Stem Cells and Regenerative Therapies for Pain: What does the science tell us? What actually works?

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AAPM 2022 38TH ANNUAL MEETING

Disclosures

- Consulting for:
  - Mainstay Medical (Data Monitoring Committee)
  - Summus (Consulting)
  - North Carolina Medical Board (Consulting)
- Current research funding:
  - DoD/NIH
  - SPR Therapeutics
  - USWorldMeds
  - Sana Health

- I receive no consulting fees, honoraria, grants or payments from products and devices discussed in this presentation

Outline

- Brief regulatory review
- Outcomes for Platelet-rich plasma (PRP), Mesenchymal cells (MSCs), and Autologous Conditioned Serum (ACS) for:
  - Knee OA
  - Hip OA
  - Rotator Cuff Tendinopathy
- Review of known and emerging mechanisms
  - Growth factor/immune function
  - Exosome/miRNA activity

Why PRP, MCSs, and ACS?

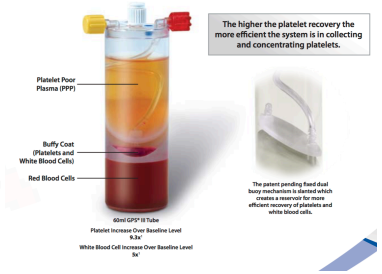
- Sufficient literature to assess clinical utility
- Meet FDA criteria for use in the US (not FDA approved)

Platelet-rich Plasma (PRP)

Platelet count above physiologic levels (typically 3-5x baseline)

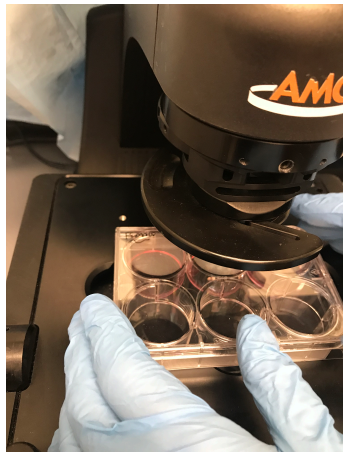
Elevated levels of growth factors

Variable concentrations of monocytes, neutrophils, growth factors, cytokines and enzyme inhibitors



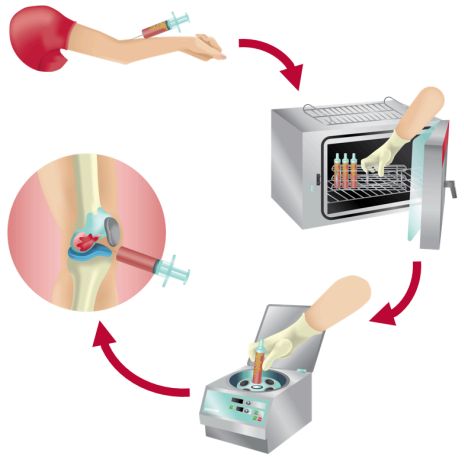
MSCs

- Mesenchymal stem cells, Mesenchymal Signaling Cells, Medicinal Signaling Cells
  - Autologous or allogeneic:
    - Bone marrow aspirate concentrate
    - Cell-Cultured bone marrow stromal cells/stem cells
    - Adipose tissue aspiration
    - Umbilical cord
    - Amniotic/Placenta



Autologous Conditioned Serum (ACS)

- Whole blood secretome/serum product
- Filtered (cell free)
- Elevated levels of:
  - IL-1Ra, IL-4, IL-10, TGF-β, etc
- Likely exosomal mechanisms



FDA Regulation of Biologic Products

- Regulation of cellular products (HCTPs) is through Center for Biologics Evaluation and Research (CBER) at the FDA
- Blood-based biologics such as platelet-rich plasma (PRP) are exempt from regulation as an HCT/P

Regulation of MSCs

- Cellular products that do not have an FDA BLA must meet “361 criteria”:
  - Minimally manipulated (definition below)
  - Homologous (definition below)
  - Not reliant on systemic effect
  - Not combined with other articles/medications
- BMAC for peripheral injection appears to meet ”361 criteria”

Other Biologic Products

- Cultured or tissue expanded MSCs
- Amniotic or umbilical tissue derived products (fluid or tissue)
- Allogeneic exosome products
- Adipose-based MSCs
- **Products that do not meet "361 criteria" are restricted unless used in context of IND/BLA**

- https://www.fda.gov/media/109176/download
- https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/questions-and-answers-regarding-end-compliance-and-enforcement-policy-certain-human-cells-tissues-or

PRP

PRP for Knee OA: Meta-Analyses

- Comparison primarily with IA-HA and steroids
  - Meheux et al. 2015
    - "In patients with symptomatic knee OA, PRP injection results in significant clinical improvement up to 12 months"
  - Dai et al. 2017
    - "compared with HA and saline, PRP may have more benefit in pain relief and functional improvement in … knee OA at 1 year"
  - Han et al. 2019
    - "PRP reduced pain more effectively than HA in patients with KOA at 6 and 12 months"
  - Belk et al. 2020
    - Ave f/u 11 months. "Mean improvement in PRP group was significantly higher in the PRP group (44.7) than the HA group (12.6)"
  - Singh et al. 2021
    - "PRP yielded improved outcome compared with PRGF, HA, CS and placebo for the treatment of symptomatic knee OA at a minimum of 6-month follow-up"

JAMA | Original Investigation

Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis
The RESTORE Randomized Clinical Trial

Kim L. Bennell, PhD; Kade L. Paterson, PhD; Ben R. Metcalf, BSc; Vicky Duong, DPT; Jillian Eyles, PhD; Jessica Kasza, PhD; Yuanyuan Wang, PhD; Flavia Cicuttini, PhD; Rachelle Buchbinder, PhD; Andrew Forbes, PhD; Anthony Harris, MSc; Shirley P. Yu, MPH; David Connell, MMed; James Linklater, MBBS; Bing Hui Wang, PhD; Win Min Oo, PhD; David J. Hunter, PhD

- Multi-center RCT 228 patients, 3 intra-articular injections
- No significant difference between PRP and saline at 12 months
- Appropriate statistical design and analysis
- Intervention arm received a low platelet count product (1.2X baseline)
    - Only published in supplemental material

Platelets: 325 x $10^3/mm^3$ ($10^9/L$)
Leukocytes: 1.16 $10^3/mm^3$ ($10^9/L$)

JAMA | Original Investigation

Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis

A Randomized Clinical Trial

Liam D. A. Paget, MD; Gustaaf Reurink, PhD; Robert-Jan de Vos, PhD; Adam Weir, PhD; Maarten H. Moen, PhD; Sita M. A. Bierma-Zeinstra, PhD; Sjoerd A. S. Stufkens, PhD; Gino M. M. J. Kerkhoffs, PhD; Johannes L. Tol, PhD; for the PRIMA Study Group

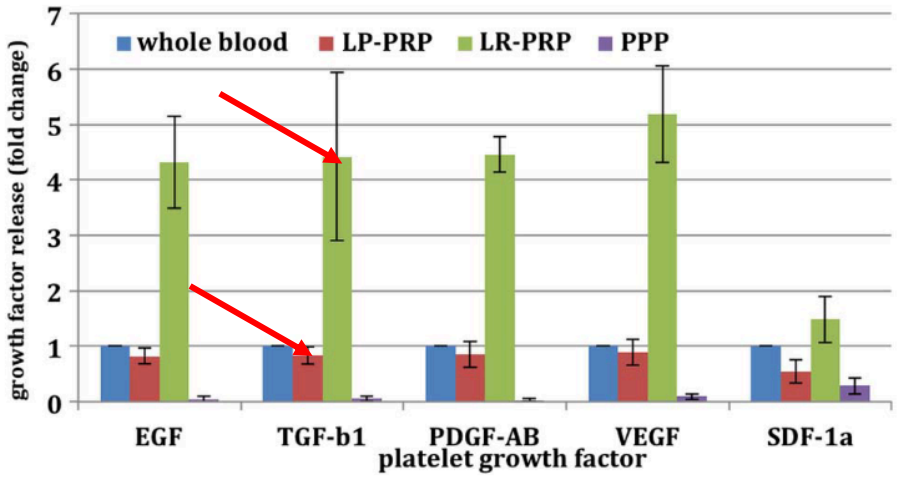
- Multi-center RCT of 100 patients treated with 2 PRP injections (Arthrex ACP)
- No significant difference between PRP and saline injection through 26 weeks
- **Platelet counts, cell counts, growth factors not reported in publication or supplemental materials**
  - A previous study noted that ACP system increases platelet count approximately 1.9X baseline[1]

1. https://www.arthrex.com/resources/white-paper/yEnl8MejfUa-DAF8wewU1g/comparison-of-the-arthrex-acp-double-syringe-system-and-regenkit-prp-regen-laba

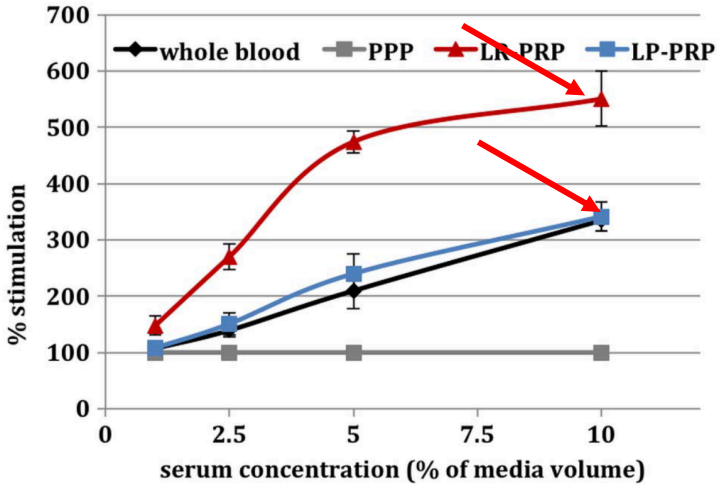
The Importance of Product Clarification

- Letter to Editor: Product characteristics should be reported in all biologic therapy publications

Do Low Platelet/Low Leukocyte Products Release Appropriate Growth Factors?



Growth Factor Release



Tendon Cell Stimulation

Parrish et al. BMJ Open Sport Exerc Med. 2016

MSCs

Meta-Analyses of MSCs in Knee OA

Several include BMAC and Adipose MSCs

- Jevetostky et al. 2017
  - "While MSC therapy has a positive impact… there is limited high quality data"
- Yubo et al. 2017
  - "MSC treatment showed significant decrease in VAS scores after 24 months"
- Ha et al. 2019
  - "MSCs provide improvements in knee OA at short term follow-up (<28 weeks)"
- Ding et al. 2020
  - "Cell-based therapies significantly improved KOOS scores at 12-months"
- Dai et al. 2021
  - "Intra-articular MSC injection was not found to be superior to placebo"
- Wei et al. 2021
  - "…findings suggested that MSCs are effective in treating KOA"

MSC RCTs:

- Several positive RCTs for the use of MSCs as adjuvants to surgery
- Several positive RCTs of cultured MSCs (most outside US)
- 1 RCT of stand-alone, non-cultured MSC treatments

1. Gobbi et al. Multipotent stem cells and scaffold for the treatment of chondral defects of the knee. *Knee Surg Sports Traumatol Arthrosc.* 2017
2. Orozco L et al. Treatment of Knee Osteoarthritis With Autologous MSCs. *Transplantation Journal.* 2013
3. Emadedin et al. Long-term f/u of intra-articular injection of autologous MSCs. Archives of Iranian Medicine. 2015
4. Vangsness et al. Adult human MSCs via intra-articular injection following partial meniscectomy. JBJS. 2014
5. Vega A, Martín-Ferrero MA. Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells. Transplantation. 2015
6. Soler R, Orozco L et al. Ex vivo expanded autologous MSCs for osteoarthritis of the knee. *Knee.* 2016.

Original Research

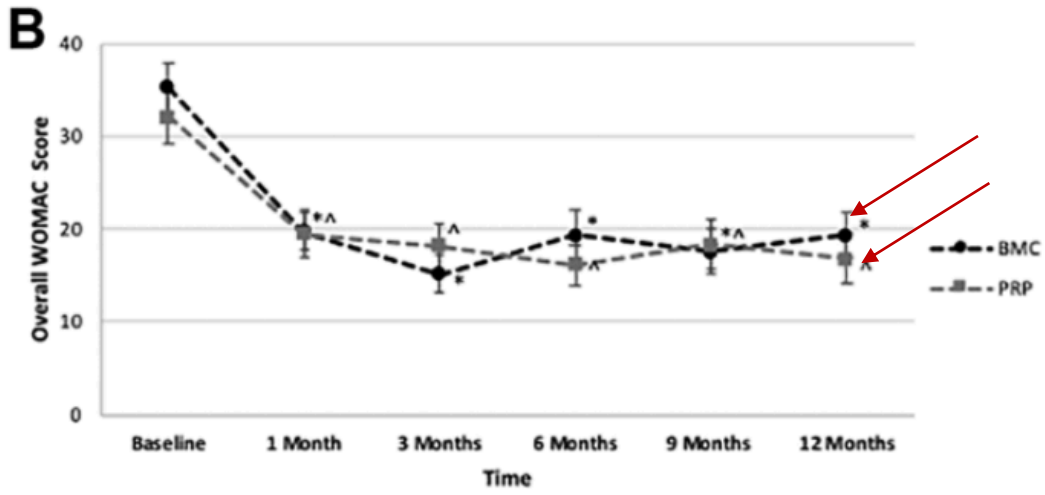
Bone Marrow Aspirate Concentrate Is Equivalent to Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis at 1 Year

A Prospective, Randomized Trial

Adam W. Anz,*† MD, Ryan Hubbard,† MD, Nicole K. Rendos,† PhD, Peter A. Everts,‡ PhD, FRSM, James R. Andrews,† MD, and Joshua G. Hackel,† MD

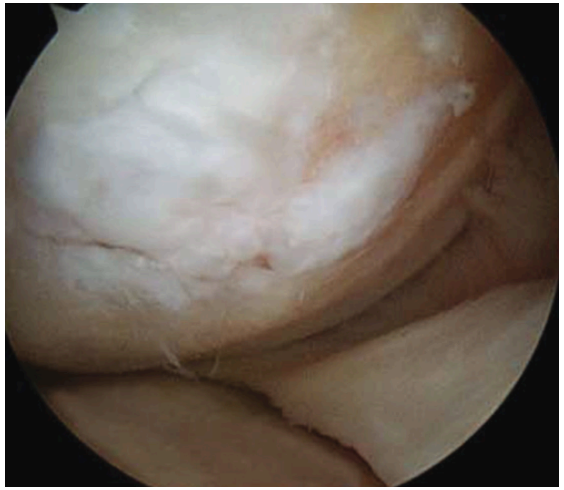
Investigation performed at the Andrews Research & Education Foundation, Gulf Breeze, Florida, USA

- 90 patients randomized to MSCs or PRP



MSCs and Cartilage Growth

- Shin et al. 2018:
  - Meta-analysis of 8 studies that evaluated symptoms and radiographic cartilage changes with treatment
    - Significant analgesia and functional improvement noted by studies
    - No evidence of cartilage re-growth by MRI

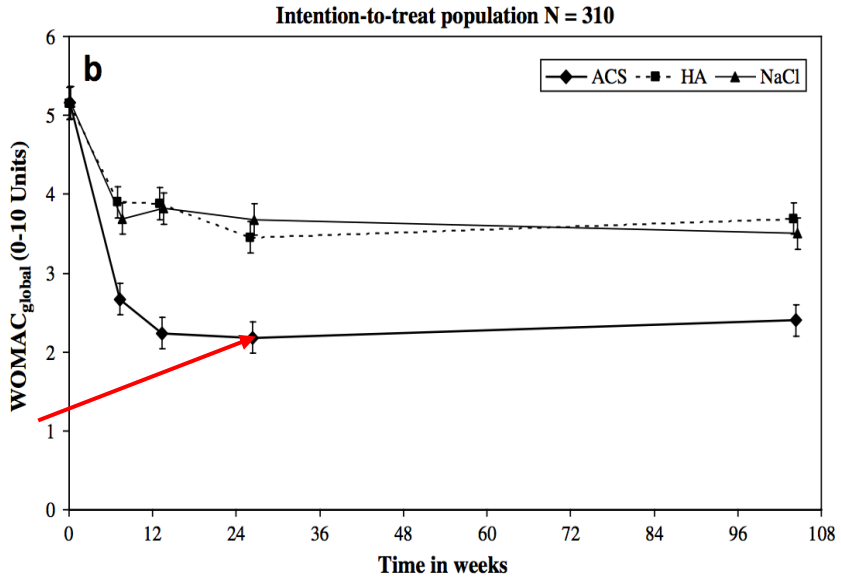


Shin et al: Intra-articular Bone Marrow MSCs in knee OA. Knee Surgery and Related Research. 2018

Autologous Conditioned Serum (ACS)

ACS: RCTs

- Baltzer et al. 376 patients
  - Blinded RCT of ACS vs HA or saline
  - Significant improvements in pain
  - Analgesia sustained at 2-year follow-up
- Yang et al. 167 patients
  - Blinded RCT of ACS vs saline
    - Significant improvements in KOOS scores in ACS group



Baltzer A. et al. Osteoarthritis and Cartilage 2009;17:152-160

Yang et al. Osteoarthritis and Cartilage. 2008. Autologous IL-1 receptor antagonist improves symptoms and function

Summary of Evidence: Knee OA

For platelet-rich plasma (12 months)

For low platelet/low leukocyte “PRP”

BM MSCs: (≥12 months)

ACS: (≥2 years)

Hip OA: PRP

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Review

Platelet rich plasma versus hyaluronic acid in patients with hip osteoarthritis: A meta-analysis of randomized controlled trials

Ye Ye[a], Xiang Zhou[b,*], Shuiwei Mao[b], Jun Zhang[b], Bingmin Lin[b]

- Meta-analysis of 4 RCTs using PRP:
  - Battaglia et al. (leukocyte poor)
  - DiSante et al. (leukocyte poor)
  - Doria et al. (Median patient age= 68)
  - Dallaria et al. (Excluded patients over 65)
- PRP not superior to HA at 6 and 12 months

Ultrasound-Guided Injection of Platelet-Rich Plasma and Hyaluronic Acid, Separately and in Combination, for Hip Osteoarthritis

A Randomized Controlled Study

Dante Dallari,*† MD, Cesare Stagni,† MD, Nicola Rani,† MD, Giacomo Sabbioni,† MD, Patrizia Pelotti,‡ MD, Paola Torricelli,§ BSc, Matilde Tschon,§ PhD, and Gianluca Giavaresi,§ MD
Investigation performed at Rizzoli Orthopedic Institute, Bologna, Italy

2016 RCT of 111 patients

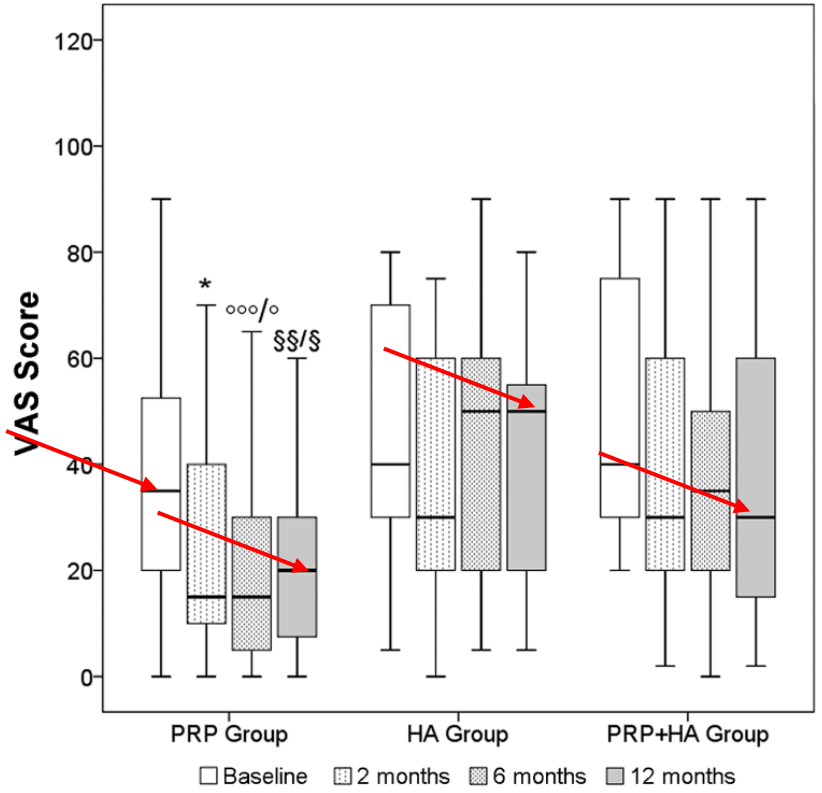
Received 3 injections:

PRP (Activated, double spin)

HA (1,500 kDa)

PRP/HA

PRP superior to HA and combination therapy at 3,6, and 12 months



MSC for Hip OA: Evidence

No RCTs of MSCs BMAC for Hip OA

- Case series of BMAC and adipose MSCs positive

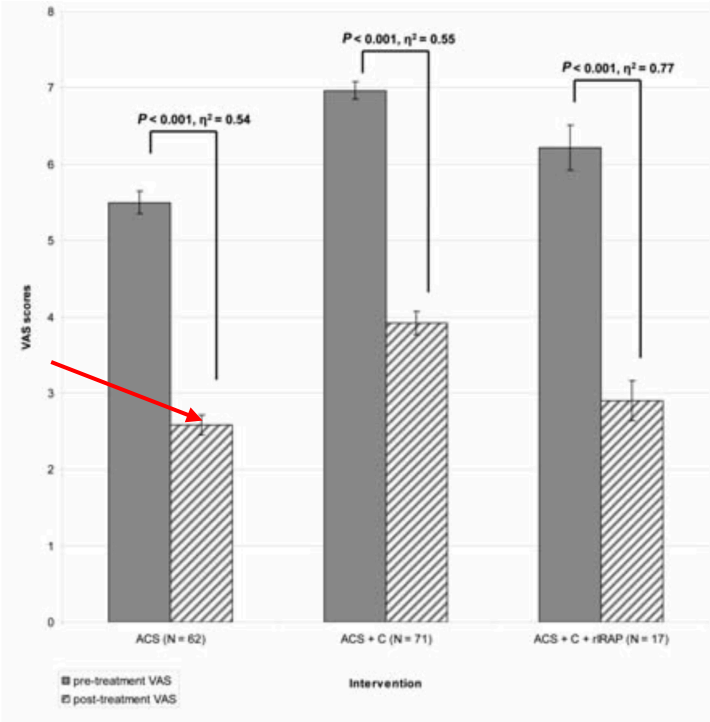
- RCTs of MSCs as surgical adjuvant
  - Limited outcomes in AVN

Darrow et al. 2018. Clinical Medicine Insights: Case Reports
Dall'Oca. Mesenchymal Stem Cells injection in hip osteoarthritis: preliminary results. Acta Biomed. 2019;90(1-s
Hauzeur et al. Inefficacy of autologous BMAC in osteonecrosis. 2018. International Orthopedics

ACS for Hip OA: Evidence

ACS for Hip OA

- Observational trial of 119 patients treated with ACS
- Significant improvement in all groups
- No advantage of addition of steroid or IL-1Ra



Baltzer et al. A new treatment for hip OA: ACS. Orthopedic Reviews. 2013

Summary of Evidence: Hip

- PRP (patients over 65 or low leukocyte) 
- PRP (younger patients, higher platelet/GF) 
- MSCs 
- ACS 

PRP for Rotator Cuff Tendinopathy: Evidence

PLOS ONE

RESEARCH ARTICLE

Platelet-rich plasma for rotator cuff tendinopathy: A systematic review and meta-analysis

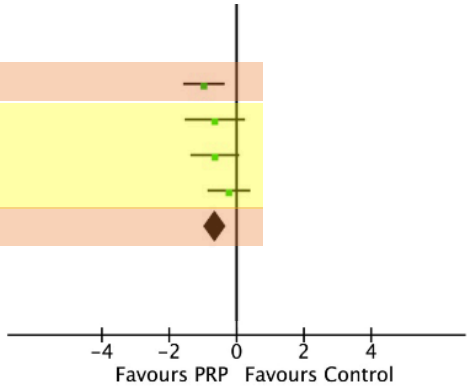
Mohamad Shariff A. Hamid[1☯], Shariff Ghazali Sazlina[2,3☯*]

1.2.8 VAS score 12 month

Cai 2019	2	6.9	45	6.9	6.8	47	5.8%	−0.71 [−1.13, −0.29]
Kesikburun 2013	1.8	2.4	20	3.3	3.7	20	5.4%	−0.47 [−1.10, 0.16]
Ilhani 2015	0.3	0.7	30	0.8	1.3	32	5.6%	−0.47 [−0.97, 0.04]
Schwitzguebel 2019	2.3	2.1	41	2.7	2.7	39	5.8%	−0.16 [−0.60, 0.27]
Subtotal (95% CI)			**136**			**138**	**22.6%**	**−0.46 [−0.70, −0.21]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.09$, df = 3 (P = 0.38); $I^2 = 3\%$

Test for overall effect: Z = 3.65 (P = 0.0003)



- Rotator Cuff Tendinopathy Conclusion:
  - PRP superior analgesia than control at 6 and 12 months
  - More effective with use of HA (1 trial)

Rotator Cuff : MSC Evidence

Original Article

Ann Rehabil Med 2021;45(4):274-283
pISSN: 2234-0645 • eISSN: 2234-0653
https://doi.org/10.5535/arm.21078

arm
Annals of Rehabilitation Medicine

Mesenchymal Stem Cells Use in the Treatment of Tendon Disorders: A Systematic Review and Meta-Analysis of Prospective Clinical Studies

Woo Sup Cho, MD[1], Sun Gun Chung, MD, PhD[2], Won Kim, MD, PhD[3], Chris H. Jo, MD, PhD[3], Shi-Uk Lee, MD, PhD[4], Sang Yoon Lee, MD, PhD[4]

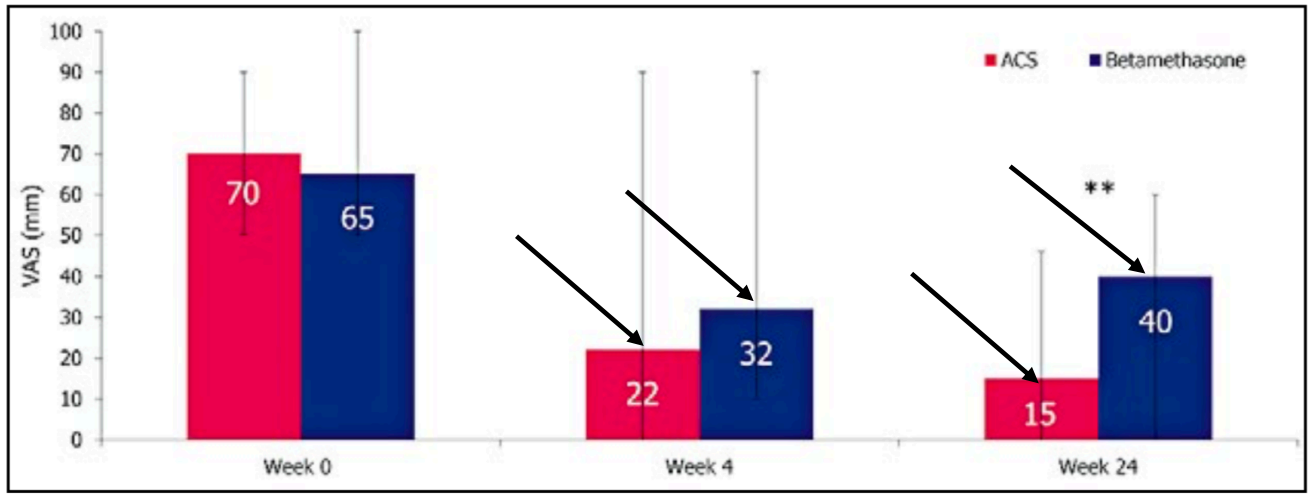
- 3 studies for MSCs in rotator cuff tendinopathy:
  - 2 studies as adjuvant to surgery:
  - 1 study for MSCs alone:
    - Jo et al: Adipose MSCs
- No studies of BMAC as solo therapy

ACS for Rotator Cuff: Evidence

The efficacy and safety of autologous conditioned serum (ACS) injections compared with betamethasone and placebo injections in the treatment of chronic shoulder joint pain due to supraspinatus tendinopathy: a prospective, randomized, double-blind, controlled study

Nemanja Damjanov[1], Branko Barać[1], Jelena Čolić[1], Vladan Stevanović[2], Ana Zeković[1], Goran Tulić[3]

[1]Institute of Rheumatology, [2]Institute for Orthopedic Surgery "Banjica", [3]Clinic for Orthopedic Surgery and Traumatology, Clinical Center of Serbia, University of Belgrade School of Medicine, Belgrade, Serbia



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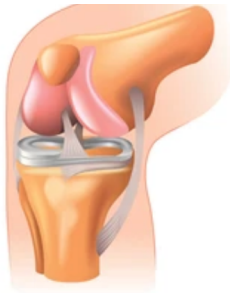
Summary of Evidence: Rotator Cuff

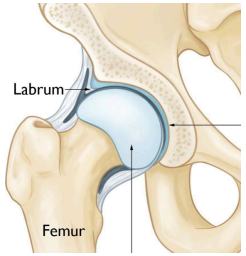
- PRP  ?
- PRP with HA  ?
- MSCs ? ?
- ACS  ?

Mechanisms and Future Investigations

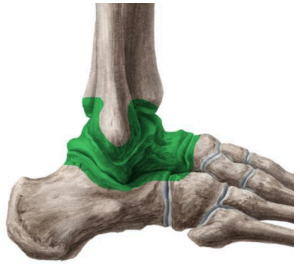
Primary OA by Site



Knee 67%



Hip 58%



Ankle: 9%

- Ankle cartilage is thinner than knee or hip but more resistant to OA
- Why?

Valderrabano et al. Etiology of Ankle OA. Clin Ortho and Res. 2008

SCIENCE ADVANCES | RESEARCH ARTICLE

DEVELOPMENTAL BIOLOGY

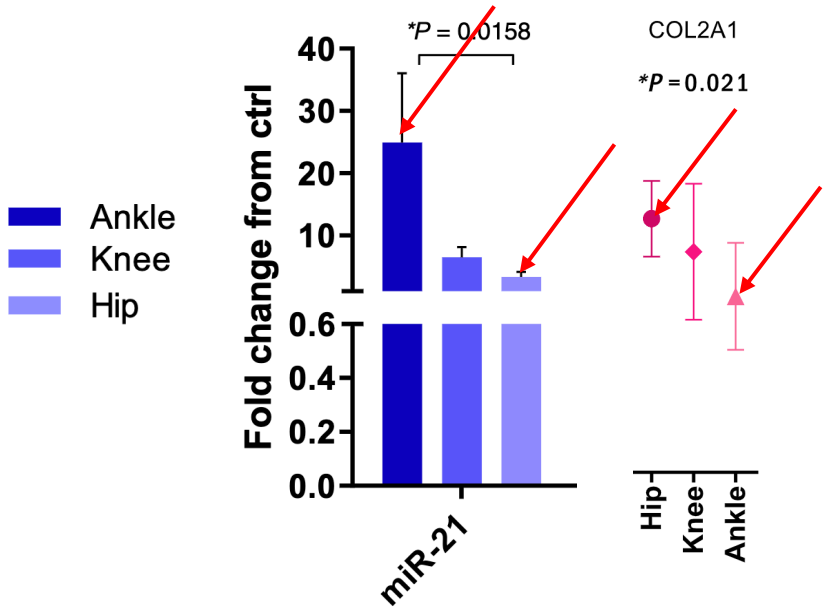
Analysis of "old" proteins unmasks dynamic gradient of cartilage turnover in human limbs

Ming-Feng Hsueh[1,3], Patrik Önnerfjord[2], Michael P. Bolognesi[3], Mark E. Easley[3], Virginia B. Kraus[1,4]*

Younger proteins increase distally:

- hip>>knee>> ankle

Epigenetically determined by miRNA

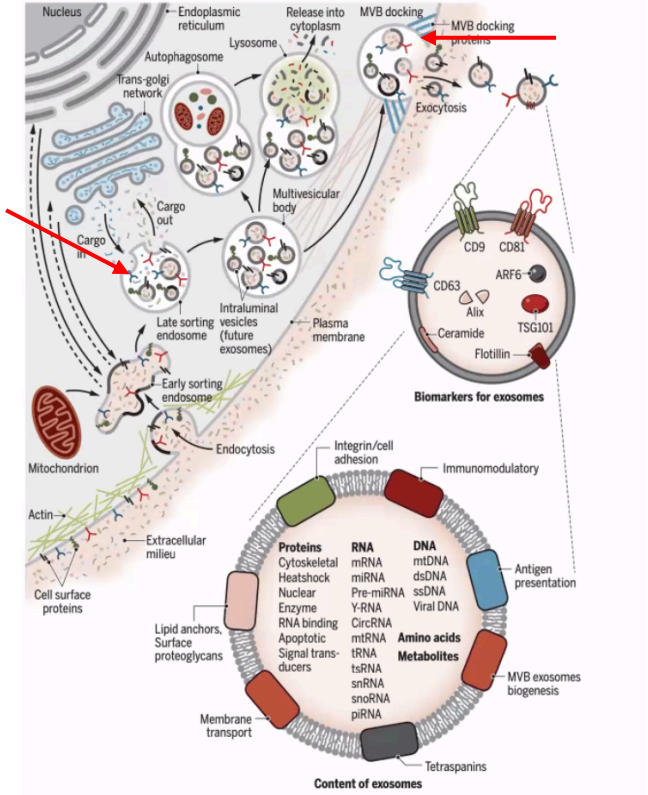


Deamidation Rates of Joint Proteins

Epigenetic Reprogramming: miRNA

- miRNAs (e.g., miR-100-5p, miRNA 140, miR-92a-3p) regulate:
  - Cytokine expression
  - Immune activation
  - TRP channel function
  - Cartilage growth
  - Nerve regeneration

Exosome Delivery of miRNA?



- Exosomes Contain over 3,000 miRNAs
- Exosomes from cells treated with IL-10 have anti-inflammatory properties
- Exosomes from arthritis patients induce arthritis in recipient joints
- Exosome depletion reduces effectiveness of biologic therapies

Börger et al. (2017). "MSC-Derived Extracellular Vesicles and Their Potential as Novel Immunomodulatory Therapeutic Agents." Int J Mol Sci **18**(7).
Shiue et al. (2019). "MSC exosomes as a cell-free therapy for nerve injury-induced pain." Pain 160
Jeon et al (2019). "Senescence cell-associated extracellular vesicles serve OA." JCI Insight

Summary

- Biologic therapies need to be assessed with greater granularity
  - These therapies are not panaceas
  - Publications must describe the product used
- “Unmeasured” factors (miRNA, exosomes) likely play an important part of the therapeutic response
  - Research ongoing