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Where do Orthobiologics have the best Evidence?

Rowan Paul, M.D.

Disclosures

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

SPEAKERS BUREAU: The Orthobiologic Institute (TOBI), ASIPP, Boston Biolife, Global Regenerative Academy
STOCK SHAREHOLDER: N/A
GRANT/RESEARCH SUPPORT: N/A
CONSULTANT: Benchmark Biomedical, MiniTC
MEDICAL ADVISORY BOARDS: Altis.AI, ROAM Robotics, DataBiologics, MONJ, Hinge Health

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The Promise

Orthobiologics are minimally invasive, safe, effective, durable and may help fill the treatment gap for patients with musculoskeletal problems.

Reduces the need and use of corticosteroids, NSAIDS and Opioids

Reduces or delays unnecessary, overly invasive surgery

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The Problem

Until recently, there has been a paucity of high-quality evidence for Orthobiologics

Lots of studies with lower quality of evidence but high rates of bias

Some with high quality methodology but poor dosing of orthobiologics

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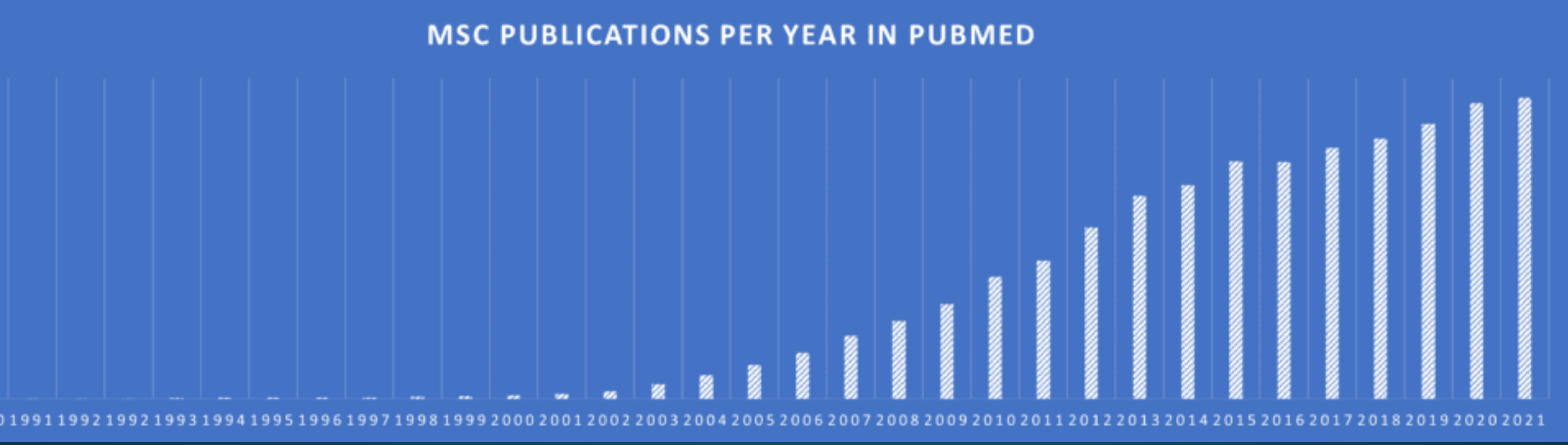

MSC Publications

https://regenexx.com/blog/mesenchymal-stem-cell-research-continues-to-increase/

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Platelet Rich Plasma Injection for Knee OA RCTs-2022

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Each circle represents a randomized controlled trial that used PRP to treat knee OA. Each circle has the number of patients treated and the comparison group listed. **Click on the text in each circle to be taken to the PubMed link**. Only studies listed in the US National Library of Medicine were included. The blue circles represent studies where PRP was effective, beat the comparison group, or was non-inferior to the standard of care. The red circles mean that PRP was inferior to a known placebo. Last updated 1/23/22

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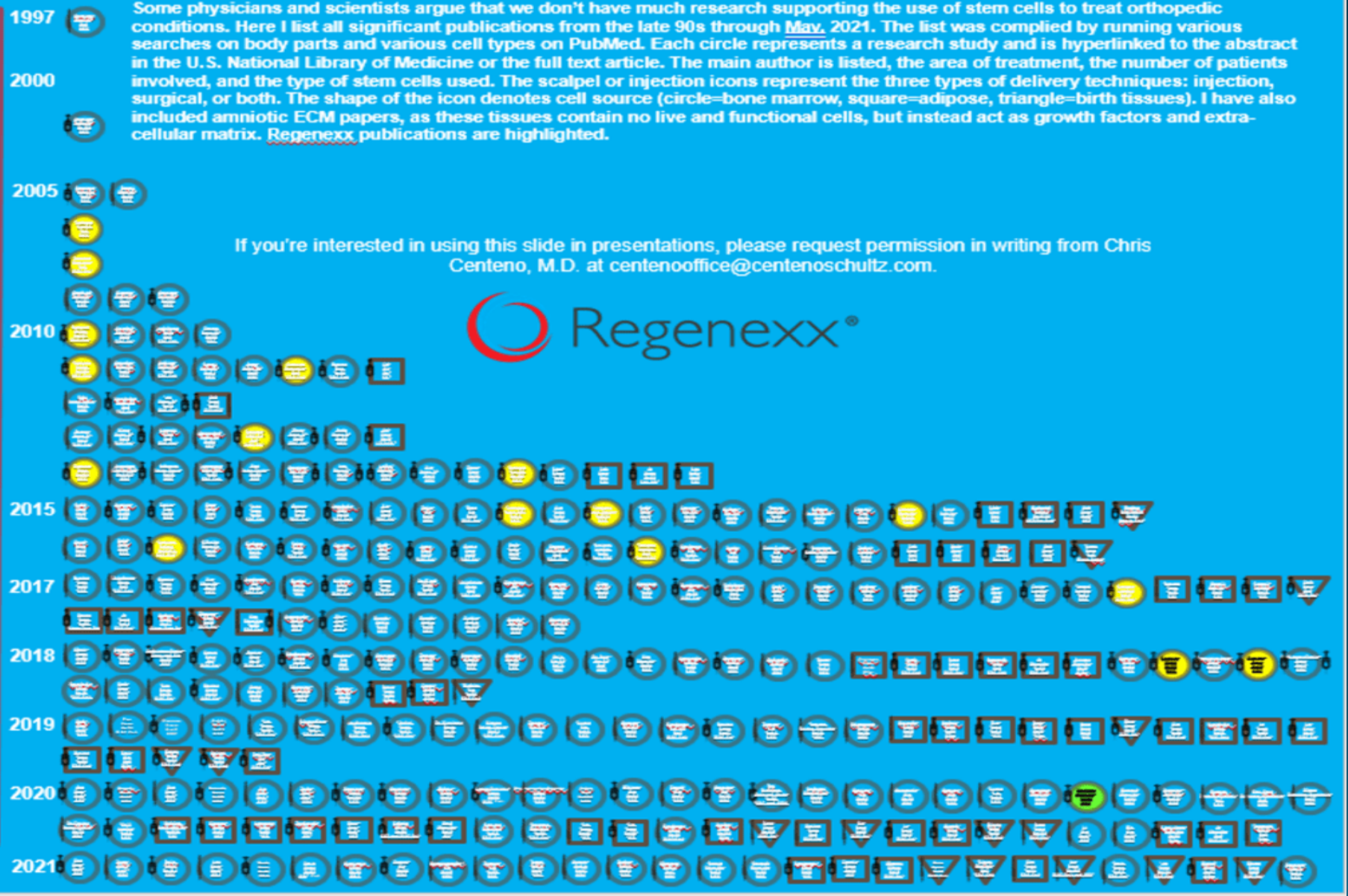
All Orthopedic Stem Cell Type and ECM Research Summary (1997-2021)

Some physicians and scientists argue that we don't have much research supporting the use of stem cells to treat orthopedic conditions. Here I list all significant publications from the late 90s through May, 2021. The list was complied by running various searches on body parts and various cell types on PubMed. Each circle represents a research study and is hyperlinked to the abstract in the U.S. National Library of Medicine or the full text article. The main author is listed, the area of treatment, the number of patients involved, and the type of stem cells used. The scalpel or injection icons represent the three types of delivery techniques: injection, surgical, or both. The shape of the icon denotes cell source (circle=bone marrow, square=adipose, triangle=birth tissues). I have also included amniotic ECM papers, as these tissues contain no live and functional cells, but instead act as growth factors and extra-cellular matrix. Regenexx publications are highlighted.



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2021 Bone Marrow Stem Cell Infographic

Some physicians and scientists argue that we don't have much research supporting the use of bone marrow stem cells to treat orthopedic conditions. Here I list all significant publications from the late 90s through April 2021. The list was complied by running various searches on body parts and bone marrow cell types on PubMed. Each circle represents a research study and is hyperlinked to the abstract in the U.S. National Library of Medicine or the full text article. The main author is listed, the area of treatment, the number of patients involved or treated with bone marrow cells, and the type of bone marrow stem cells used (either Autologous Bone Marrow Concentrate (BMC), Bone Marrow Aspirate (BMA) or Cultured Mesenchymal Stem Cells (MSC Cult) [autologous or allogeneic]. The scalpel or injection icons represent the three types of delivery techniques: injection, surgical, or both. Regenexx publications are highlighted in yellow. Case series smaller than 5 patients, unless publishing on original concepts were excluded.

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PRP Variables

- Patient selection
- Image guidance
- Leukocyte rich vs poor
- Activated or inactivated
- Concentration and dose!
- Age
- Tendons, ligaments vs joints vs nerves
- Platelet Lysate, releasate vs PRP
- Use of Plasma Rich in Growth factors/A2M
- Single location vs functional unit vs I/O

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Bone Marrow Variables

- Patient Selection
- Image guidance
- Trochar type, equipment and draw technique
- Bone Marrow Aspirate vs Bone Marrow Concentrate
- No spin, 1 spin, 2 spin
- Activation or not
- Use of Cell Poor plasma
- Single location injection under guidance vs functional unit, I/O

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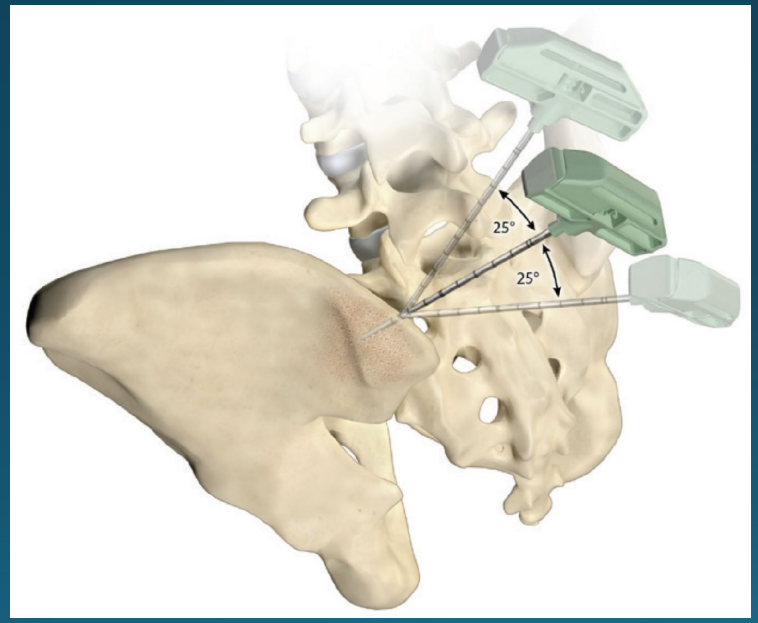
Adipose variables

- Patient selection
- Image guidance
- SVF-not allowed in the U.S.
- Micro-fragmentation-not allowed vs grey zone?
- Aspiration needle technology
- Single injection vs functional unit vs I/O

Where is the Best Clinical Evidence for Orthobiologics?



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Excellent Clinical Evidence for PRP in KL Grade 1-3 Osteoarthritis

- 39 RCT's showing that PRP works in Knee Osteoarthritis as of 2022
- Laver et al- Systematic Review 2017
  - 26 studies knee, 3 hip osteoarthritis
  - Different processing, all I/A no peri-articular, or functional unit
  - PRP Can be beneficial for both knee and hip O/A in pain and functionality
- Shen et al- Systematic review 2017
  - I/A PRP more efficacious that controls (saline, HA, Ozone, Corticosteroids), for pain and functional improvement at 3,6,12

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- 24 RCT's
  - 21 knee, 3 hip
- Results:
  - PRP significantly improved WOMAC, VAS, IKDC, HHS
  - WOMAC, pain, stiffness, physical function scores were significantly better in the PRP group vs controls
  - Knee>hip effect at 1,2,3,6,12 months, but not at 18 month
- Conclusions
  - I/A PRP better than other injections for improving pain and function in O/A patients particularly in Knee OA.

Original Article | Published: 12 June 2020

The effects of platelet-rich plasma injection in knee and hip osteoarthritis: a meta-analysis of randomized controlled trials

Yujie Dong, Butian Zhang, Qi Yang, Jiajing Zhu & Xiaojie Sun

Clinical Rheumatology **40**, 263–277 (2021) | Cite this article

Bone Marrow Aspirate Concentrate

- Eight studies met inclusion criteria
- 94% significant improvement
- 5 studies with significant VAS, NRS improvement
- 3 showed no clinical Superiority vs PRP, MFAT, placebo
- Improvement for short to midterm

Bone Marrow Aspirate Concentrate for the Treatment of Knee Osteoarthritis: A Systematic Review

Laura E. Keeling, MD*, John W. Belk, BA, Matthew J. Kraeutler, MD, more... Show all authors

First Published July 8, 2021 | Research Article | Find in PubMed | Check for updates
https://doi.org/10.1177/03635465211018837

2021 Metanalysis

- 43 RCT's
- AD-MSCs were the best for pain relief
- LP-PRP most effective for functional improvement
- BM-MSCs had potentially beneficial effects
- HA efficacy was lower that the others

Meta-Analysis > Arthroscopy. 2021 Jul;37(7):2298-2314.e10. doi: 10.1016/j.arthro.2021.02.045. Epub 2021 Mar 10.

Intra-Articular Injections of Platelet-Rich Plasma, Adipose Mesenchymal Stem Cells, and Bone Marrow Mesenchymal Stem Cells Associated With Better Outcomes Than Hyaluronic Acid and Saline in Knee Osteoarthritis: A Systematic Review and Network Meta-analysis

Di Zhao [1], Jian-Ke Pan [2], Wei-Yi Yang [2], Yan-Hong Han [2], Ling-Feng Zeng [3], Gui-Hong Liang [3], Jun Liu [4]

Large Tendinopathy Metanalysis

- 18 RCT's, 8 low bias
- Strong positive effect with a single Leukocyte Rich PRP with good equipment, prepared well and with intra-tendinous ultrasound guided injection.(SMD 36.38%)
- Leukocyte poor PRP still had a standardized mean difference of 26.77
- Different controls (saline, local anesthetic, corticosteroid, dry needling) no clear difference

Meta-Analysis > Am J Sports Med. 2017 Jan;45(1):226-233. doi: 10.1177/0363546516643716. Epub 2016 Jul 21.

The Effectiveness of Platelet-Rich Plasma in the Treatment of Tendinopathy: A Meta-analysis of Randomized Controlled Clinical Trials

Jane Fitzpatrick [1], Max Bulsara [2], Ming H Zheng [1]

Affiliations + expand

PMID: 27268111 DOI: 10.1177/0363546516643716

Strong Clinical Evidence PRP-Tendinopathy

- Achilles and patellar tendinopathy
  - Improved Pain and good functional outcomes for years
- Rotator Cuff tendinopathy
  - Gumina, et al-PRF intra-operative improved repair integrity for large tears, without improvement of function.
  - Lower re-tear rates for small to large tears at 1 year

Spine Data is emerging

- PRP
  - Building Level 1-4 evidence for intradiscal and facet PRP, epidurals, SI
- Prolotherapy
  - Level 3-4 for Prolotherapy for intradiscal, level 4 facets
  - One level 4 showed no statistical significance supporting
  - Level 4 for epidural but one level 1 study showed no benefit after 48 hours
  - Level 1-3 for SI

Review > Pain Pract. 2020 Apr;20(4):437-453. doi: 10.1111/papr.12868. Epub 2020 Jan 28.

Regenerative Medicine for Axial and Radicular Spine-Related Pain: A Narrative Review

Mehul J Desai [1 2 3], John Taylor Mansfield [4], David M Robinson [5], Benjamin C Miller [4], Joanne Borg-Stein [6]

Spine Data cont.

- MSC's
  - Level 1-4 studies for intradiscal MSC except for one level 4 study that showed no improvement at 12 months.
- Platelet Lysates for radiculopathy
- Autologous Conditioned Serum
  - Level 1 for epidural
- No intervention has multiple Level 1 studies

Review > Pain Pract. 2020 Apr;20(4):437-453. doi: 10.1111/papr.12868. Epub 2020 Jan 28.

Regenerative Medicine for Axial and Radicular Spine-Related Pain: A Narrative Review

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Peripheral Nerves

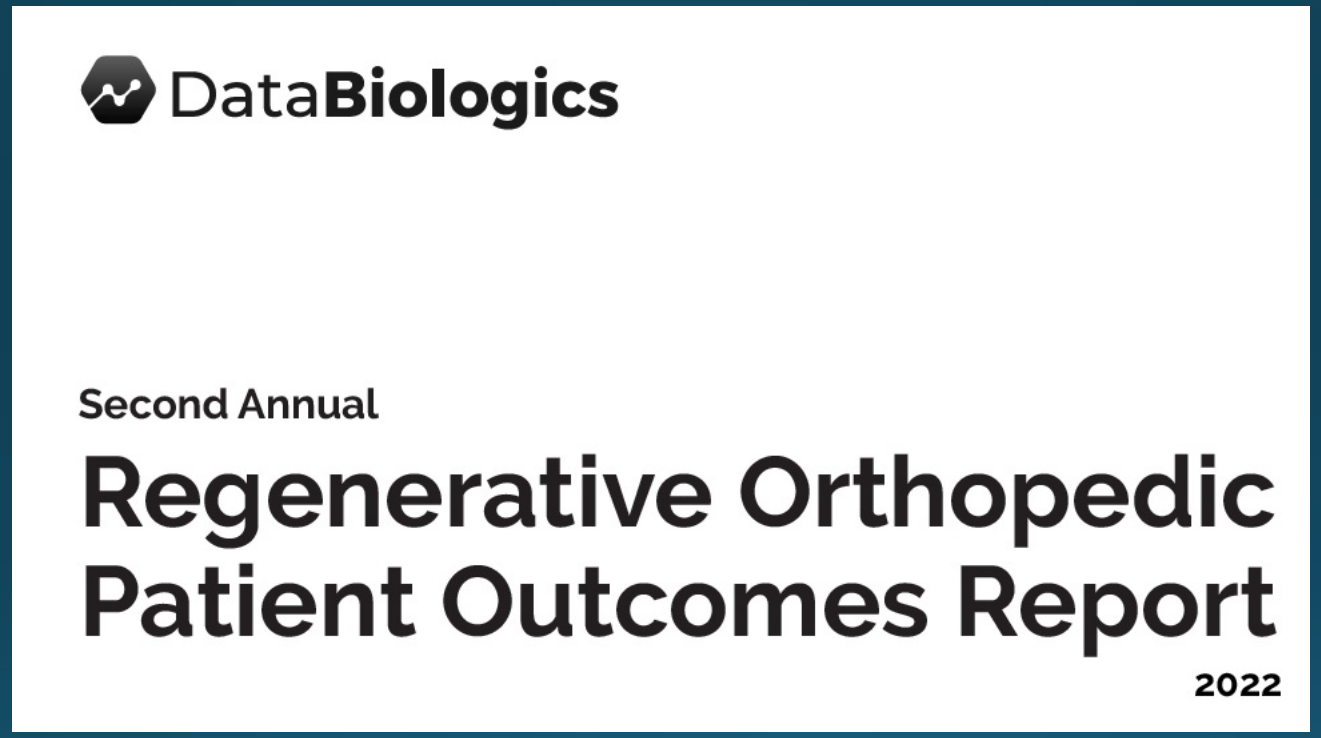
- Emerging supportive evidence for pain relief from carpal tunnel syndrome
- 4 RCT's, 191 cases, 3 or 6 months follow-up
- Vs splinting in 2 studies
- SSS (symptom severity) favors PRP but not FSS (Function)
- VAS and NCV similar to controls
- More studies needed

Meta-Analysis > Arch Phys Med Rehabil. 2020 May;101(5):897-906.
doi: 10.1016/j.apmr.2019.10.193. Epub 2019 Dec 7.

Effectiveness of Platelet-Rich Plasma Injections for Nonsurgical Management of Carpal Tunnel Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Michael Catapano [1], Joseph Catapano [2], Gregory Borschel [2], Seyed Mohammad Alavinia [1], Lawrence R Robinson [1], Nimish Mittal [3]

Real World Outcomes



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Disclosure:

Gerard Malanga, MD

Jay Bowen, DO

Christopher Rogers, MD

Scientific Advisory Board

Steve Sampson, DO, founder of Orthohealing Method and The Orthobiologic Insitute (TOBI)
Ken Mautner, MD, Director of Sports Medicine at Emory Healthcare
William Murrell, MD, Fellow at Plancher Orthopaedics & Sports Medicine
Rowan Paul, MD, Medical Director at RegenCore Method

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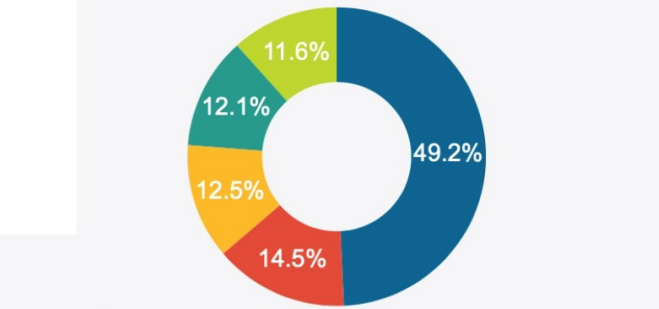
Platelet Rich Plasma

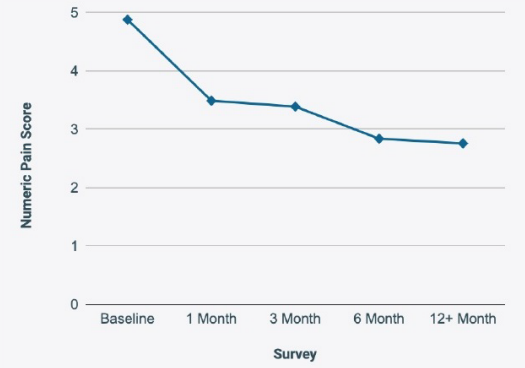
Platelet Rich Plasma is a procedure that uses concentrated platelets from a patient's own blood to harness the body's ability to heal. Platelets are small cells in the blood that help prevent bleeding and also contain large reservoirs of growth factors known to accelerate tissue repair and regeneration. By utilizing the increased concentration of growth factors present in PRP, studies show we can stimulate healing in tendons, ligaments and bone as well as promote the growth of new blood vessels essential for health.

Products/Devices Used

Most common diagnoses



Average patient reported pain



43%

average decrease in patient reported pain at 12+ months post treatment

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Platelet Rich Plasma (PRP)

The Research

The use of platelet rich plasma (PRP) for treating orthopedic conditions has risen over the past decade. Estimates suggest that approximately 86,000 athletes are treated with PRP annually in the United States.[20] The safety of PRP has been widely supported in published scientific studies, but when it comes to effectiveness, there have been conflicting conclusions.[21] In recent years, more refined PRP methodology combined with a better understanding of the potential uses of the treatment have led to research demonstrating the effectiveness for PRP in treating osteoarthritis and tendon injuries of the elbow (tennis and golfers elbow).[4,5]

High-Quality Evidence

Supports the use of PRP injection for **lateral epicondylitis** and PRP for **knee osteoarthritis**.[22,23]

Strong Evidence

Supports the use of PRP injection for **patellar tendinopathy** and PRP injection for **plantar fasciosis**.[22]

Emerging Evidence

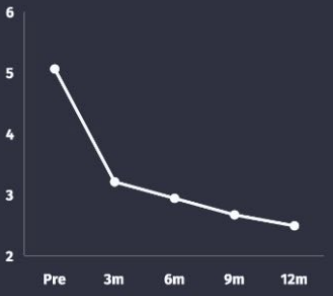
For **rotator cuff tendinopathy**, **osteoarthritis of the hip**, or **high ankle sprains**.[22]

PRP Systems

Our Outcomes Data

73%

of patients experienced a meaningful reduction in pain within 12-months following treatment



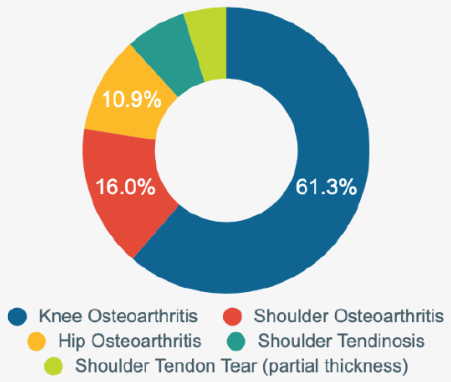
Average patient reported pain (0-10) following PRP treatment across all conditions

Adipose Tissue

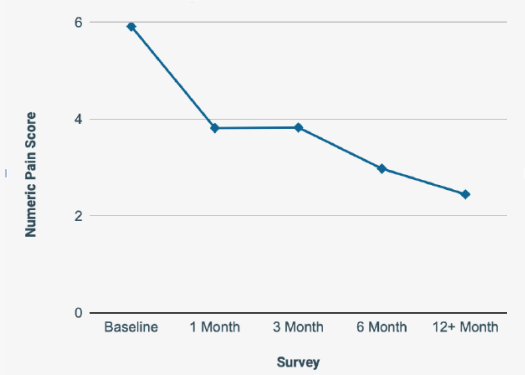
Autologous adipose tissue, commonly referred to as Microfragmented Adipose Tissue (MFAT), has become an increasingly validated source of cells and proteins in the treatment of various orthopedic conditions.[24] Recent studies have shown great potential to reduce pain and inflammation, as well as support the native cartilage tissue in patients with knee osteoarthritis.

Products/Devices Used

Most common diagnoses



Average patient reported pain



56%

average decrease in patient reported pain at 12+ months post treatment

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Adipose Tissue Therapy

The Research

Autologous adipose tissue has become an increasingly validated source of cells and proteins in the treatment of various orthopedic conditions.[24] In general, adipose treatments are used for patients with more severe conditions. Adipose tissue is a good source of naturally occurring regenerative cells particularly due to its abundance and easy access. In addition, it can provide cushioning and help to fill structural defects.[25] Although clinical trials of adipose tissue based treatments are limited, recent studies have shown great potential to reduce pain and inflammation, as well as support the native cartilage tissue in patients with knee osteoarthritis.[10]

Strong Evidence

Supports the use of adipose injections for **knee osteoarthritis**.[10]

Emerging Evidence

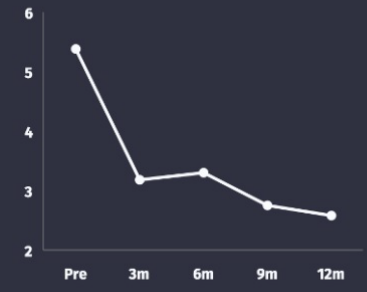
For **rotator cuff and labral tears, osteoarthritis of the hip**.[9,26]

Adipose tissue processing methods

Our Outcomes Data

70%

of patients experienced a meaningful reduction in pain at 12-months following treatment



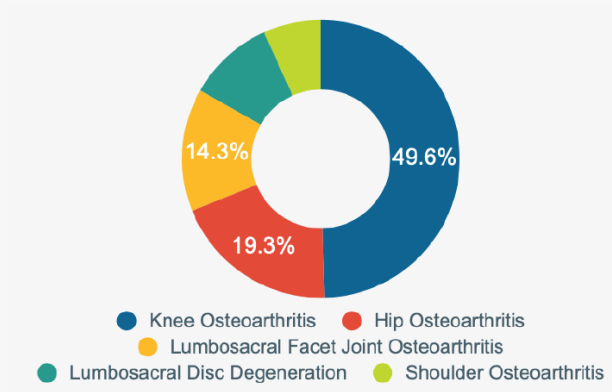
Average patient reported pain (0-10) following adipose tissue based treatment across all conditions

Bone Marrow Concentrate

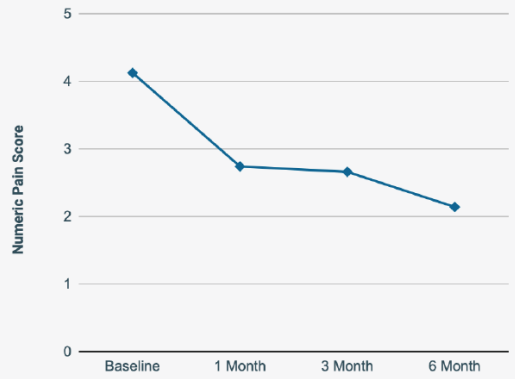
In a BMAC procedure, bone marrow is obtained through aspiration from the back of the pelvis area. Under certain conditions, regenerative cells from the bone marrow are capable of replicating into various types of tissue, allowing for a robust, concentrated mixture of regenerative cells following extraction. This concentrate contains various cells and proteins which modulate pain and inflammation and can facilitate tissue healing such as tendon, cartilage and bone repair.

Products/Devices Used

Most common diagnoses



Average patient reported pain



48%

average decrease in patient reported pain at 6 months post treatment

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Bone Marrow Aspiration Concentrate

The Research

In clinical studies, bone marrow aspiration concentrate (BMAC) injections have been evaluated as an alternative to knee, hip or spine surgery.[27] Bone marrow cells and platelets along with cytokines and growth factors in the bone marrow, may help in tissue healing.[14] In addition, BMAC has been shown to decrease inflammation, assist with wound healing and repair non healing bone or cartilage injuries.[11,12,14] Although BMAC has shown promising results, much like PRP, more research will be necessary to fully understand the benefits of this emerging treatment.

Strong Evidence

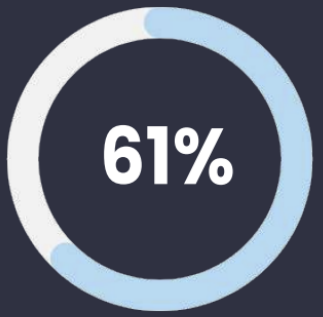
Supports the use of bone marrow injection for **knee osteoarthritis** and **low back pain**.[11,28]

Emerging Evidence

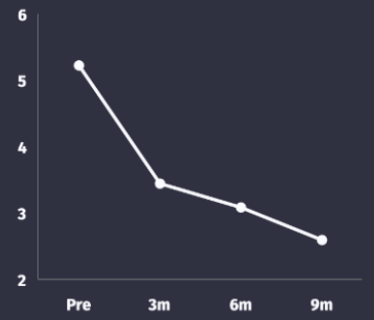
For **degenerative meniscal tear**, or **hip capsular injury, intervertebral disc repair** and **patellar tendinopathy**.[29,30,31]

BMAC processing methods

Our Outcomes Data



of patients experienced a meaningful reduction in pain at 12-months following treatment



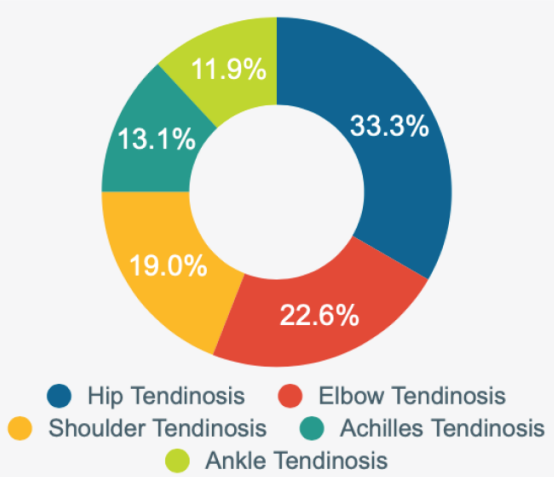
Average patient reported pain (0-10) following BMAC treatment across all conditions

Percutaneous Tenotomy

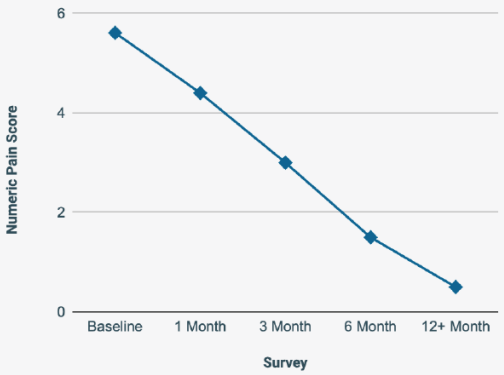
Percutaneous tenotomy is most commonly used to treat chronic tendon degeneration, calcific tendinosis and bone spurs. The treatment traditionally involves the use of a small needle to break up scar tissue and promote an inflammatory response to help the body heal the tendon.

Products/Devices Used

Most common diagnoses



Average patient reported pain



91%

average decrease in patient reported pain at 12+ months post treatment

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Summary: Where is there Level 1,2 Evidence supporting Orthobiologics?

- Abundant:
  - PRP for KL Grade 1-3 knee O/A, lateral and medial epicondylosis
- Moderate:
  - PRP for patellar tendinosis, plantar fasciosis
  - PRP for donor Site Pain for BTB Patellar Tendon ACL recon pain
  - PRP for short term pain relief from Hip Osteoarthritis with PRP and HA
  - BMAC and Adipose (Mixed SVF and MFAT) for knee osteoarthritis
- Emerging:
  - Gluteal Tendinosis
  - Rotator Cuff Pain, particularly post operative
  - Possibly with small to medium cuff tears with double row repair
  - Nerve conditions like carpal tunnel syndrome

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Summary- Insufficient Evidence :

- Rotator Cuff Tendinopathy
- Osteoarthritis Hip
- High Ankle Sprains
- Lumbar, cervical discs, facets and stenosis

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Summary- Lack of Efficacy of PRP:

- Achilles Tendinopathy (controversial)
- Muscle Injuries
- Acute Fracture or non-unions
- Surgical Augmentation of cuff, achilles repairs
- ACL reconstruction augmentation

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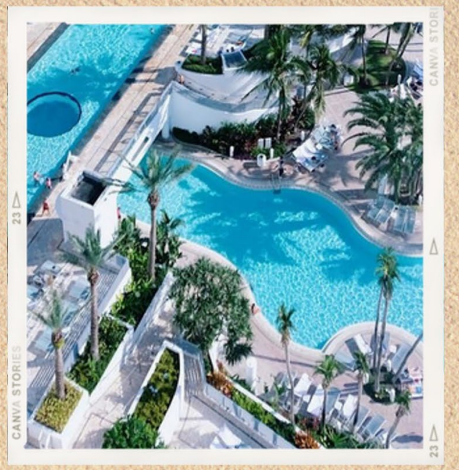

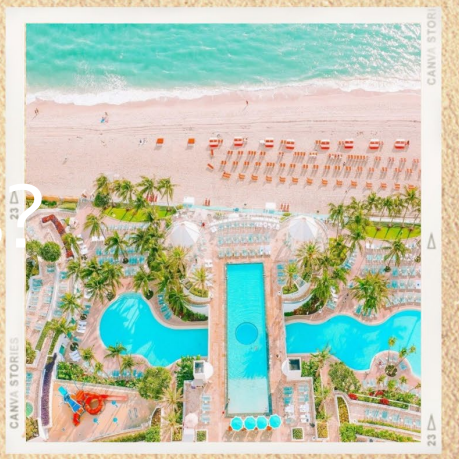

Thank You!

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References:

- 1) Wu PI Diaz R Borg-Stein J. Platelet-rich plasma. *Phys Med Rehabil Clin N Am*. 2016;27(4):825-53
- 2) Gosens T Peerbooms JC van Laar W den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med*. 2011;39(6):1200-8.
- 3) Peerbooms JC Sluimer J Bruijn DJ Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med*. 2010;38(2):255-62.
- 4) Mishra AK, Skrepnik NV, Edwards SG, Jones GL, Sampson S, Vermillion DA, Ramsey ML, Karli DC, Rettig AC. 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):463-71. doi: 10.1177/0363546513494359. Epub 2013 Jul 3. PMID: 23825183.
- 5)Charousset C Zaoui A Bellaiche L Bouyer B. Are multiple platelet-rich plasma injections useful for treatment of chronic patellar tendinopathy in athletes9. a prospective study. *Am J Sports Med*. 2014;42(4):906-11. [PubMed] [Google Scholar]
- 6)Deans VM Miller A Ramos J. A prospective series of patients with chronic Achilles tendinopathy treated with autologous-conditioned plasma injections combined with exercise and therapeutic ultrasonography. *J Foot Ankle Surg*. 2012;51(6):706-10. [PubMed] [Google Scholar]
- 7) Ferrero G Fabbro E Orlandi D et al. Ultrasound-guided injection of platelet-rich plasma in chronic Achilles and patellar tendinopathy. *J Ultrasound*. 2012;15(4):260-6. [PMC free article] [PubMed] [Google Scholar]
- 8)Finnoff JT Fowler SP Lai JK et al. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. *Phys Med Rehabil*. 2011;3(10):900-11. [PubMed] [Google Scholar]
- 9). Gaweda K Tarczynska M Krzyzanowski W. Treatment of Achilles tendinopathy with platelet-rich plasma. *Int J Sports Med*. 2010;31(8):577-83. [PubMed] [Google Scholar]
- 10). Gosens T Den Oudsten BL Fievez E van 't Spijker P Fievez A. Pain and activity levels before and
- after platelet-rich plasma injection treatment of patellar tendinopathy: a prospective cohort study and the influence of previous treatments. *Int Orthop*. 2012;36(9):1941-6. [PMC free article] [PubMed] [Google Scholar]
- 11) Kon E Filardo G Delcogliano M et al. Platelet-rich plasma: new clinical application: a pilot study for treatment of jumper's knee. *Injury*. 2009;40(6):598-603. [PubMed] [Google Scholar]
- 12) Monto RR. Platelet rich plasma treatment for chronic Achilles tendinosis. *Foot Ankle Int*. 2012;33(5):379-85. [PubMed] [Google Scholar]
- 13) Oloff L Elmi E Nelson J Crain J. Retrospective analysis of the effectiveness of platelet-rich plasma in the treatment of Achilles tendinopathy: Pretreatment and posttreatment correlation of magnetic resonance imaging and clinical assessment. *Foot Ankle Spec*. 2015;8(6):490-7. [PubMed] [Google Scholar]
- 14) Volpi P Quaglia A Schoenhuber H et al. Growth factors in the management of sport-induced tendinopathies: results after 24 months from treatment. A pilot study. *J Sports Med Phys Fitness*. 2010;50(4):494-500. [PubMed]
- 15) Gumina S Campagna V Ferrazza G et al. Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: a prospective randomized study. *J Bone Joint Surg Am*. 2012;94(15):1345-52.
- 16) Castricini R Longo UG De Benedetto M et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. *Am J Sports Med*. 2011;39(2):258-65. [PubMed] [Google Scholar]
- 17) Chahal J Mall N MacDonald PB et al. The role of subacromial decompression in patients undergoing arthroscopic repair of full-thickness tears of the rotator cuff: a systematic review and meta-analysis. *Arthroscopy*. 2012;28(5):720-7. [PubMed] [Google Scholar]
- 18) Randelli P Arrigoni P Ragone V Aliprandi A Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. *J Shoulder Elbow Surg*. 2011;20(4):518-28.

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