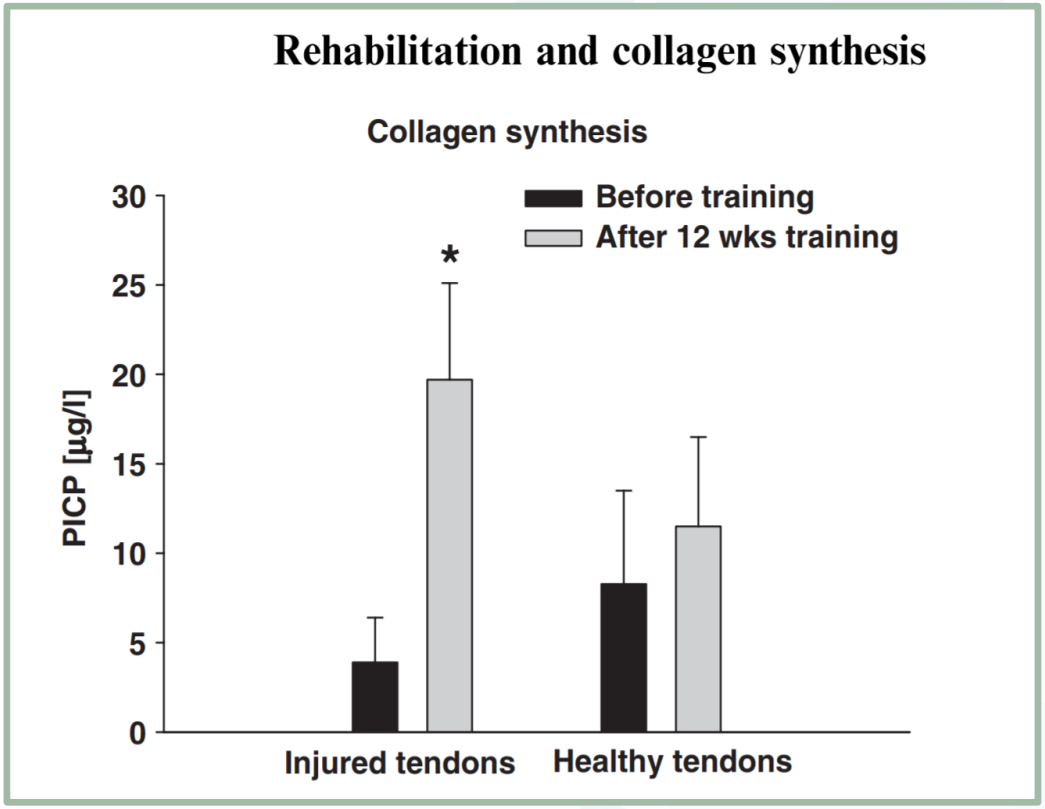
RCT for Achilles Tendinopathy (54 pts)

At 6 months, no difference in:

- Eccentric Exercise + 2 ml Marcaine + 4 ml PRP
- Eccentric Exercise + 2 ml Marcaine + 4 ml Saline

De Vos RJ, Weir A, van Schie H et al. Platelet-Rich Plasma Injection for Chronic Achilles Tendinopathy. A Randomized Controlled Trial. JAMA. 2010:303(2);144-149.

Eccentric Training and Type I Collagen



Langberg H, Ellingsgaard H, Madsen T et al. Eccentric Rehabilitation Exercise Increases Peritendinous I Collagen Synthesis in Humans with Achilles Tendinosis. *Scand J Med Sci Sports*. 2007:17;61-66.

PRP for Tendinopathy

Double Blind RCT for Tennis Elbow (60 pts)

At 3 months, no difference in:

10-15 ml Lidocaine 1% +

- 3 ml PRP or
- 3 ml Kenalog 40 mg or
- 3 ml Normal Saline

Krogh TP et al. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. Am J Sports Med. 2013 Mar;41(3):625-35

PRP for Tendinopathy

Double Blind RCT for Tennis Elbow (230 pts)

At 6 months, improvement in:

84% of 2 to 3 ml PRP Group

68% of 2 to 3 ml Bupivacaine Group

Mishra AK et al. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. Am J Sports Med. 2014 Feb;42(2

Acute MCL Injury

Curry injury update: Grade 1 MCL sprain, out two weeks or more

," said Dr. **Marko Bodor**, a sports-medicine and r
Queen of the **Valley Medical Center** in Napa. "I
xcellent for complete recovery in a matter of three

Acute MCL Injury in Rabbits

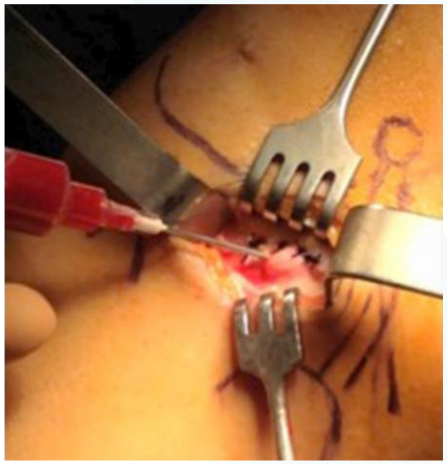
No difference following:

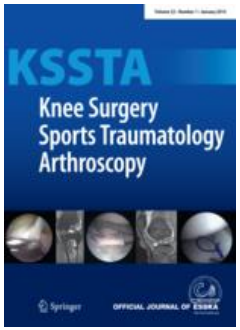
Normal Saline, PPP, or 2x PRP.

4x PRP were weaker.

LaPrade et al. Use of Platelet-Rich Plasma Immediately After an Injury Did Not Improve Ligament Healing, and Increasing Platelet Concentrations Was Detrimental in an In Vivo Animal Model. Am J Sports Med. 2018 Mar;46(3):702-712.

PRP during Surgery?

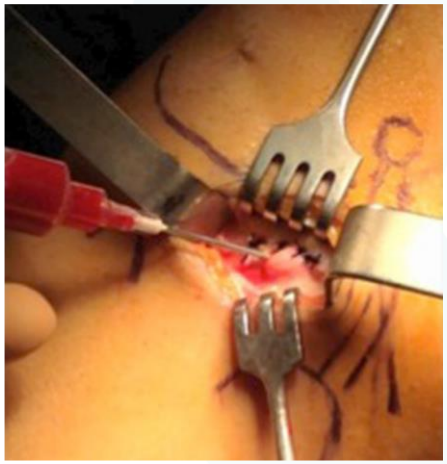


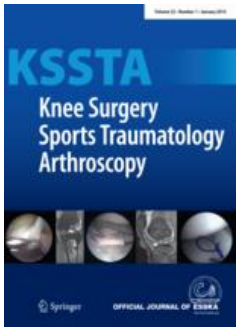


Pujol N et al. Platelet-rich plasma for open meniscal repair in young patients: any benefit? Knee Surg Sports Traumatol Arthrosc. 2015 Jan;23(1):51-8

PRP during Surgery?

Majority of studies show lack of efficacy.





Pujol N et al. Platelet-rich plasma for open meniscal repair in young patients: any benefit? Knee Surg Sports Traumatol Arthrosc. 2015 Jan;23(1):51-8

Platelets for Healing and Repair

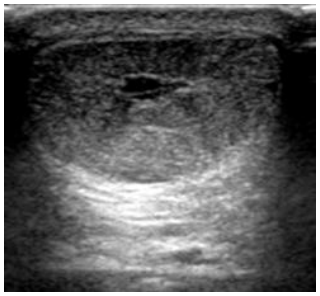
Since 2007, our best outcomes have been in:

- avascular zones

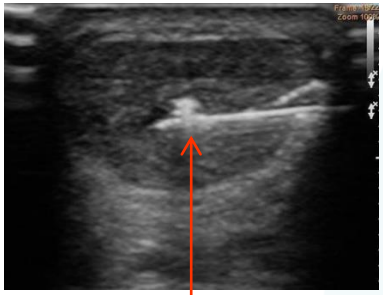
- where a distinct tear or defect is present

- where a broad surface area or scaffold present

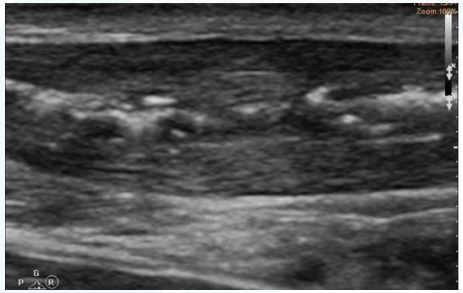
Chronic Achilles Tendon Tear

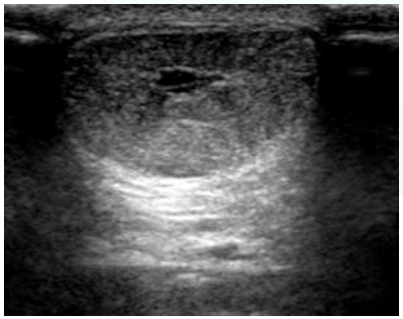


0 wks



PRP injected while on Plavix





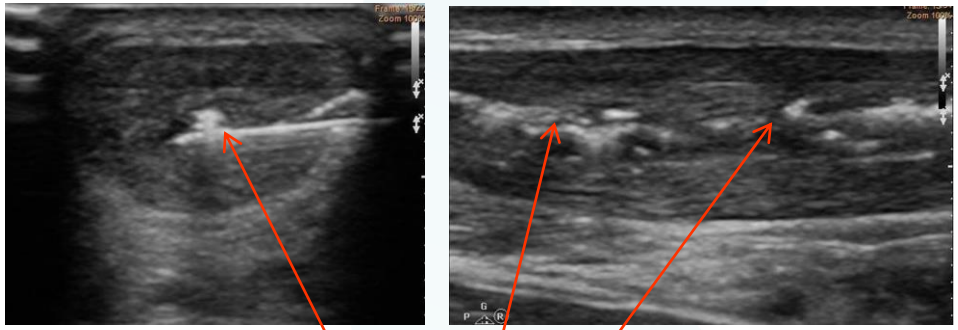
6 wks

PRP repeated while off Plavix

7.5 wks

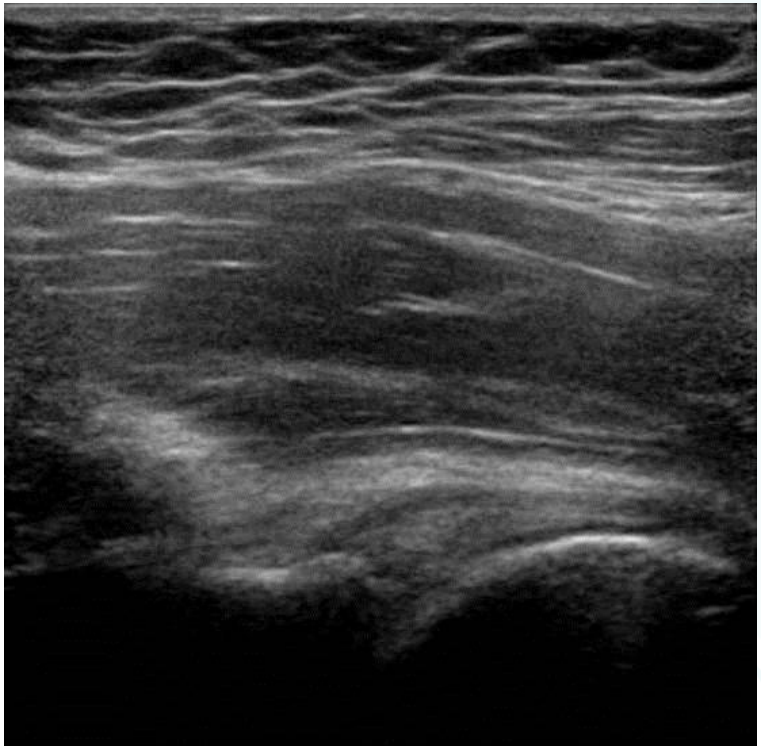
10 wks

Chronic Achilles Tendon Tear



Size of defect = 0.3 cm x 0.3 cm x 9.0 cm = 0.81 cm^3 = 0.8 ml

Chronic Hip Labrum Tear

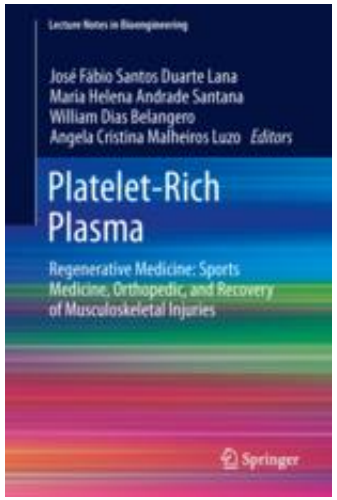


PRP for Discs Case Series

58 pts, CLBP ≥ 1 year; (+) response to anesthetic discography.

2.5x LP-PRP 1-2 ml at 1-2 levels.

58% (21/36) of all and 73% (16/22) of disc-pain-only patients had a good (significant improvement) or excellent (substantial resolution of pain) response at 2-3 months.



Bodor M, Toy A, Aufiero. Disc Regeneration with Growth Factors. In: Platelet Rich Plasma: Lectures in Bioengineering. Springer-Verlag, Heidelberg, 2014.

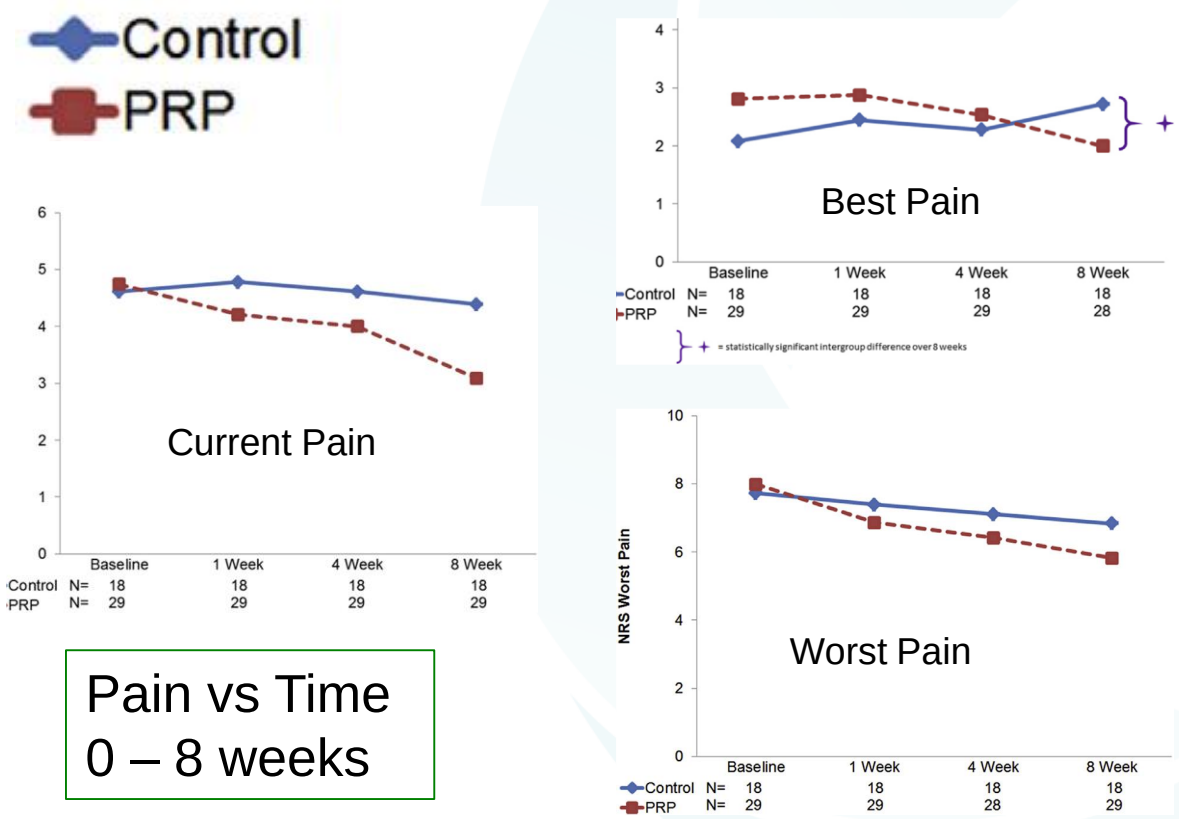
PRP for Discs Double-Blind RCT

LBP > 6 m, annular fissure, concordant pain on discography (47 pts):

-Contrast Dye + LR-PRP (29 pts)
-Contrast Dye only (18 pts)

Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, Harrison JR, Gribbin CK, LaSalle EE, Nguyen JT, Solomon JL, Lutz GE. Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study. *PMR.* 2016

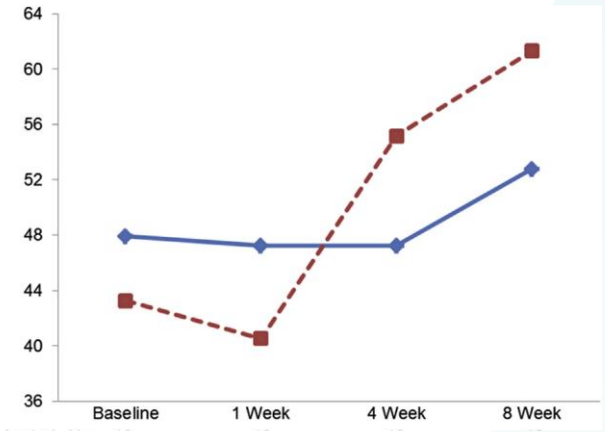
PRP for Discs Double-Blind RCT



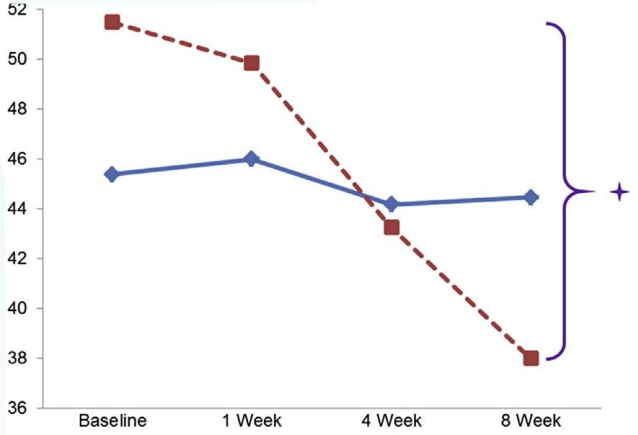
Pain vs Time
0 – 8 weeks

Tuakli-Wosornu et al. Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: Prospective, Double-Blind, Randomized Controlled Study. *PMR.* 2016

PRP for Discs Double-Blind RCT



SF-36

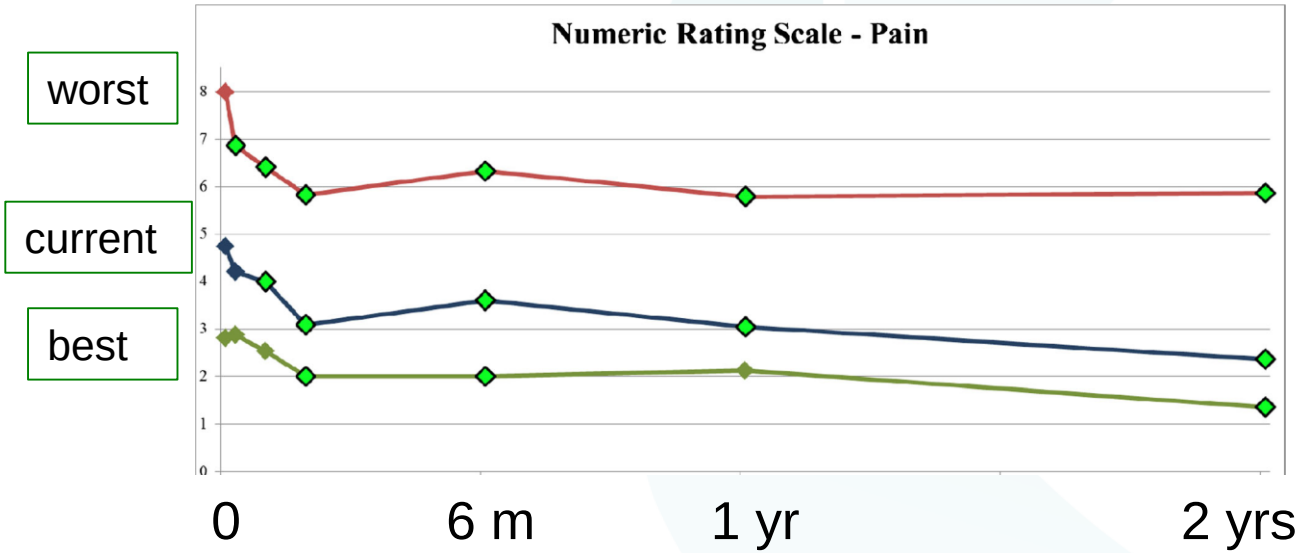


Functional Rating Index

Control
PRP

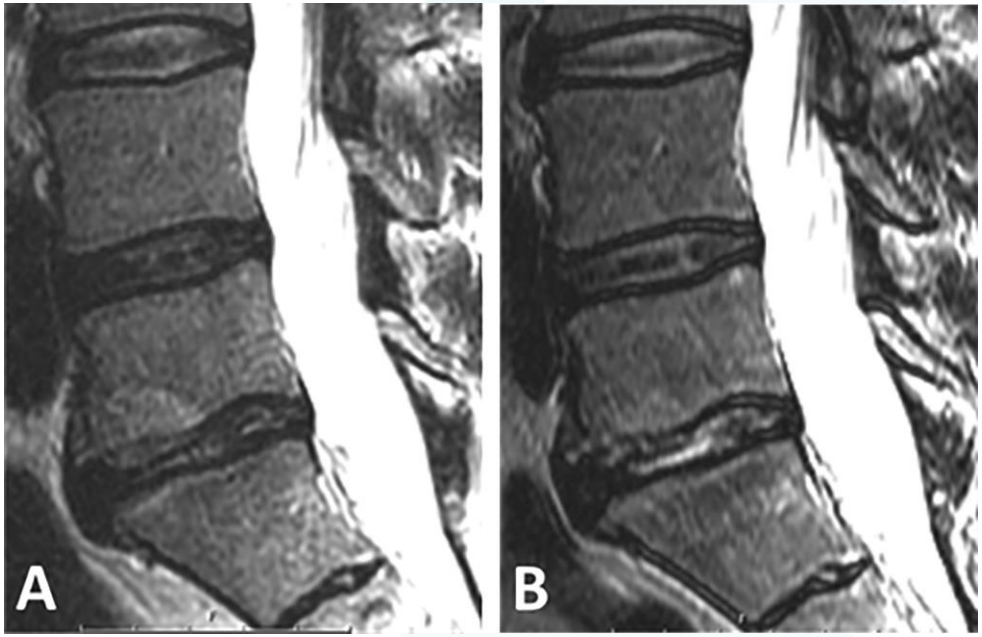
Tuakli-Wosornu et al. Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: Prospective, Double-Blind, Randomized Controlled Study. *PMR.* 2016

PRP for Discs Double-Blind RCT



Monfett M, Harrison J, Boachie-Adjei K, Lutz G. Intradiscal platelet-rich plasma (PRP) injections for discogenic low back pain: an update. *Int Orthop.* 2016;40(6):1321-8.

PRP for Discs Double-Blind RCT



MRI before and 1 year after L5-S1 PRP

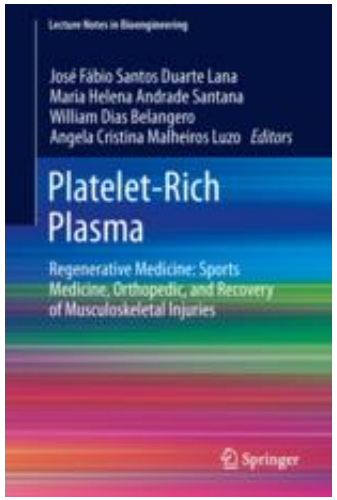
Lutz, GE. Increased Nuclear T2 Signal Intensity and Improved Function and Pain in a Patient One Year After an Intradiscal Platelet–Rich Plasma Injection.

PRP for Discs Case Series

As of 4/19/19, 308 patients and 723 discs treated, 60-70% of disc-pain-only have had a good to excellent response.

4 pts got worse, 3 had good outcomes when an additional disc was injected;1 declined additional treatment.

No nerve injuries or infections. Several vasovagal responses.



Bodor M, Toy A, Aufiero. Disc Regeneration with Growth Factors. In: Platelet Rich Plasma: Lectures in Bioengineering. Springer-Verlag, Heidelberg, 2014.

35 yo Large Animal Veterinarian

LBP x 5-6 years

Best Oswestry: 16%
Worst Oswestry: ~40%

Recurrent incidents of severe pain; difficulty working.

Stopped running and doing sports.

35 yo Large Animal Veterinarian

LP-PRP 1 ml to L5-S1.

0 m: Oswestry 16-40%
2 m: Oswestry 8%.
6 m: Oswestry 8%.

Now able to lift, carry, ride horses, sit in car.

Running >10 miles and planning to do a 20 mile trail race.

35 yo Large Animal Veterinarian

LP-PRP
1.5 ml

-11 months

0 m

+ 17 months

40 yo Police Officer

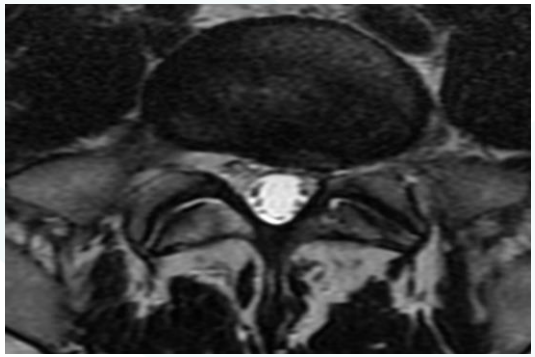
0 m: LBP > 2 yrs, on work comp, has not worked 4 months. Oswestry 24%.

LP-PRP to L5-S1 disc.

2 m: Returned to work.

7 m: Oswestry 9%

Running, cycling, working full-time and gardening.



42 yo Homemaker

LBP since first birth of first child 9 m prior.

0 m pain 8/10
2 m pain 4/10.
6 m pain 1-2/10.
48 m pain 1/10, with intermittent exacerbations.

LP-PRP
1.5 ml

-3 m

0 m

12 m

43 yo office manager

LBP > 25 yrs, 8-9/10 x 3 m, s/p L5-S1 discectomy 1988

0 m: L5-S1 PRP

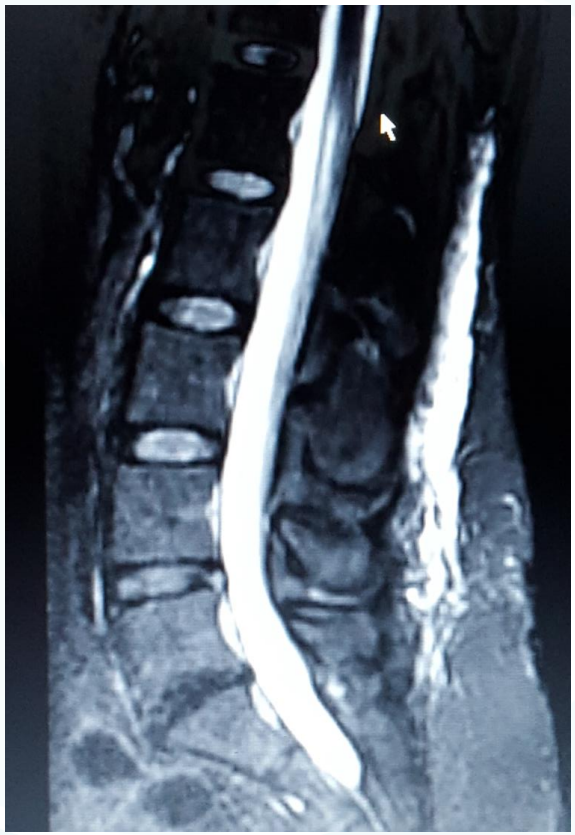
3 m: worse pain

3 m: L4-5 PRP

4 m: pain 1-2/10

8 m: pain 1-2/10

12 m: severe pain recurrence.
She opted for L4-5, L5-S1 fusion.



32 yo Entrepreneur

0 m: LBP >10 years, Oswestry 52%.
LP-PRP to T12-L1, L1-2, L2-3, L5-S1 discs.

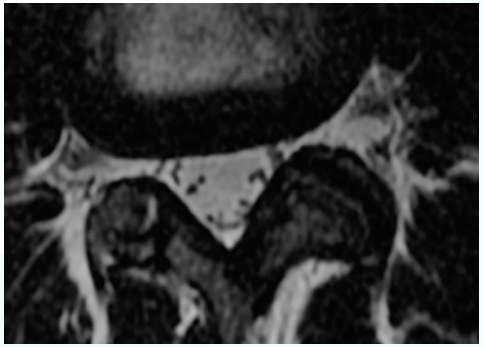
2 m: Oswestry 42%.

3 m: negative response to medial branch blocks L3-4, L4-5, L5-S1

6 m: LP-PRP to L3-4, L4-5 discs.

10 m: Unable to sleep, stand, walk for long periods of time without Tramadol or Vicodin. Oswestry 34%.

17 m: Facet injections provided near complete immediate relief, able to sleep through night.



58 yo Long Distance Runner

LBP since 1990's.

"Unable to sit, stand, walk, or lay without pain."

Best pain: 0/10
Worst pain: 10/10
Best Oswestry: 12%
Worst Oswestry: 54%

PE: Focal tenderness in midline at L5-S1.

58 yo Long Distance Runner

LP-PRP 1.5 ml.
Pain up to 10/10!

- 0 m: Oswestry 12-54%.
- 2 m: Oswestry 0%.
- 3 m: Oswestry 0%, resumed running.
- 12 m: Oswestry 0%, continues to run.

65 yo Business Woman

Low back, hip and thigh pain x 12 years.

PRP to L4-5 and L5-S1 disc and facets.

0 m: Oswestry 22%.
1 m: Oswestry 7%.
2 m: Oswestry 5%.
3 m: Oswestry 0%

Back to tennis and plans to go skiing.

15 m: “Pain starting to return. I had a good year, still better than before.”

72 yo Lawyer

Mild to Moderate Pain > 2 years, Oswestry 8%.

LP-PRP to L4-5 and L5-S1 discs (3 ml + 1 ml).

2 m: No Pain, Oswestry 2%.

4 m: No Pain, Oswestry 2%.

73 yo Weight Lifter

Mild LBP since 1978.
Moderate LBP x 6 months, following lifting injury.
Oswestry 33%.

LP-PRP to L5-S1 disc 1.5 ml

1 m: Mild Pain, Oswestry 10%
2 m: No Pain, Oswestry 5%
12 m: No Pain, Oswestry 0%

LR-PRP Disc Prospective Trial

22 pts, LBP > 6 m, injected with LR-PRP 1.5-3 ml + 1 ml omnipaque + 2 mg gentamicin.

Δ VAS > 50%, Δ ODI > 30% achieved at

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

Levi D et al. Intradiscal Platelet-Rich Plasma Injection for Chronic Discogenic Low Back Pain: Preliminary Results from a Prospective Trial. *Pain Med.* 2016;17(6):1010-22.

LP-PRP to Spine

86 pts, LBP ± sciatica > 3m.
LP-PRP to discs, facets and epidural space.

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.

Alpha-2-Macroglobulin (A2M) for Discs

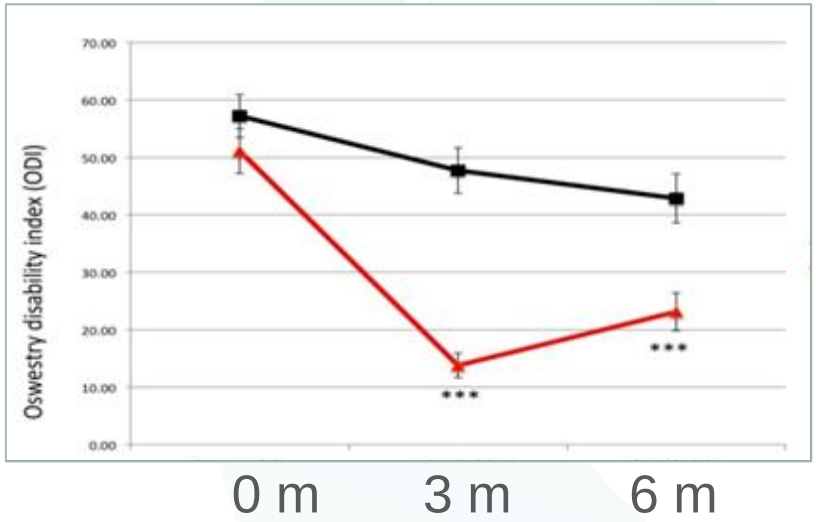
A2M is a protease inhibitor obtained from platelet poor plasma (PPP). Also present in PRP.

24 pts, LBP> 6m, had disc lavage to assess for FAC (Fibronectin-Aggrecan Complex), then were injected with A2M.

Intradiscal Injection of an Autologous Alpha-2-Macroglobulin (A2M) Concentrate Alleviates Back Pain in FAC-Positive Patients. Montesano PX, Cuellar, JM, Scuderi GJ. Orthopedics and Rheumatology Open Access. January 2017

Alpha-2-Macroglobulin (A2M) for Discs

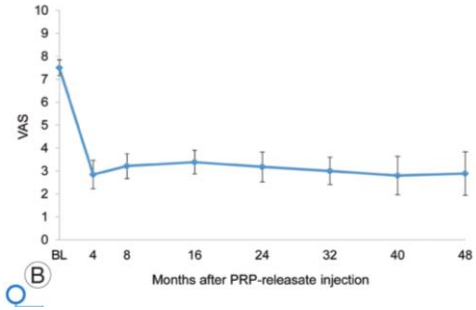
Black = FAC (-)
Red = FAC (+)

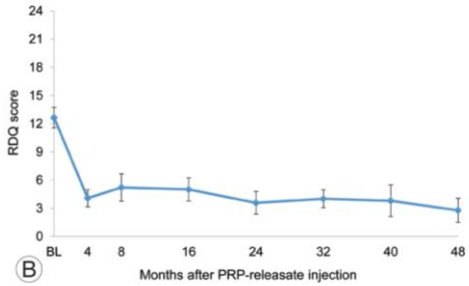


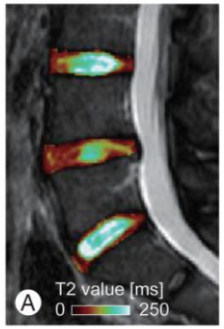
Intradiscal Injection of an Autologous Alpha-2-Macroglobulin (A2M) Concentrate Alleviates Back Pain in FAC-Positive Patients. Montesano PX, Cuellar, JM, Scuderi GJ. Orthopedics and Rheumatology Open Access. January 2017

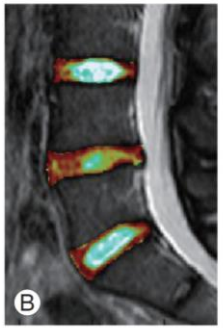
LP-PRP Releasate for Discs

14 pts, (+) anesthetic or provocative discography.
11/14 (79%) had > 50% Δ in VAS and RDQ for 4 years.
Disc height maintained on radiographs and 3 T MRI



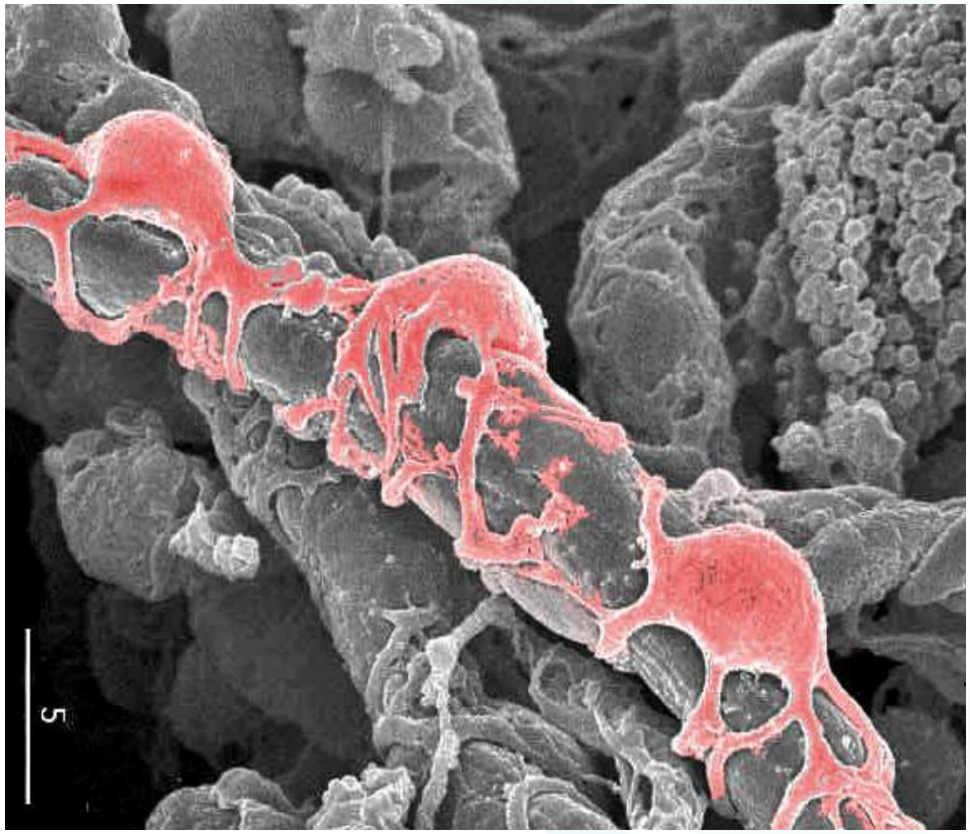






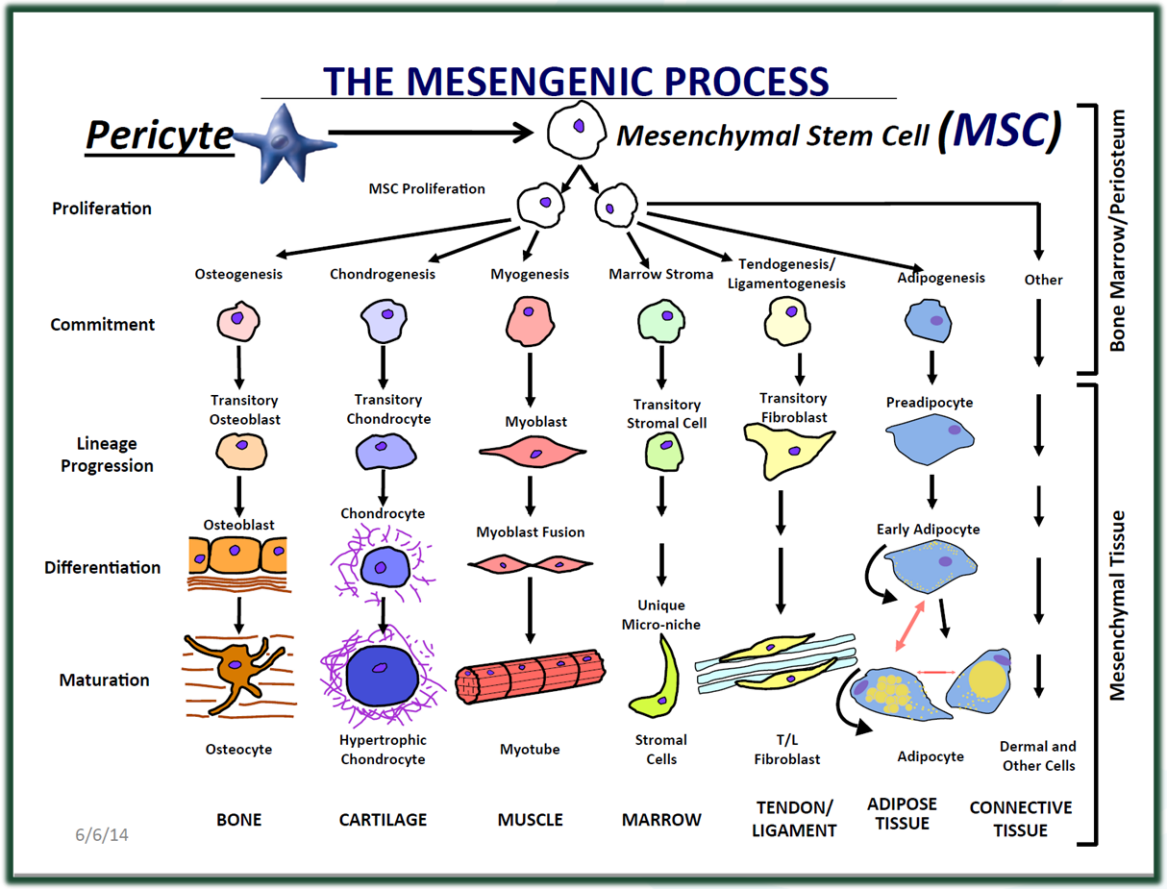
Akeda K, Ohishi K, Masuda K et al. Intradiscal Injection of Autologous Platelet-Rich Plasma Releasate to Treat Discogenic Low Back Pain: A Preliminary Clinical Trial. *Asian Spine Journal*. 2017;11(3):380-389.

Mesenchymal Stem Cells (MSCs)



From Arnold Caplan PhD, Case Western Reserve University, with permission.

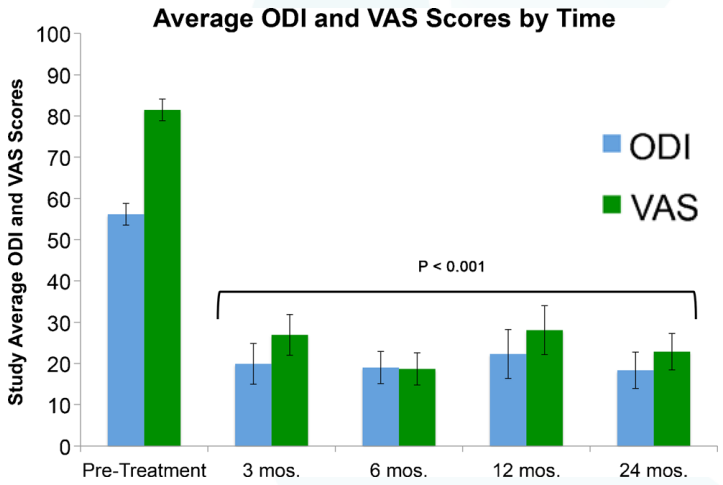
Mesenchymal Stem Cells (MSCs)

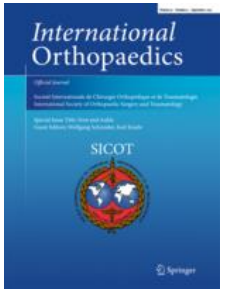


From Arnold Caplan PhD, Case Western Reserve University, with permission.

Bone Marrow Aspirate Concentrate (BMAC) for Discs (aka “Stem Cells”)

26 pts, severe DDD, candidates for fusion.

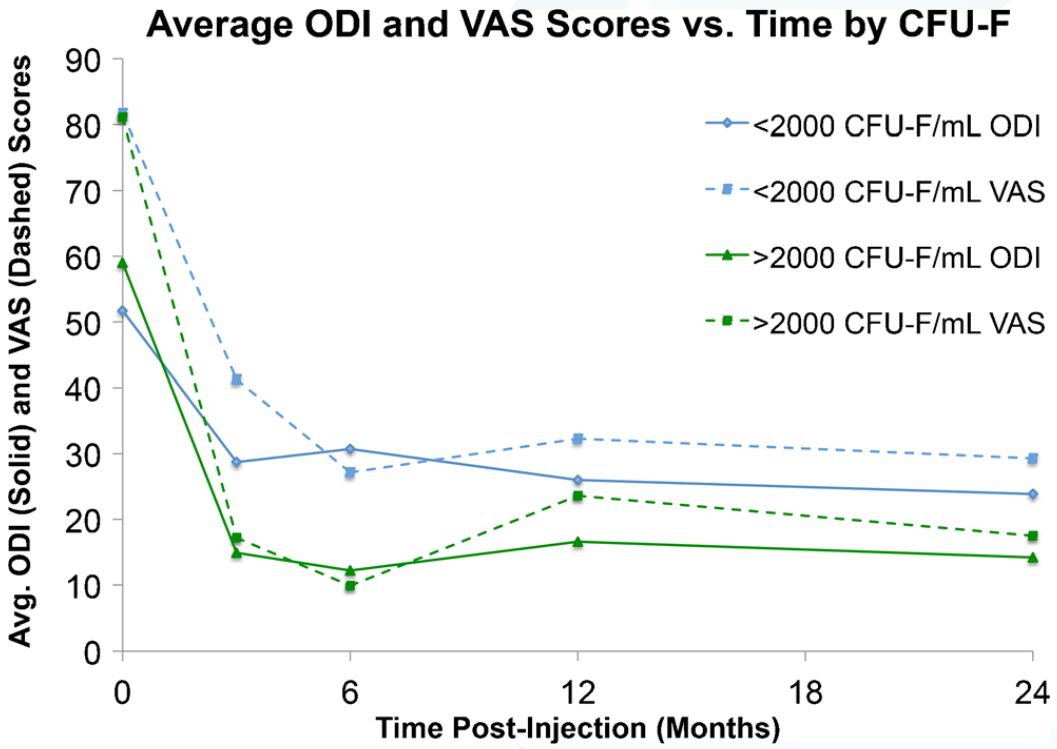


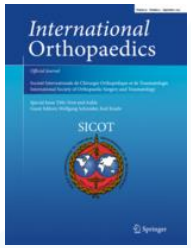


21/26 (80%) avoided surgery at 24 months

Pettine K, Suzuki R, Sand T, Murphy M. Treatment of discogenic back pain with autologous bone marrow concentrate injection with minimum two year follow-up. *Int Orthop.* 2016 Jan;40(1):135-40.

BMAC for Discs

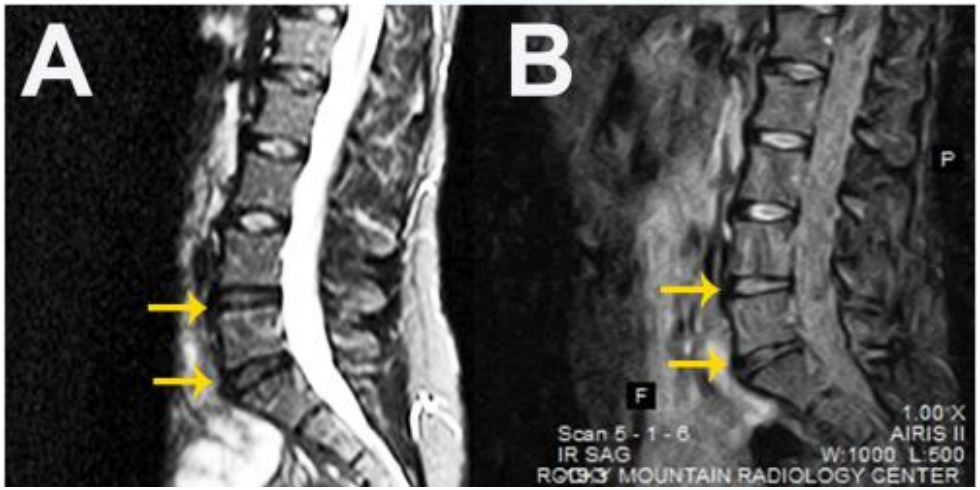


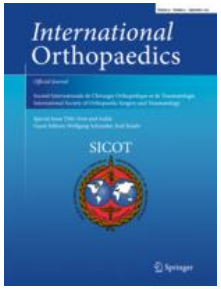


Pettine K, Suzuki R, Sand T, Murphy M. Treatment of discogenic back pain with autologous bone marrow concentrate injection with minimum two year follow-up. *Int Orthop.* 2016 Jan;40(1):135-40.

BMAC for Discs

"MRI improved by 1 Pfirrmann grade in 8/20 patients"



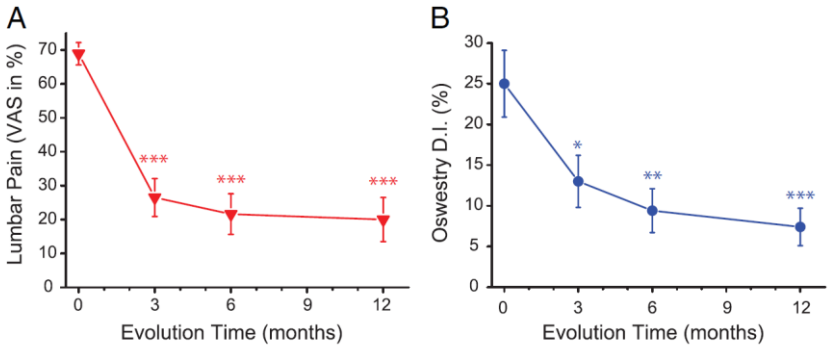


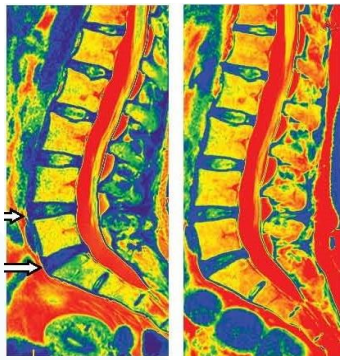
Pettine K, Suzuki R, Sand T, Murphy M. Treatment of discogenic back pain with autologous bone marrow concentrate injection with minimum two year follow-up. *Int Orthop.* 2016 Jan;40(1):135-40.

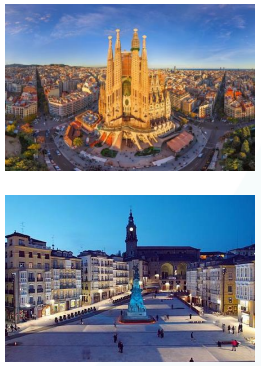
Bone Marrow Cultured MSCs

10 pts, LBP ± sciatica > 6 months, mean age 35, mean number of cells injected 23 million per disc.

"Improved T2 signal on MRI" but not disc height.



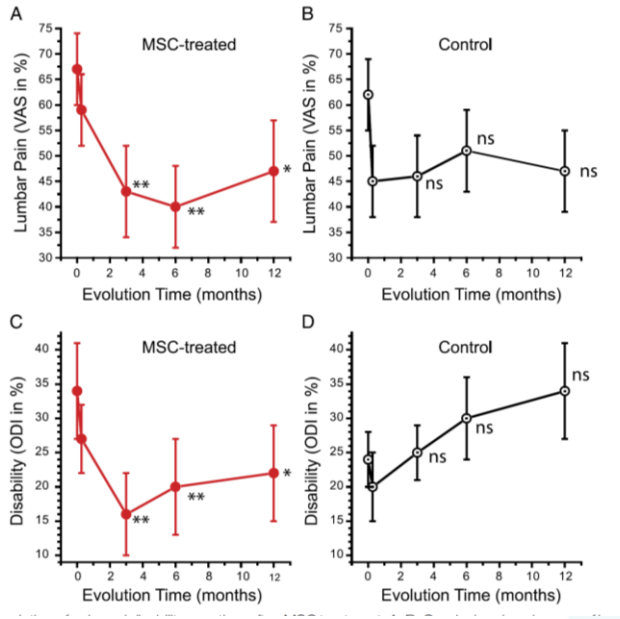




Orozco L et al. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. *Transplantation*. 2011; 92(7):822-8.

Allogeneic Bone Marrow Cultured MSCs

24 pts, cells obtained from 5 donors: “Results not as good as using autologous cells.”



Noriega D, Ardura F, Hernandez-Ramajo R et al. Intervertebral Disc Repair by Allogeneic Mesenchymal Bone Marrow Cells: A Randomized Control Trial. *Transplantation.* 2017:101(8);1945-1951.

Allogeneic Cultured Bone Marrow MSCs RCT

Mesoblast Study

100 patients, 4 groups:

1) HA + 6 million MSCs, 2) HA + 18 million MSCs
3) Hyaluronic Acid, and 4) Saline

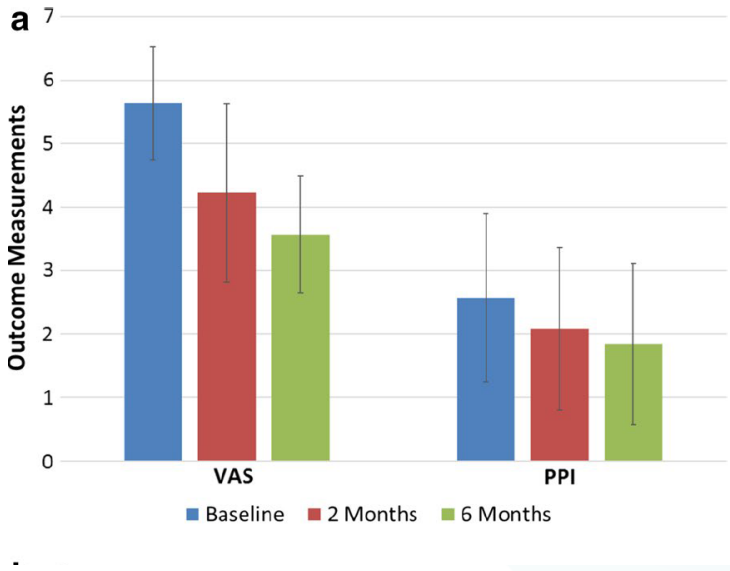
>50% improvement in VAS was achieved
up to 36 months in:

39% of HA + 6M MSCs
35% of HA + 18M MSCs
18% of HA
13% of saline

DePalma, M. Abstract from SIS 2016 Meeting, Pain 2016.
www.mesoblast.com

Adipose MSCs + PRP

15 patients, CLBP > 6 m.

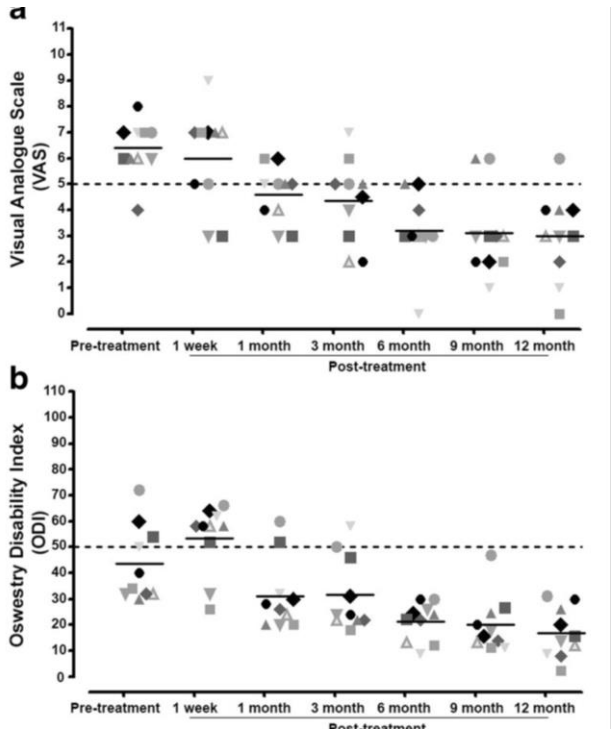


Journal of Translational Medicine

Comella and US Stem Cell stopped by the FDA May 2018!

Comella K, Silbert R, Parlo M. Effects of the Intradiscal Implantation of Stromal Vascular Fraction Plus Platelet Rich Plasma In Patients with Degenerative Disc Disease. *J Transl Med.* 2017;15(12):1-8.

Adipose Cultured MSCs + Hyaluronic Acid



10 patients, CLBP > 3 m.

Stem Cell Research & Therapy

Kumar H, Ha D, Lee E et al. Safety and Tolerability of Intradiscal Implantation of Combined Autologous Adipose-Derived Mesenchymal Stem Cells and Hyaluronic Acid in Patients with Chronic Discogenic Low Back Pain: 1-year follow-up of a Phase I Study. *Stem Cell Research & Therapy.* 2017:8(262);1-14.

Take Home Points

1) 8 Level I studies show positive results for PRP for chronic tendinopathy.

2) 6 Level I studies show positive results for LP-PRP for knee osteoarthritis.

3) 1 Level I study shows positive results for LR-PRP for discogenic back pain.

4) There is no evidence that PRP or BMAC can regenerate discs.

Practice and Research Gaps

1) Is PRP better than saline? Additional RCTs would be desirable.

2) Is LP-PRP better than LR-PRP for discs? Is BMAC indicated and when?

3) Who are the best candidates and which discs?

Marko Bodor MD

Physical Medicine and Rehabilitation,
Spine and Sports Medicine
Napa, California

Assistant Professor
Departments of Neurological Surgery
University of California San Francisco
Physical Medicine and Rehabilitation
University of California Davis

References

1. Yoshikawa T, Ueda Y, Miyazaki K, Koizumi M, Takakura Y. Disc regeneration therapy using marrow mesenchymal cell transplantation: a report of two case studies. Spine. 2010;35(11):E475-480.
2. Orozco L, Soler R, Morera C, Alberca M, Sánchez A, García-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. Transplantation. 2011; 92(7):822-8.
3. Goodman BS, Sowa GA, Buzanowska M, Willey MR, Smith MT, Mallempati S, Kennedy DJ. Intradiskal steroids: a viable treatment for low back pain? PM R. 2014; 6(6):547-55.
4. Pang X, Yang H, Peng B. Human umbilical cord mesenchymal stem cell transplantation for the treatment of chronic discogenic low back pain. Pain Physician. 2014;17(4):E525-30.
5. Pettine K, Murphy M, Suzuki R, Sand T. Percutaneous Injection of Autologous Bone Marrow Concentrate Cells Significantly Reduces Lumbar Discogenic Pain through 12 Months. Stem Cells Translational and Clinical Research. 2014; 1-17.
6. Mochida J, Sakai D, Nakamura Y, Watanabe T, Yamamoto Y, Kato S. Intervertebral disc repair with activated nucleus pulposus cell transplantation: a three-year, prospective clinical study of its safety. *Eur Cell Mater.* 2015;29:202-12.
7. Wang Z, Perez-Terzic CM, Smith J, Mauck WD, Shelerud RA et al. Efficacy of intervertebral disc regeneration with stem cells - a systematic review and meta-analysis of animal controlled trials. *Gene.* 2015;564(1):1-8.
8. Zeckser J, Wolff M, Tucker J, Goodwin J. Multipotent Mesenchymal Stem Cell Treatment for Discogenic Low Back Pain and Disc Degeneration. *Stem Cells International.* 2016; 1-14.
9. Bhatia R, Chopra G. Efficacy of Platelet Rich Plasma via Lumbar Epidural Route in Chronic Prolapsed Intervertebral Disc Patients-A Pilot Study. *J Clin Diagn Res.* 2016;10(9):UC05-UC07.

References (continued)

10. Elabd C, Centeno CJ, Schultz JR, Lutz G, Ichim T, Silva FJ. Intra-discal injection of autologous, hypoxic cultured bone marrow-derived mesenchymal stem cells in five patients with chronic lower back pain: a long-term safety and feasibility study. *J Transl Med.* 2016;14:253.

11. Holton J, Imam M, Ward J, Snow M. The Basic Science of Bone Marrow Aspirate Concentrate in Chondral Injuries. *Orthop Rev (Pavia).* 2016;8(3):80-84

12. Levi D, Horn S, Tyszko S, Levin J, Hecht-Leavitt C, Walko E. Intradiscal Platelet-Rich Plasma Injection for Chronic Discogenic Low Back Pain: Preliminary Results from a Prospective Trial. *Pain Med.* 2016;17(6):1010-22.

13. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, Harrison JR, Gribbin CK, LaSalle EE et al. Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study. *PM R.* 2016 Jan;8(1):1-10.

14. Monfett M, Harrison J, Boachie-Adjei K, Lutz G. Intradiscal platelet-rich plasma (PRP) injections for discogenic low back pain: an update. *Int Orthop.* 2016;40(6):1321-8.

15. Pettine K, Suzuki R, Sand T, Murphy M. Treatment of discogenic back pain with autologous bone marrow concentrate injection with minimum two year follow-up. *Int Orthop.* 2016;40(1):135-40.

16. Basso M, Cavagnaro L, Zanirato A, Divano S et al. What is the clinical evidence on regenerative medicine in intervertebral disc degeneration? *Musculoskelet Surg*. 2017; ahead of print.

17. Montesano P, Cuellar J, Scuderi G. Intradiscal Injection of an Autologous Alpha-2-Macroglobulin (A2M) Concentrate Alleviates Back Pain in FAC-positive Patients. *Orthopedics and Rheumatology.* 2017;4(2):1-5.

References (continued)

18. Akeda K, Ohishi K, Masuda K et al. Intradiscal Injection of Autologous Platelet-Rich Plasma Releasate to Treat Discogenic Low Back Pain: A Preliminary Clinical Trial. *Asian Spine Journal*. 2017;11(3):380-389.

19. Cheng X, Zhang G, Zhang L et al. Mesenchymal Stem Cells Deliver Exogenous miR-21 via Exosomes to Inhibit Nucleus Pulposus Cell Apoptosis and Reduce Intervertebral Disc Degeneration. *J. Cell. Mol. Med.* 2018;22(1):261-276.

20. Comella K, Silbert R, Parlo M. Effects of the Intradiscal Implantation of Stromal Vascular Fraction Plus Platelet Rich Plasma In Patients with Degenerative Disc Disease. *J Transl Med.* 2017;15(12):1-8.

21. Kumar H, Ha D, Lee E et al. Safety and Tolerability of Intradiscal Implantation of Combined Autologous Adipose-Derived Mesenchymal Stem Cells and Hyaluronic Acid in Patients with Chronic Discogenic Low Back Pain: 1-year follow-up of a Phase I Study. *Stem Cell Research & Therapy.* 2017:8(262);1-14.

22. Noriega D, Ardura F, Hernandez-Ramajo R et al. Intervertebral Disc Repair by Allogeneic Mesenchymal Bone Marrow Cells: A Randomized Control Trial. *Transplantation.* 2017:101(8);1945-1951.

23. Pettine K, Suzuki RK, Sand T et al. Autologous Bone Marrow Concentrate Intradiscal Injection for the Treatment of Degenerative Disc Disease with Three-Year Follow-up. *International Orthopaedics.* 2017:41;2097-2103.

24. Pang H, Bow C, Cheung J et al. The UTE Disc Sign on MRI: A Novel Imaging Biomarker Associated with Degenerative Spine Changes, Low Back Pain and Disability. *Spine.* 2018:43(7);503-511.

References (continued)

25. Meisel HJ, Ganey T, Hutton WC et al. Clinical Experience in Cell-based Therapeutics: Intervention and Outcome. *Eur Spine J*. 2006:15;S397-S405.

26. Meisel HJ, Siodla Vilma, Ganey T et al. Clinical Experience in Cell-based Therapeutics: Disc Chondrocyte Transplantation A Treatment for Degenerated or Damaged Intervertebral Disc. *Biomolecular Engineering.* 2007:24;5-21.

27. Tschugg A, Diepers M, Simone S et al. A Prospective Randomized Multicenter Phase I/II Clinical Trial to Evaluate Safety and Efficacy of NOVOCART Disc Plus Autologous Disk Chondrocyte Transplantation in the Treatment of Nucleotomized and Degenerative Lumbar Disks to Avoid Secondary Disease: Safety Results of Phase I – A Short Report. *Neurosurg Rev.* 2017:40;155-162.

28. Reeves KD, Mathews RS, Miller M. Treatment of Painful Advanced Internal Lumbar Disc Derangement with Intradiscal Injection of Hypertonic Dextrose. *Pain Physician*. 2006:9(2);115-121.

29. Friedman BW, Dym A, Davitt M et al. Naproxen with Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial. JAMA. 2015:314(15);1572-1580.

30. De Vos RJ, Weir A, van Schie H et al. Platelet-Rich Plasma Injection for Chronic Achilles Tendinopathy. A Randomized Controlled Trial. JAMA. 2010:303(2);144-149.

31. Langberg H, Ellingsgaard H, Madsen T et al. Eccentric Rehabilitation Exercise Increases Peritendinous I Collagen Synthesis in Humans with Achilles Tendinosis. *Scand J Med Sci Sports*. 2007:17;61-66.

32. Krogh T, Ellingsen T, Christensen R et al. Ultrasound-Guided Injection Therapy of Achilles Tendinopathy With Platelet-Rich Plasma or Saline. A Randomized, Blinded, Placebo-Controlled Trial. *AJSM.* 2016:44(8);1990-1997.

#1) Which of the following is not released by platelets?

A. Platelet Derived Growth Factor (PDGF)

B. Vascular Endothelial Growth Factor (VEGF)

C. Transforming Growth Factor β (TGFβ)

D. Epidermal Growth Factor (EGF)

E. Growth Hormone

#2) Which of the following has Level I evidence for knee osteoarthritis pain?

A. Leukocyte Rich Platelet Rich plasma

B. Leukocyte Poor Platelet Rich plasma

C. Platelet Poor plasma

D. Platelet Releasate

E. Normal Saline

#3) Which of the following is true for nucleus pulposus (NP) cells?

A. NP cells are present at concentrations of 9,000,000/mm3.

B. NP cells are concentrated next to matrix defects.

C. NP cells do not have stem cell markers after the age of 10.

D. NP cells can be derived from injected bone marrow mesenchymal stem cells in vivo.

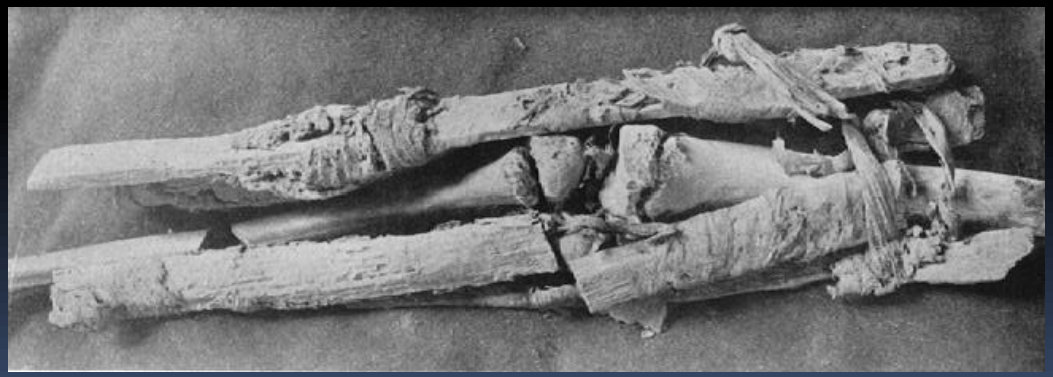
#4) There is good evidence to show disc height can be improved with bone marrow stem cells.

A. True

B. False

What is the purpose for pain?

1) Intrusion Alert
2) Avoidance of Injury
3) Guide to Optimizing the Environment for Healing



Corticosteroid for Tendinopathy

RCT for Tennis Elbow (84 pts)

At 1 year, persistent symptoms in:

17% of Corticosteroid Injection Group

4% of Lidocaine Injection Group

Coombes BK et al. Effect of corticosteroid injection, physiotherapy, or both on clinical outcomes in patients with unilateral lateral epicondylalgia: a randomized controlled trial. *JAMA.* 2013; 309: 461-469.

Bone Marrow Hypoxic Cultured MSCs

L5-S1 discs of patients with LBP 3 months to 5 years were injected with ~26 million cells: All patients remained improved at 5 years with no neoplasms or side effects.

Elabd C, Centeno CJ, Schultz JR, Lutz G, Ichim T, Silva FJ. Intra-discal injection of autologous, hypoxic cultured bone marrow-derived mesenchymal stem cells in five patients with chronic lower back pain: a long-term safety and feasibility study. *J Transl Med.* 2016;14:253

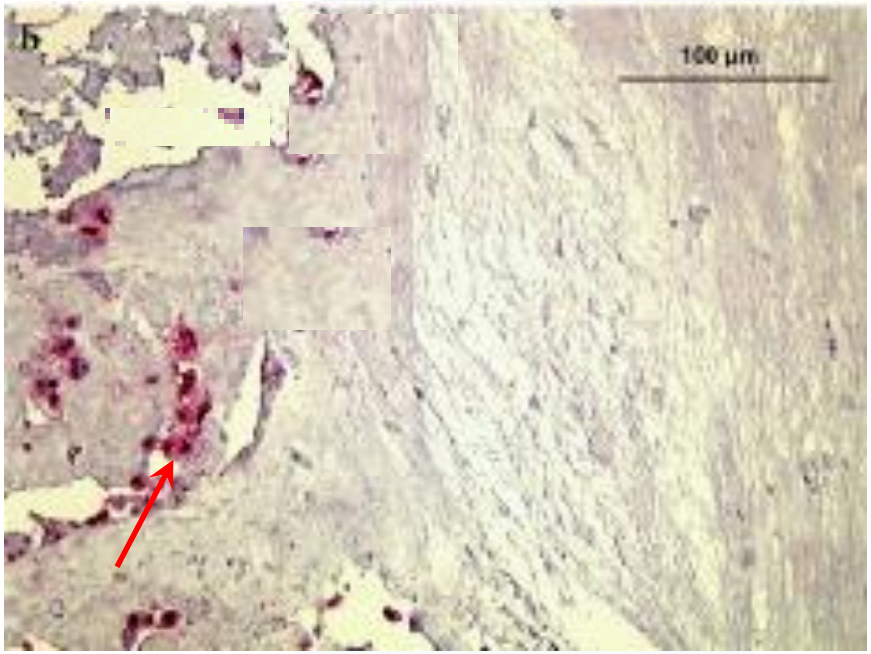
49 Yr Old

Pre-BMAC

6 mos. Post-BMAC

1 yr. Post-BMAC

Normal Disc Microanatomy



NP cells cluster adjacent to matrix defects

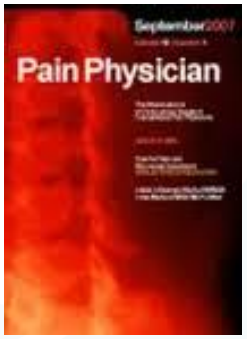
Weiler C, Nerlich AG, Schaaf R, Bachmeier BE, Wuertz K, Boos N. Immunohistochemical identification of notochordal markers in cells in the aging human lumbar intervertebral disc. *Eur Spine J.* 2010.

Hypertonic Dextrose

76 patients, provocative CT discography positive.

3 to 4 injections of dextrose/bupivacaine 2 wks apart

43% of pts had sustained response of 70% reduction in VAS.



Reeves KD, Mathews RS, Miller M. Treatment of Painful Advanced Internal Lumbar Disc Derangement with Intradiscal Injection of Hypertonic Dextrose. *Pain Physician*. 2006:9(2);115-121.