Innovations for Active Healing

Supported by an educational grant from Bioventus

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- **Thomas J. Chang, DPM**
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Program Information

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Unlocking PRP's Full Potential:

Techniques and Trends Shaping Regenerative Care

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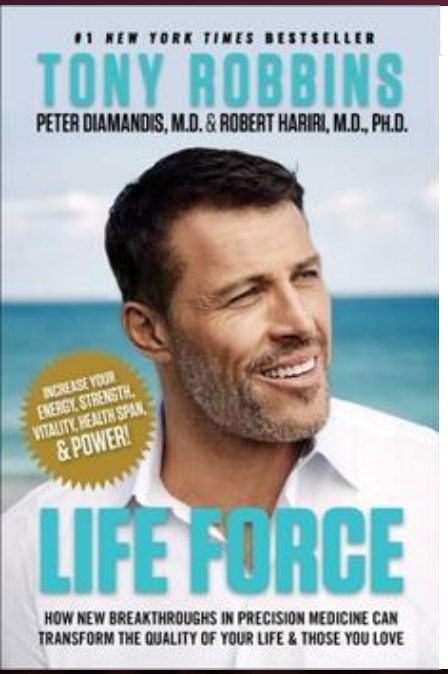
Learning Objectives

- Identify how platelet-rich plasma (PRP) and platelet-poor plasma (PPP) are made and the technologies used to create protein-rich PRP (PR-PRP)
- Compare the key growth factors in PRP and PPP and their roles in healing and reducing inflammation
- Explain how PR-PRP supports tissue repair by interacting with cells and releasing healing proteins over time
- Identify key strategies and emerging considerations for optimizing PRP therapies

PRP = platelet-rich plasma; PPP = platelet-poor plasma; PR-PRP = protein-rich platelet-rich plasma.



Bartolo Colon New York Yankees Pitcher – Shoulder & Elbow Injury

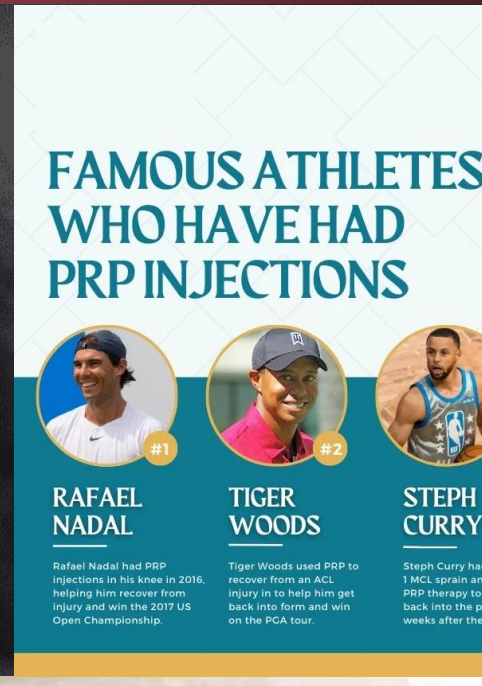
New Met and medical miracle Bartolo Colon gets another chance to defy the odds

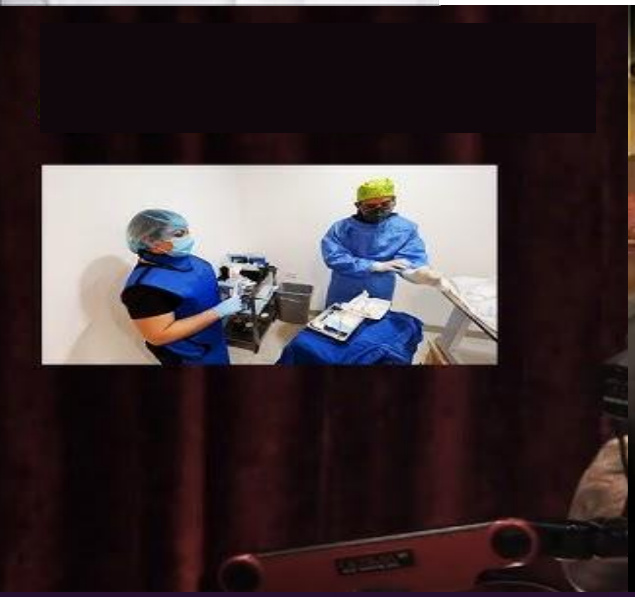
April 2010, a team of doctors extracted stem cells from fatty tissue in **Colon's** hip and bone marrow and reinjected them into his shoulder and elbow. They hoped the stem cells might promote healing, both in his partially torn rotator cuff and his damaged elbow ligaments. Six weeks later, **Colon** underwent platelet-rich plasma therapy, another measure intended to spur the healing process.

Medical experts at the time insisted there hadn't been enough studies done to prove a conclusive link between the procedure and Colon's seemingly instant results. Nevertheless, by the winter of 2010, he was pitching in the Dominican Republic and drawing attention from scouts who were impressed with his velocity. **Colon** touted the procedure as a success and went on to become one of the season's best bargains.

Published: December 14, 2013
By MARC CARIG

Tijuana's Stem Cell Therapy for Athletes: Advanced Treatments for Sports Injuries





Lessons from Mayo Clinic's Regenerative Medicine Consult Service

npj | Regenerative Medicine

www.nature.com/npjregenmed

ARTICLE OPEN

Patients seeking stem cell therapies—a prospective qualitative analysis from a Regenerative Medicine Consult Service

Jennifer R. Arthurs[1], Lisa M. Nordan[2], Brian H. Hultgren[1], Michael G. Heckman[3], Dayana Martinez[4,7], Zubin Master[5,8✉] and Shane A. Shapiro[6,8✉]

Despite patient demand for stem cell therapies (SCTs) for musculoskeletal conditions, there remains limited research on why patients seek SCTs or their sources of information. We employ three questions into a consult intake form: (1) Why are you interested in stem cell treatment for your condition? (2) How did you find out about stem cell treatment for your condition? (3) Have you contacted a stem cell clinic? Responses analyzed, using a qualitative content analysis approach to identify themes reveal many patients seek SCTs to treat pain or delay surgery which may align with some current clinical evidence while other patients express motivations as expected outcomes (e.g., SCTs are better than standard of care or can regenerate tissue) which are not supported by current medical evidence. These differences suggests that patient-centered counseling may help patients by addressing misconceptions and increasing health literacy about expected outcomes of SCTs for treating musculoskeletal conditions.

npj Regenerative Medicine (2022)7:20; https://doi.org/10.1038/s41536-022-00215-w

INTRODUCTION

Orthobiologics are substances derived from the body that are used to reduce pain and aid in the repair of musculoskeletal diseases or injuries. One component of orthobiologic medicine becoming more prevalent in use over the last decade involves point of care interventions for musculoskeletal pain and injuries[1]. In which human cells are concentrated but not manipulated or added to other substances and subsequently reimplanted or reinjected back to the site of orthopedic injury in a regulatory compliant manner. Though robust supporting evidence is lacking for most conditions, emerging support for others has demonstrated the potential for orthobiologics to improve validated patient outcomes in orthopedic disease[2–4]. Perhaps as a result of such early progress, promises of regenerative medicine have once again become hyped, accompanied by misleading claims related to the clinical readiness of regenerative and stem cell interventions. This has contributed to inflated patient expectations and a skewed public understanding of such treatments[5]. Public demand for stem cell and regenerative interventions to some degree, have created a direct-to-consumer market with about 60% of these in the orthopedic space[6–9]. Furthermore, some orthobiologic options, like platelet rich plasma do not contain stem cells yet are captured within the "stem cell" treatment (SCT) market. The growth of orthobiologics has resulted in many orthopedic and sports medicine societies publishing statements and recommending the responsible use of cell-based interventions[10–13]. As a result, responsible practitioners have attempted to navigate the difficult task of appropriately translating orthobiologic therapies despite the absence of clear clinical evidence in some applications and the presence of confounding and misleading claims permeating the field.

Patients with unmet needs actively seek potential treatments for their condition from a range of sources. In addition to online website, blog and social media searches[5,14–18], many patients seeking information about regenerative options also actively ask advice from friends, family, providers, and consultation services[19–22]. Among one of the most prolific regenerative medicine consult services in the U.S., nearly 60% of patients queried information and advice surrounding regenerative interventions for orthopedic conditions[19]. Several studies have highlighted the skewed marketing of the direct-to-consumer regenerative interventions which tends to overemphasize benefits, underestimate risks, and promote regenerative options over standard of care among[23,42], including in the use of stem cell or orthobiologic therapies[24]. These studies suggest that some patients may be misinformed about the science, safety, and efficacy of novel orthobiologics, and may choose options that are not in their best health interest. Yet not all patients considering an unproven stem cell and regenerative intervention are duped by misinformation. Patients have reported that they are well-informed having conducted extensive research[18,25] and know about the risks and have reasonable expectations about the benefits of unproven regenerative products (unpublished observations). This gets further complicated in orthobiologics where clinical studies of specific interventions for specific musculoskeletal conditions have been shown to be safe and may have some benefit[26]. Here, patients may consider a regenerative option as less invasive way to delay surgery or to provide temporary relief.

Despite the growing demand for orthobiologics by the public, little is known about why patients are considering these interventions, their expectations, and their sources of information[27]. Knowing sources of information and the reasons and values patients bring when deciding whether to undertake an orthobiologic or SCT is important to provide patients evidence-based information and counseling. This information may also help physicians reduce unrealistic optimism and taper expectations about orthobiologic and SCTs.

As part of the responsible advancement of regenerative medicine, we have developed a Regenerative Medicine Consult

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Several studies show that clinic websites and social media have significant misinformation about regenerative medicine including the level of clinical evidence, safety, and efficacy

Arthurs, et al.

Approximately 50% of patients found out about stem cell therapy online or with social media

Table 3. Responses for how patients found out about a SCT for their condition.

Responses	No. (%) of patients ($N = 576$)
"Internet" Research or Online "Search"	212 (39.8%)
Recommended by friend/family	106 (19.9%)
Healthcare provider referral or existing Mayo Clinic patient	103 (19.3%)
Social Media, video or TV segment (non-advertisement), etc.,	49 (9.2%)
Mayo Clinic Story, Media or Communications	47 (8.8%)
Stem cell seminar or stem cell clinic	29 (5.4%)
Advertisement (TV or print)/non-internet	17 (3.2%)
Clinicaltrials.gov	4 (0.8%)
I am also scientist or healthcare provider	4 (0.8%)
Other or unclear response	5 (0.9%)

Kingery, et al. examined websites of 896 clinic practices offering stem cell therapy for musculoskeletal conditions and found that websites had:

- **<u>At least 1 piece of misinformation (96%)</u>**
- An average of 4.6 statements of misinformation

Arthurs JR, et al. *NPJ Regen Med*. 2022;7(1):20. Erratum in: *NPJ Regen Med.* 2023;8(1):5. Kingery MT, et al. *J Bone Joint Surg Am.* 2020;102(1):2-9.

Patients in search of a miracle cure end up in critical condition.

Editorial

Direct-to-Consumer Marketing

The Ethics of Snake Oil Sales?

Advertising is based on one thing: happiness. It's the freedom from fear . . . you are going to be OK!
—Don Draper (Jon Hamm), *Mad Men*

I waited with anticipation for the start of the Super Bowl; it promised to be a tight showdown between 2 talented teams with each quarterback in the spotlight. Because New England was sidelined before the playoffs started, my focus would be on the shrewd commercials that cost $7 million for 30 seconds of airtime and would surely keep everyone in the OR talking for days after the game. Those commercials wittingly target the audience while providing information about products and services from the sponsors. The commercials during the game are created with the intention of generating a feverish buzz that perpetuates the advertising cycle by keeping the company at the forefront as people continue to discuss the advertisement long after it was viewed. It's a brilliant strategy for direct-to-consumer marketing.

DIRECT-TO-CONSUMER MARKETING BY THE PHARMACEUTICAL AND MEDICAL DEVICE INDUSTRY

Over the past 40 years, we have witnessed an explosion in direct-to-consumer marketing of pharmaceutical products, medical devices, medical procedures, hospitals, and insurance plans.

The United States and New Zealand are the only countries in the world that permit direct-to-consumer marketing of pharmaceuticals.[3] In 1997, the FDA eased restrictions in order to permit the pharmaceutical industry to advertise directly to the consumer; previously, that advertising was directed toward physicians.[5] We've all seen the television advertisements that promote treatments for a wide spectrum of diseases and maladies including diabetes, hair loss, arthritis, cancer, psoriasis, heartburn, erectile dysfunction, memory loss, exocrine pancreatic insufficiency . . . the list continues to grow. Ironically, the FDA has required pharmaceutical companies to communicate the potential side effects of the drugs that are being advertised, such as hair loss, erectile dysfunction, heartburn, ketoacidosis, and death. The pharmaceutical companies suggest that patients have a conversation with their physician about treatment options and side-effects. As direct-to-consumer marketing expands, there are several areas of consequence to the patient and health care providers.

The promoters of direct-to-consumer marketing suggest that as health care costs escalate, patients are becoming consumers of health care. Patients are becoming more engaged in their own care, and an educated patient is capable of making an informed, shared decision with the physician. Direct-to-consumer marketing provides power to the patient through education and knowledge, and this can enable a robust discussion between the patient and the provider. Advocates suggest that direct-to-consumer marketing can create awareness of diseases and conditions that can lead to the early diagnosis and treatment of the problem. The pharmaceutical companies can raise the public awareness of certain diseases, and this can be broadcast to millions of consumers. Supporters suggest that direct-to-consumer marketing reduces the stigma of diseases such as obesity, mental illness, and erectile dysfunction; it has the ability to normalize medical conditions that were previously beneath the societal threshold for open discussion in any forum.

A negative consequence of direct-to-consumer marketing is the overdiagnosis and treatment of patients. The majority of patients lack the sophisticated medical knowledge necessary to make complex diagnostic and therapeutic decisions. The pharmaceutical companies often provide asymmetric information to consumers that does not include alternative forms of treatment or less expensive options. Through direct-to-consumer marketing, patients may be convinced that they have a particular medical condition that warrants a specific medication. This can alter the doctor-patient relationship and create a conflict with physicians who are reluctant to prescribe the medication. Some physicians may feel pressured to prescribe the medication rather than engage in a discussion regarding alternative treatments, including conservative measures such as diet and exercise. This can lead to the overuse and overprescribing of medication that creates a true *subscription model* with repeated refills, which can escalate health care costs without providing improved health benefits to the patient. The potential exists for the *medicalization* of normal body aches and the natural aging process that can lead to the overtreatment of patients with unnecessary, costly medication.

The change in the FDA regulations in 1997 heralded a dramatic change in medical marketing in the United

Keywords: direct-to-consumer; marketing; orthobiologics

The American Journal of Sports Medicine
2023;51(5):1133-1135
DOI: 10.1177/03635465231163567

Armando Veve, special to ProPublica

The Birth-Tissue Profiteers

How well-meaning donations end up fueling an unproven, virtually unregulated $2 billion stem cell industry.

by Caroline Chen, May 7, 2019, 5 a.m. EDT

Propublica

HEALTH

How do you separate scientifically sound stem cell therapies from scams?

By Natalya Ortolano Aug. 18, 2020 Reprints

For Better Science. Published Dec. 8, 2015. Accessed Sept. 12, 2025. forbetterscience.com/2015/12/08/stem-cell-cures-for-everything-made-in-germany-by-ticeba/ Foster TE. *Am J Sports Med.* 2023;51(5):1133-1135. ProPublica. Published May 7, 2019. Accessed Sept. 12, 2025. propublica.org/article/amniotic-stem-cell-treatment-transplant-therapy Stat10. Published Aug. 18, 2020. Accessed Sept. 12, 2025. statnews.com/2020/08/18/separate-scientific-scam-stem-cell/

Our Societies Expect Providers to Be Able to Discuss Orthobiologic Treatments

Position Statement

American Medical Society for Sports Medicine Position Statement: Principles for the Responsible Use of Regenerative Medicine in Sports Medicine

Jonathan T. Finnoff, DO,* Tariq M. Awan, DO,† Joanne Borg-Stein, MD,‡ Kimberly G. Harmon, MD,§ Daniel C. Herman, MD, PhD,¶ Gerard A. Malanga, MD,‖ Zubin Master, PhD,** Kenneth R. Mautner, MD,†††‡‡‡ and Shane A. Shapiro, MD§§

Abstract: Many sports medicine physicians are currently considering introducing regenerative medicine into their practice. Regenerative medicine and the subclassification of orthobiologics are a complicated topic and have produced widely varying opinions. Although there is concern by government regulators, clinicians, scientists, patient advocacy organizations, and the media regarding the use of regenerative medicine products, there is also excitement about the potential benefits with growing evidence that certain regenerative medicine products are safe and potentially efficacious in treating musculoskeletal conditions. Sports medicine physicians would benefit from decision-making guidance about whether to introduce orthobiologics into their practice and how to do it responsibly. The purpose of this position statement is to provide sports medicine physicians with information regarding regenerative medicine terminology, a brief review of basic science and clinical studies within the subclassification of orthobiologics, regulatory considerations, and best practices for introducing regenerative medicine into clinical practice. This information will help sports medicine physicians make informed and responsible decisions about the role of regenerative medicine and orthobiologics in their practice.

Key Words: orthobiologics, osteoarthritis, regenerative medicine, tendinopathy

(*Clin J Sport Med* 2021;31:530–541)

BACKGROUND AND PURPOSE

In the United States, the number of clinics offering "stem-cell therapy" is estimated to be well over 1000.[1,2] Many clinics advertise unproven and unapproved regenerative medicine interventions for musculoskeletal conditions.[1,2] A press release from the US Food and Drug Administration (FDA) in 2018 stated that, "The potential health benefits of regenerative medicine have spurred major progress in stem-cell biology over the past several decades. But we continue to see bad actors exploiting [illegible] mislead vulnerable [illegible] safe, effective [illegible]

producers are leveraging the field's hype to push unapproved, unproven, illegal, and potentially unsafe products."[1]

Many sports medicine physicians are currently considering the role of regenerative medicine in their practice. The purpose of this position statement created by the American Medical Society for Sports Medicine (AMSSM) is to provide sports medicine physicians with information regarding regenerative medicine terminology, a brief review of the basic science and clinical studies related to the musculoskeletal field (now commonly referred to as orthobiologics), regulatory considerations, and best practices for

tions. This information should be considered when formulating a treatment algorithm.

Although there is strong interest among patients for regenerative medicine to treat orthopedic and sports-related conditions, the provider must explain the evidence-based rationale for such treatments and avoid patient motivations that are not supported by evidence.[139] Similarly, the provider must guard against the potential to be unduly influenced by internal and external commercial motivations when completing their evaluation of the scientific support for a given procedure.

AAOS American Academy of Orthopaedic Surgeons
American Association of Orthopaedic Surgeons

Position Statement

Use of Emerging Biologic Therapies

This Position Statement was developed as an educational tool based on the opinion of the authors. It is not a product of a systematic review. Readers are encouraged to consider the information presented and reach their own conclusions.

The increasing use of biologics to try to improve outcomes for orthopedic patients presents new questions of safety and effectiveness for those products. As we note in the statement "Innovation and Novel Technologies in Orthopaedic Surgery," surgeons must be aware of the scientific basis for the different treatment options available to their patients, including the benefits and risks. Biologic therapies vary widely with regards to the requirements for evidence of safety and effectiveness needed for clearance by regulatory bodies, including the US Food and Drug Administration (FDA). Not all biologic products require extensive FDA regulation, and in some cases, the FDA has primarily focused on safety concerns and has ceded responsibility for determining the efficacy of these products to the clinician.

The American Academy of Orthopaedic Surgeons (AAOS) believes that surgeons should be cognizant of the risks, benefits, regulatory status and labeled indications of the products they use.

For all products, but particularly those which the FDA does not critically evaluate effectiveness data, clinicians bear a greater responsibility to independently weigh that evidence. This responsibility also extends to off-label use of FDA-regulated products, and cases where the devices used to create or deliver the biologic product, rather than the product itself, are what has been approved by the FDA. It also applies to cases where a manufacturer believes they are exempt from certain FDA regulations without formal review of exemption, such as the so-called 361 exemption for human cell and tissue products. In all of these examples, the clinicians using these biologic products need to be particularly careful to weigh the available evidence and conduct shared decision-making with the patient in the informed consent process.

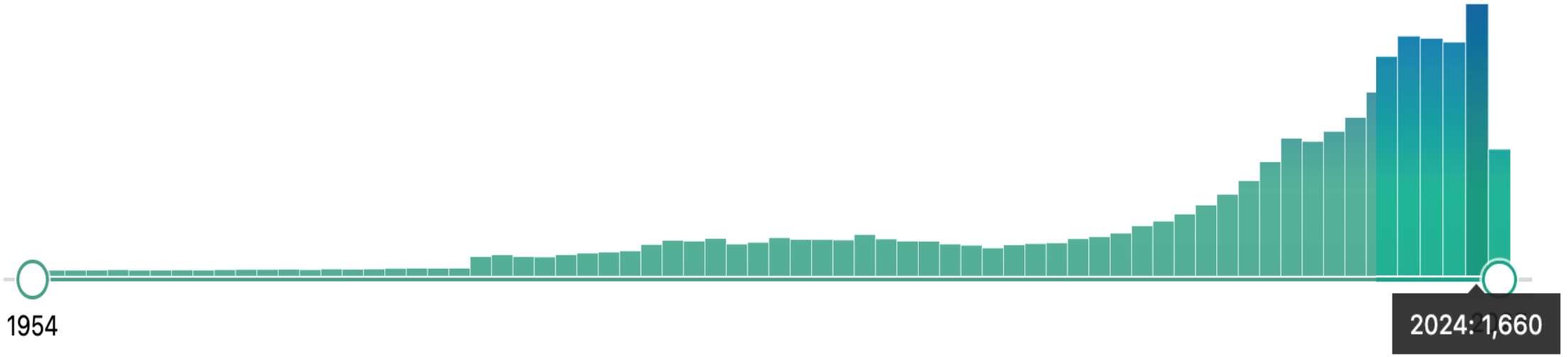
The AAOS Standards of Professionalism state "An orthopaedic surgeon, or his or her qualified designee, shall present pertinent medical facts and recommendations to, and obtain informed consent from, the patient or the person responsible for the patient."
The mandatory standard obligates surgeons to disclose any products that may be used during the episode of care and engage in frank discussion regarding the risks and benefits of biologics when they are part of that episode of care.

AMSSM & AAOS Position Statements

- Standards of Professionalism obligate us to be able to have frank discussion regarding biologics, including:
  - Explain the evidence-based rationale for such treatments
  - Avoid patient motivations that are not supported by evidence
  - Guard against commercial motivations
  - Consider how these procedures fit into the broader treatment algorithm
  - If the decision is made to perform an orthobiologic procedure, then the least invasive, safest, most cost-effective treatment with the highest level of evidence should be implemented first

Finnoff JT, et al. *Clin J Sport Med.* 2021;31(6):530-541. AAOS. Position Statement: Use of Emerging Biologic Therapies. Revised Sept. 2020. Accessed Sept. 12, 2025. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.aaos.org/globalassets/about/position-statements/1187-use-of-emerging-biologic-therapies-updated2020.pdf

What's the Evidence?



2025 (PubMed search)

- 18,6465 **"platelet-rich plasma"** articles published to date

What's the Evidence?


EXPERT OPINION
ON BIOLOGICAL THERAPY

EXPERT OPINION ON BIOLOGICAL THERAPY
2025, VOL. 25, NO. 3, 309–318
https://doi.org/10.1080/14712598.2025.2465833

Taylor & Francis

SYSTEMATIC REVIEW

OPEN ACCESS

Corticosteroids, hyaluronic acid, platelet-rich plasma, and cell-based therapies for knee osteoarthritis - literature trends are shifting in the injectable treatments' evidence: a systematic review and expert opinion

Alessandro Bensa, Luca Bianco Prevot, Giacomo Moraca, Alessandro Sangiorgio, Angelo Boffa and Giuseppe Filardo

ABSTRACT

Introduction: The aim of this systematic review was to quantify the data available on corticosteroids (CS), hyaluronic acid, (HA), platelet-rich plasma (PRP), and cell-based therapies for knee osteoarthritis (OA) treatment.

Methods: A literature search was conducted on PubMed, Cochrane, and Web of Science according to the PRISMA guidelines. Inclusion criteria: clinical studies of any level of evidence, written in English, evaluating the intra-articular use of CS, HA, PRP, or cell-based therapies for knee OA treatment.

Results: The initial search identified 17,415 records. A total of 766 studies from 1959 were included. Of these, 401 were randomized controlled trials (RCTs), 110 comparative studies, and 255 case series, for a total of 75,834 patients. (11,245 treated with CS, 40,862 with HA, 16,174 with PRP, and 7,553 with cell-based therapies). The number of placebo-controlled RCTs remains limited and a negligible percentage of studies investigated possible disease-modifying effects of these treatments for knee OA.

Conclusions: The evidence on injective knee OA treatments is increasing at different speeds with a more rapidly growing literature focusing on orthobiologics. Currently, HA has the largest evidence, followed by PRP that recently surpassed the number of studies evaluating CS. Cell-based therapies are also growing rapidly, although the number of studies is still lower. The rapid literature shift toward orthobiologics urges an update in societies' guidelines to align with the new body of evidence on knee OA treatments.

Protocol registration: www.crd.york.ac.uk/prosperoi dentifier is CRD42024592972.

ARTICLE HISTORY
Received 26 November 2024
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KEYWORDS
Intra-articular; knee; osteoarthritis; corticosteroids; hyaluronic acid; platelet-rich plasma; cell-based therapies

1. Introduction

Knee osteoarthritis (OA) has a global prevalence of 23% among individuals aged >40 years and is constantly increasing, representing a considerable global burden [1–4]. Patients experience symptoms such as pain, swelling, and functional limitation, with a considerable impact on their quality of life [5]. Non-surgical treatments of knee OA entail weight loss, physical therapy, dietary supplements, and non-steroidal anti-inflammatory drugs (NSAIDs) [6,7]. When these strategies fail to provide satisfactory results, intra-articular injections are a common option in the clinical practice to provide benefits and delay the need for more invasive and expensive surgical solutions.

Injective treatments aim to provide clinical improvement by restoring joint homeostasis through the direct local administration of therapeutic products [8,9]. This maximizes the intra-articular product concentration, optimizing its therapeutic potential while minimizing systemic exposure and related side effects [9]. Corticosteroids (CS) and hyaluronic acid (HA) are the most commonly used products in the clinical practice, with platelet-rich plasma (PRP) becoming an increasingly more available option followed by the newer cell-based therapies. CS have been used for decades in the treatment of symptomatic knee OA, exploiting the anti-inflammatory and immunosuppressive effects to target the joint inflammatory process leading to symptomatic relief [10–13], and represent the most endorsed injective option by international guidelines for knee OA management [14–17]. However, their results are suboptimal, with recent evidence showing that the clinical effect is perceivable by patients only up to 6 weeks [18]. HA represents another widely used injective option thanks to its ability to provide joint lubrication and shock absorbency with documented benefits in terms of pain relief and functional improvement [19]. Nonetheless, HA is not currently supported by the same level of recommendation as CS across the guidelines proposed by international societies [14–17], and recent evidence demonstrated a lack of superiority in terms of pain relief and functional improvement both at short- and long-term follow-ups compared to CS [20]. This fostered the emergence of new

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Table 1. Number of studies, study design, and number of patients for each injectable product type.

Injectable product	N. studies (N. patients)	RCT	Comparative	Case series
CS	**162** (11,245)	**110** (5,700)	**20** (2,700)	**32** (2,845)
HA	**369** (40,862)	**236** (19,049)	**56** (12,027)	**77** (9,786)
PRP	**236** (16,174)	**127** (6,557)	**36** (2,234)	**73** (7,383)
Cells	**142** (7,553)	**44** (1,813)	**31** (2,007)	**67** (3,733)

CS: corticosteroids, HA: hyaluronic acid, PRP: platelet-rich plasma, RCT: randomized controlled trial.

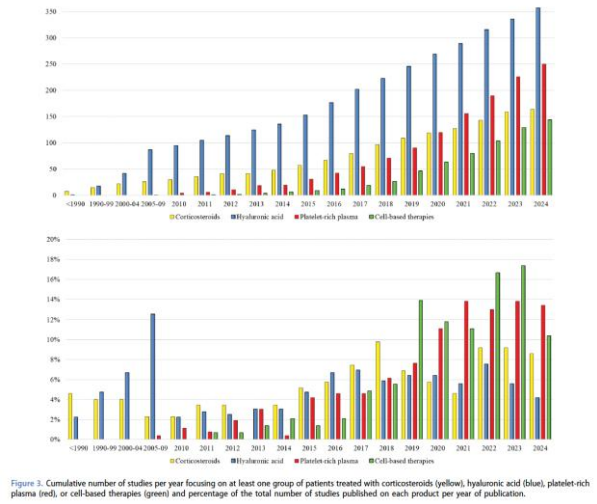


Figure 3. Cumulative number of studies per year focusing on at least one group of patients treated with corticosteroids (yellow), hyaluronic acid (blue), platelet-rich plasma (red), or cell-based therapies (green) and percentage of the total number of studies published on each product per year of publication.

Blue=HA; Red=PRP; Yellow=CS

Bensa, et al. 2025

Systematic review

- Review performed on IA inj of CS, HA, PRP, and cell-based therapies for knee OA
- Included all clinical studies (at least 6 patients) of any level of evidence

Results

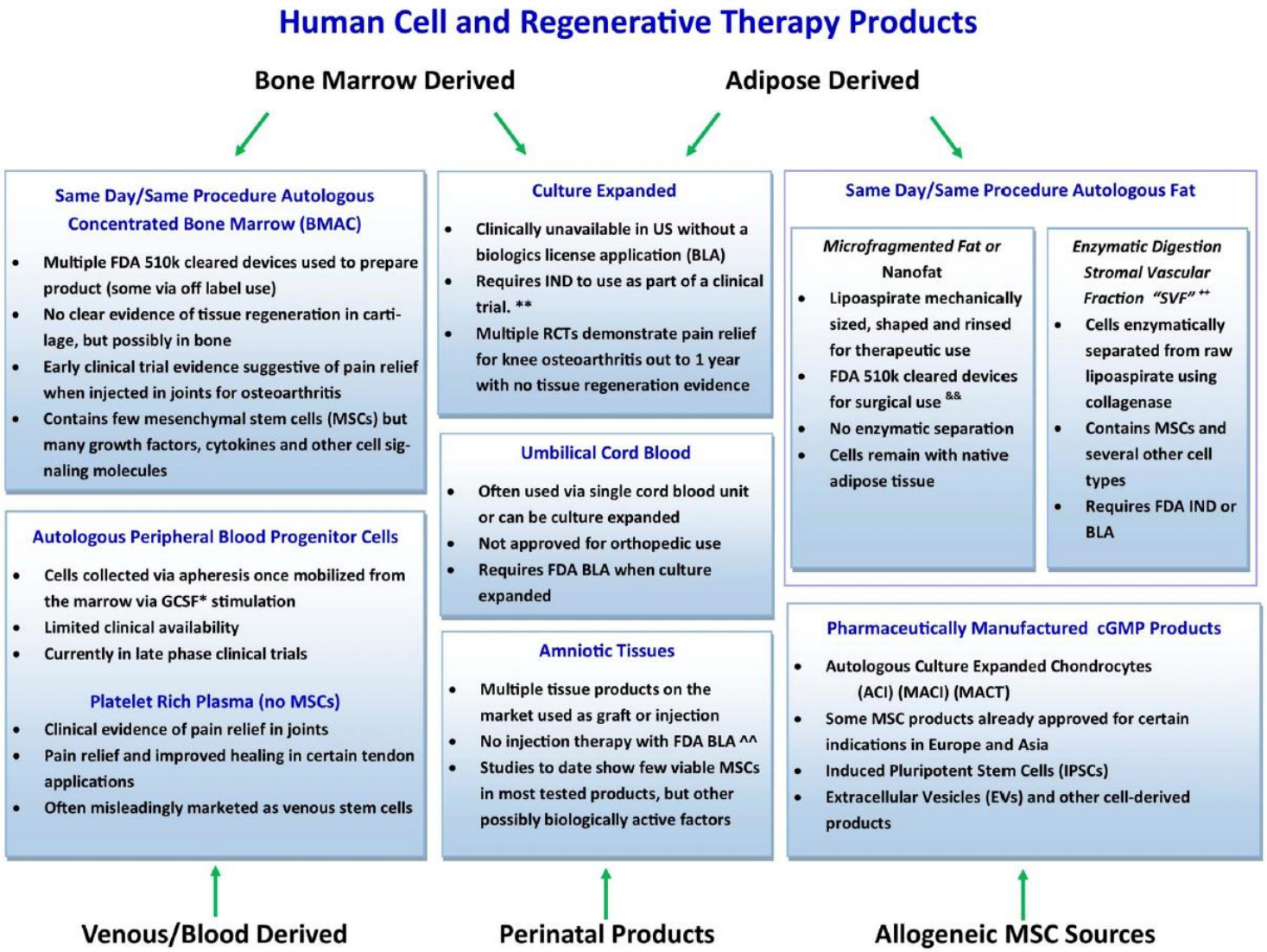
- 766 studies analyzed (*75,834 patients)*
- 401 RCT

Outcomes

- **PRP showed comparable short-term results to CS but provided better results at mid- and long-term follow-ups, exceeding the MCID**
- Currently, HA has the largest evidence, followed by PRP
- PRP recently surpassed the number of studies and patients evaluating CS for KOA
- Published RCTs focusing on PRP exceeds CS

IA = intra-articular; CS = corticosteroid; HA = hyaluronic acid; OA = osteoarthritis; MCID = minimal clinically important difference; KOA = knee osteoarthritis.

The Field of *Regenerative Medicine* Is Broader than Just PRP



Outline

- Background of Orthobiologics
- Platelet-Rich Plasma Injections
- Bone Marrow Concentrate
- Microfragmented Adipose Tissue

History of PRP

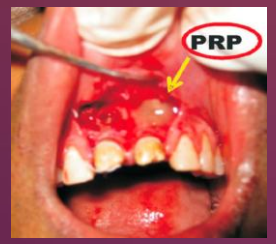
PRP was initially developed for transfusions

1970s

1987

CT surgery uses PRP to accelerate sternotomy healing in Italy

MFS added PRP to bone grafts accelerating rate of bone formation



1990s

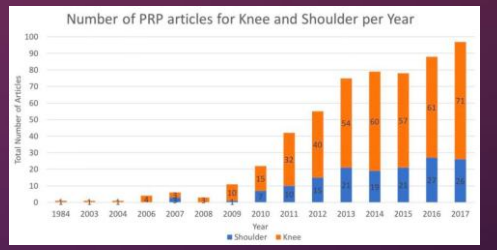
2006

Mishra and Pavelko publish first PRP study on MSK application, chronic elbow tendinosis, in *Am J Sports Med*

Kim Kardashian receives Vampire facial on *Keeping up with the Kardashians*

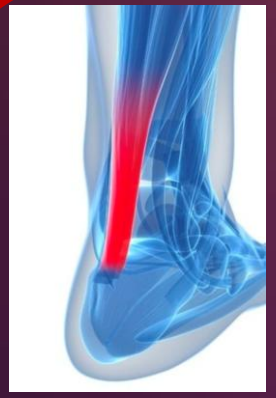
2013

2019

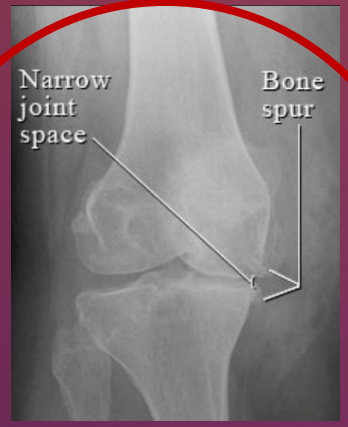


PRP articles and applications continue to expand

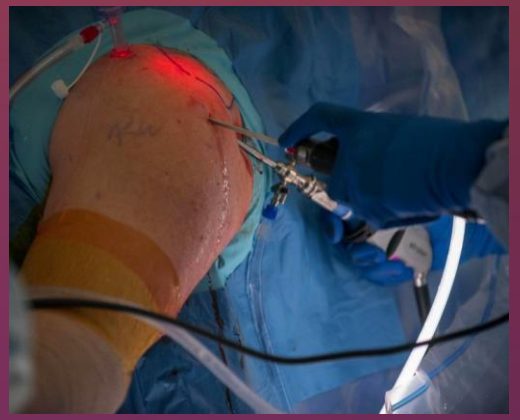
MSK/Ortho Applications for Orthobiologics



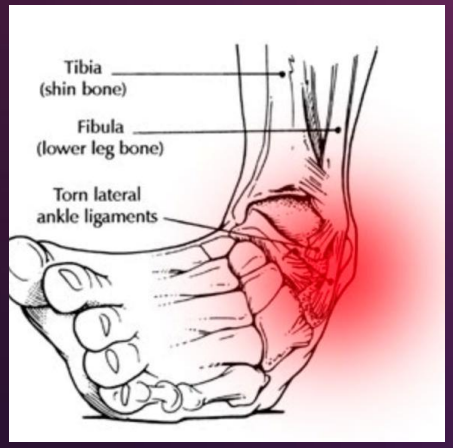
Tendons



Osteoarthritis

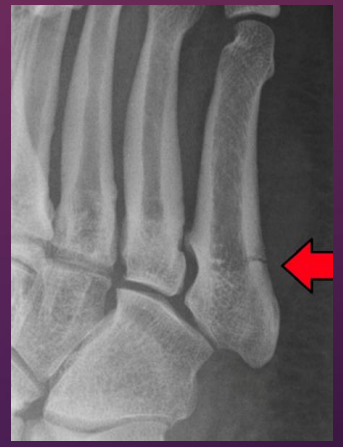


Augment Surgery



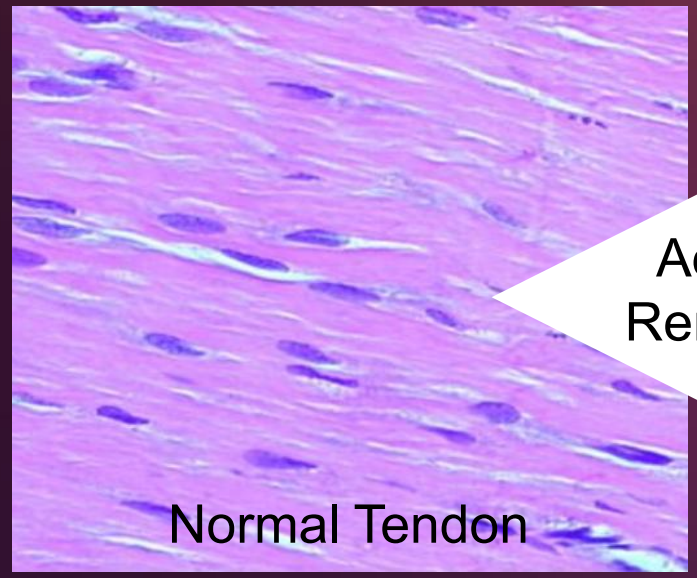
Ligament

Intra-discal



Fracture
Non-union

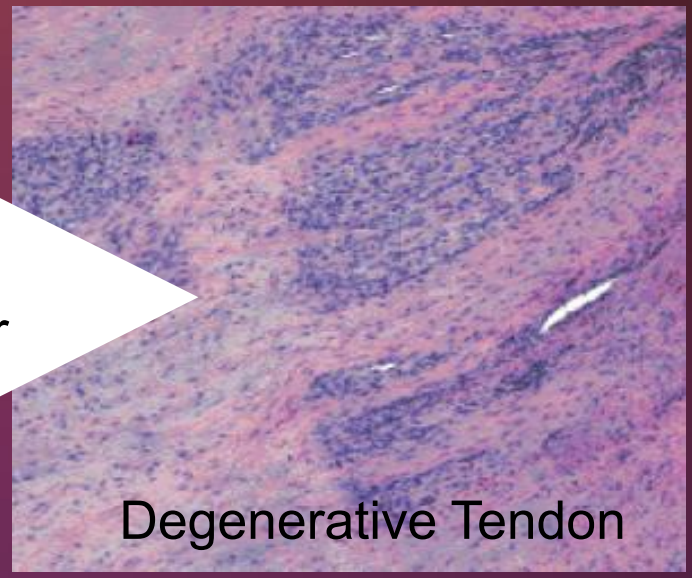
Traditional Orthopedic Approach

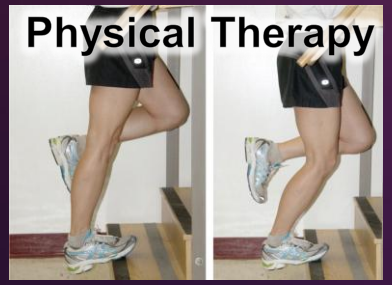


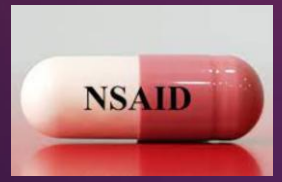
Adaptive Remodeling

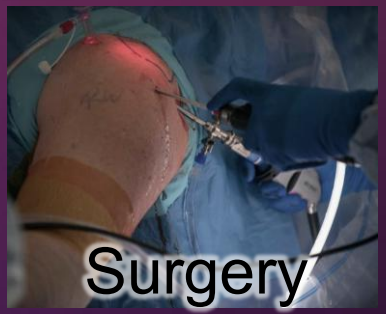
Reactive Tendinopathy

Tendon Disrepair

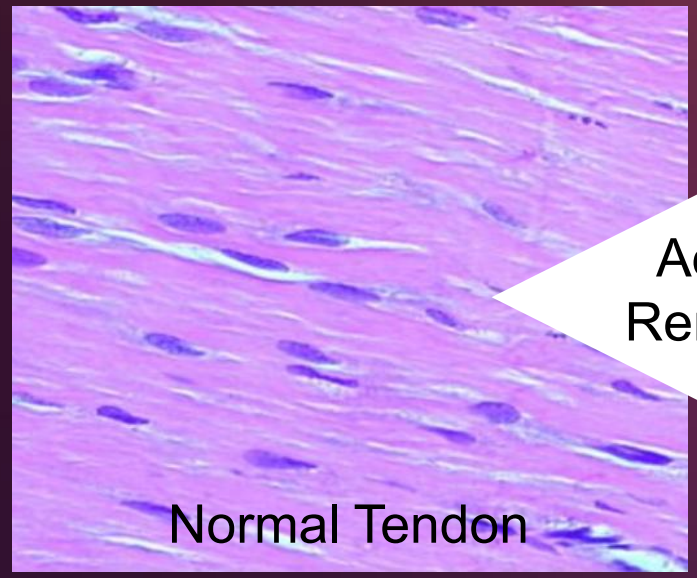








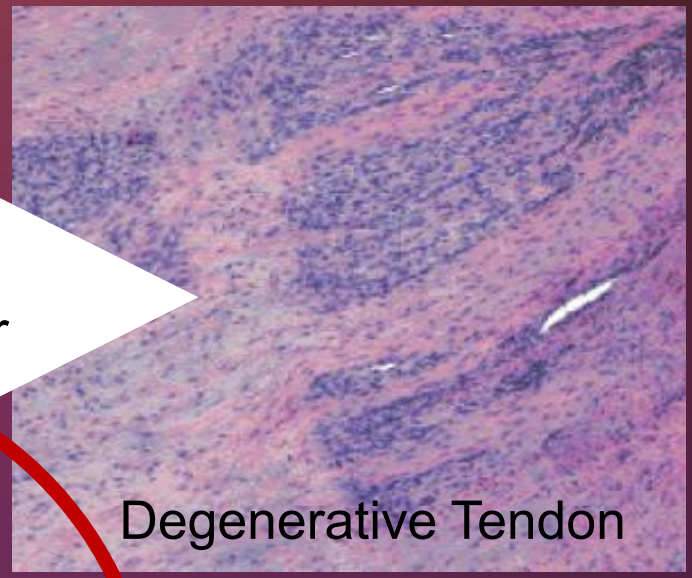
Traditional Orthopedic Approach

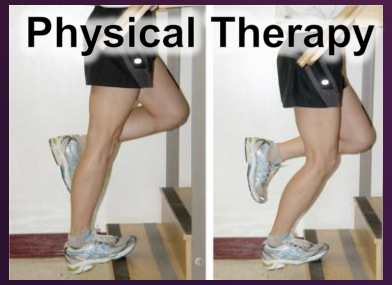


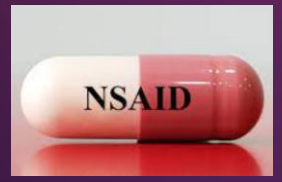
Adaptive Remodeling

Reactive Tendinopathy

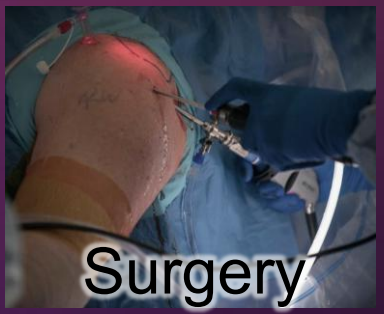
Tendon Disrepair







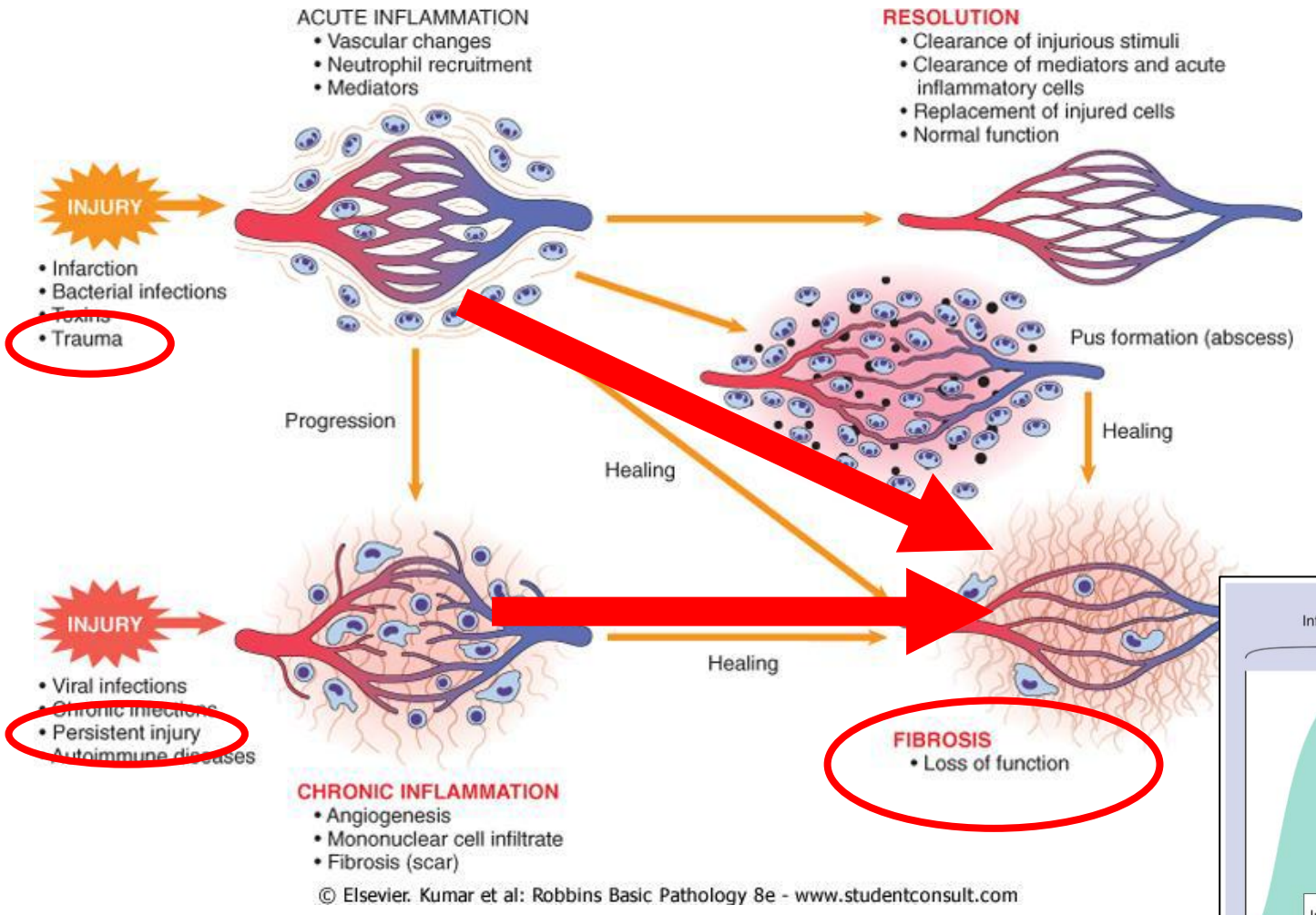
Treatment Gap



Treatments available for tendon disease have continued to develop, and a multitude of therapies are available that are supported by varying degrees of clinical evidence.

- Percutaneous needle fenestration and tenotomy
- Sclerotherapy
- Prolotherapy
- High-volume injections (hydrodissection)
- Sodium hyaluronate/viscosupplementation
- Percutaneous pulley release
- Extracorporeal shockwave therapy
- Barbotage for calcific tendinopathy
- Radiofrequency ablation/TOPAZ coblation
- Minimally invasive ultrasonic energy debridement tool
- Platelet-rich plasma (PRP)
- Autologous blood
- Bone marrow-derived stem cells (BMA or BMAC)
- Micronized adipose-derived stem cells (MFAT)
- Cryopreserved human amniotic membrane

MFAT = micronized adipose-derived stem cells.



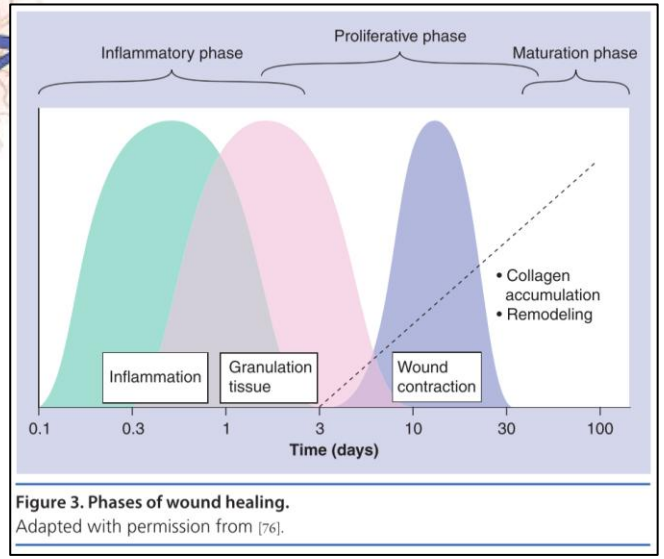
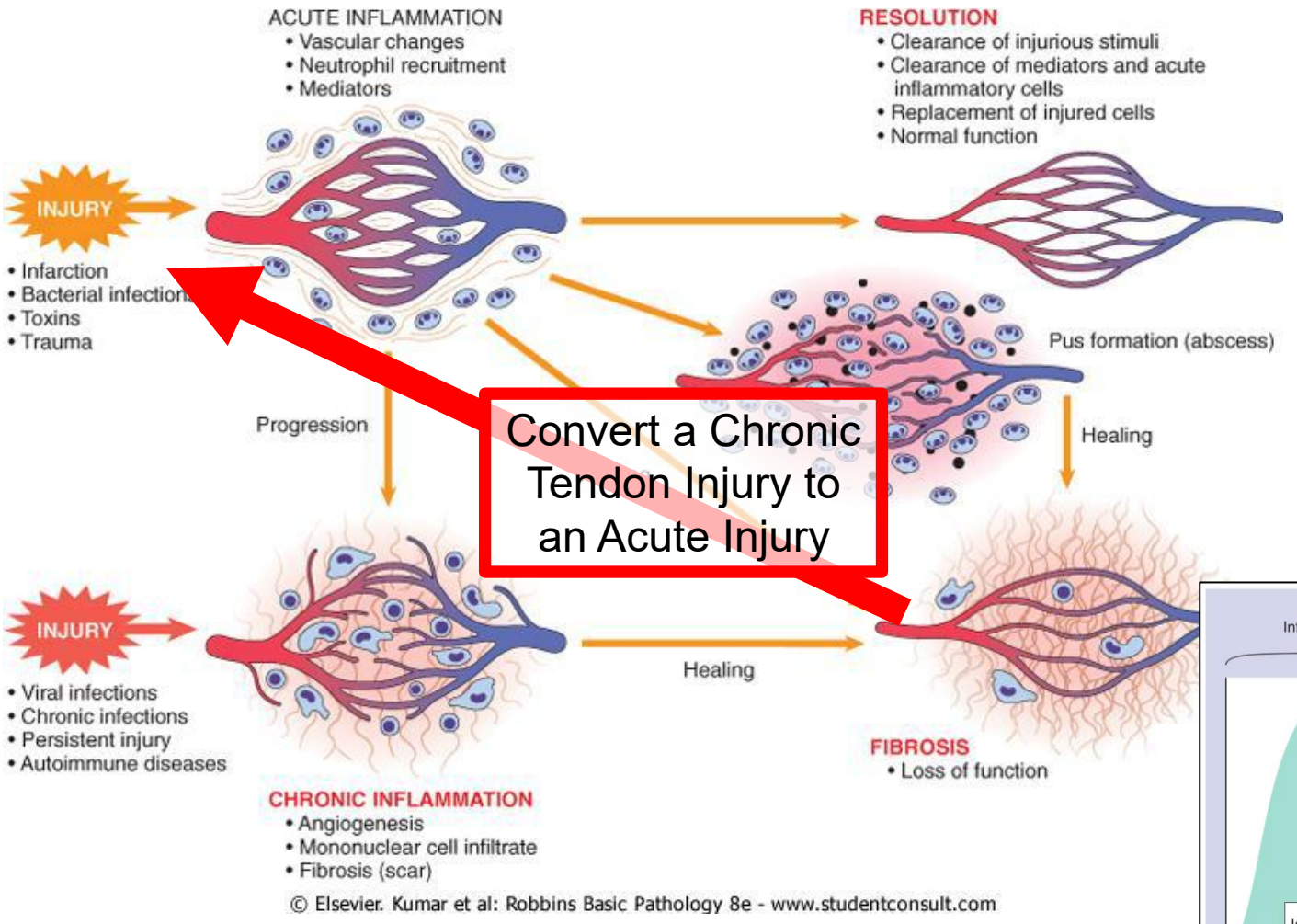
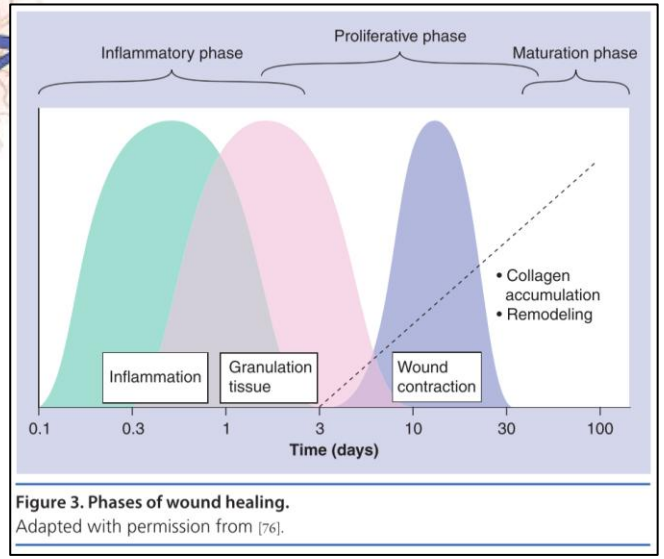


Figure 3. Phases of wound healing.
Adapted with permission from [76].

The holy grail of tendon treatment is finding a way to regenerate injured tissue to its original state.





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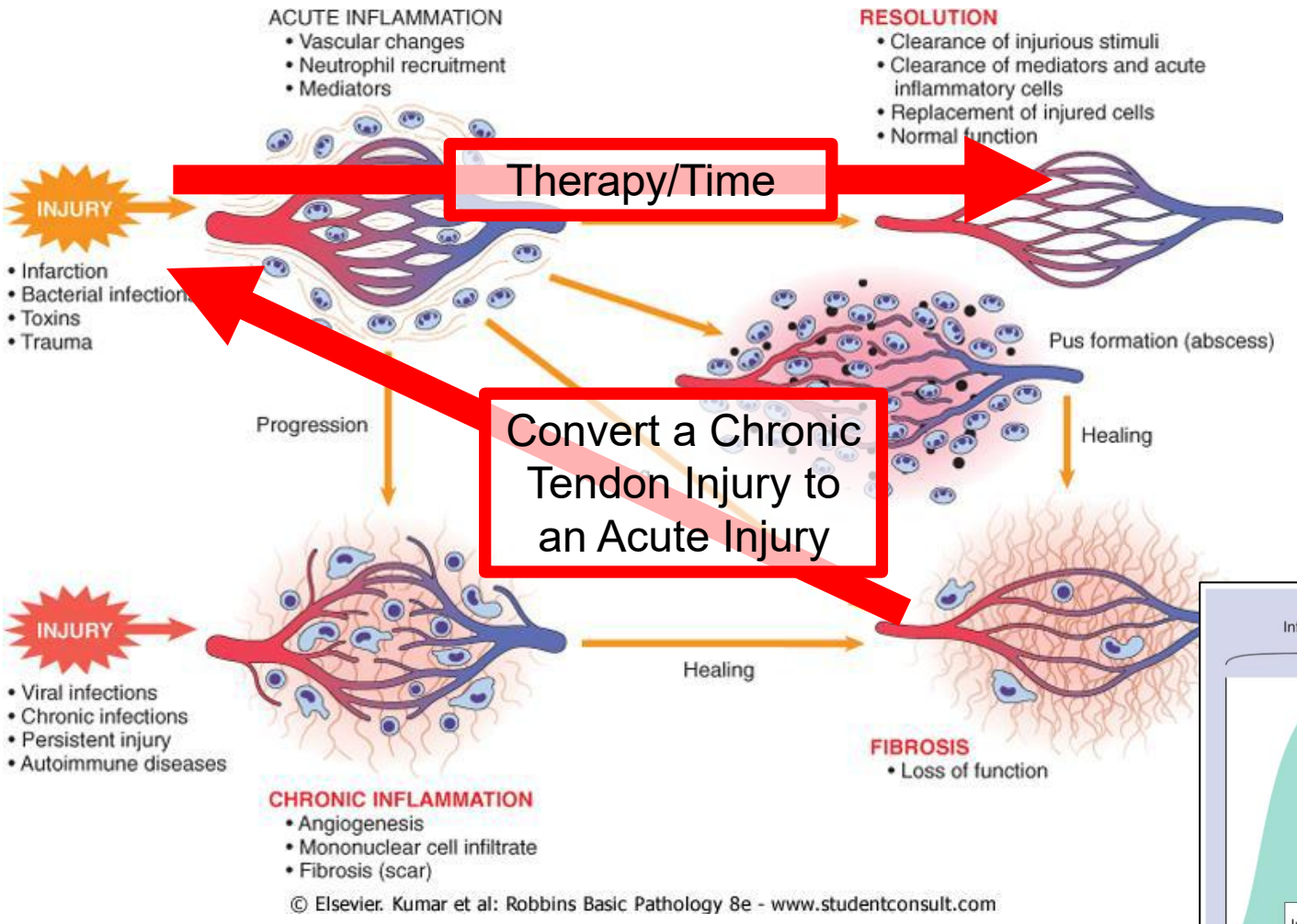

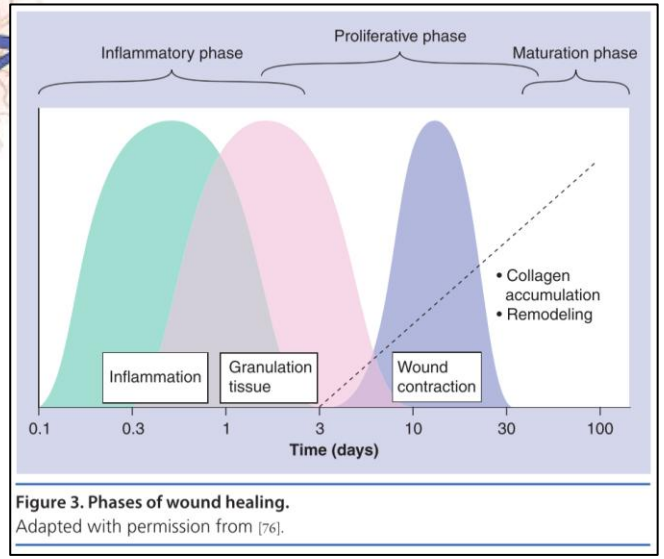

Figure 3. Phases of wound healing.
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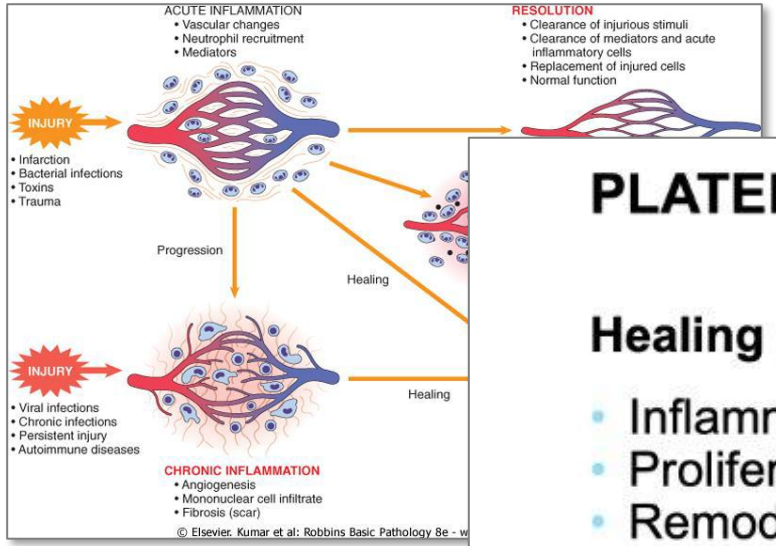
The holy grail of tendon treatment is finding a way to regenerate injured tissue to its original state.

Healing Cascade

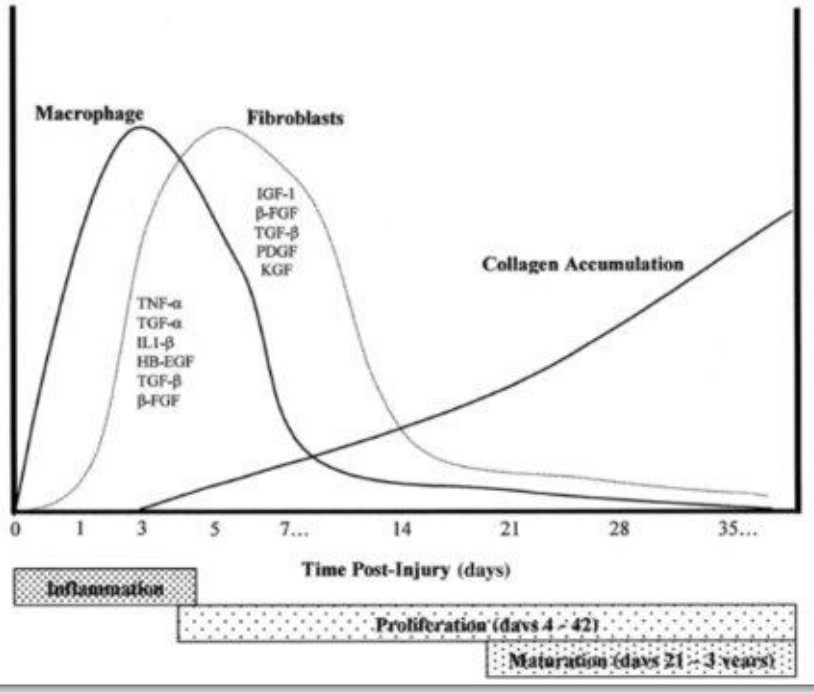


PLATELET RICH PLASMA (PRP)

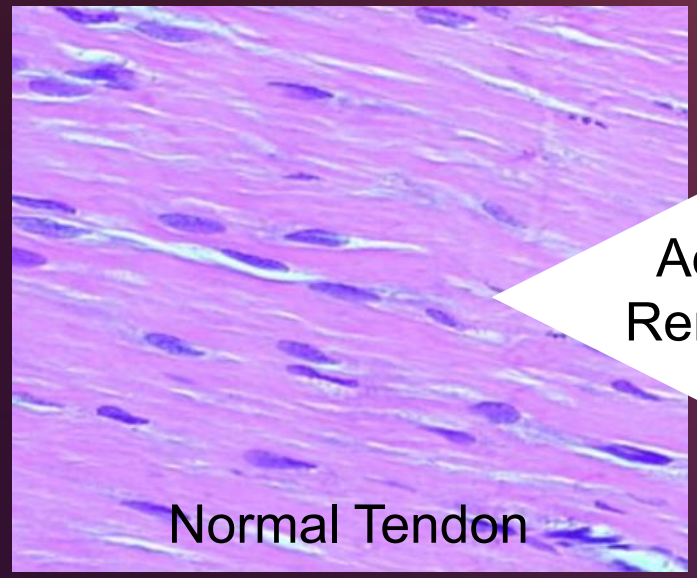
Healing through 3 phases

- Inflammation
- Proliferation
- Remodeling

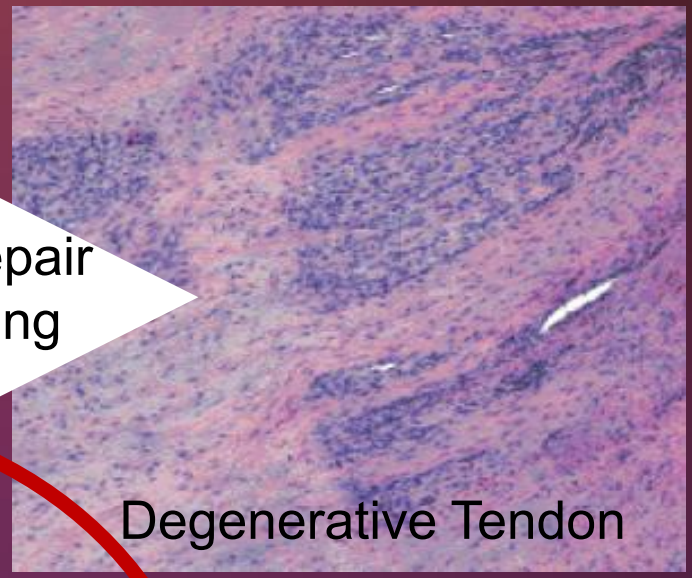
Cytokines and growth factors released from PRP are known to affect the basic metabolic processes in soft tissues of the musculoskeletal system such as tendon, ligament, and muscle

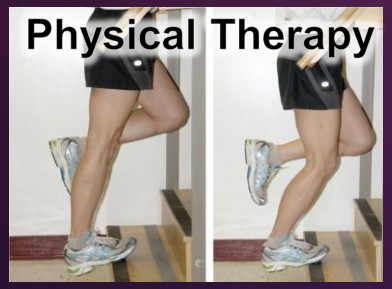


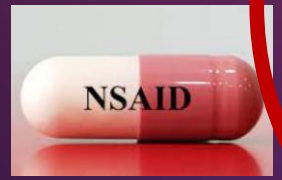
Traditional Orthopedic Approach



Adaptive Remodeling → Reactive Tendinopathy → Tendon Disrepair Failed Healing







Percutaneous tenotomy

Platelet-rich plasma

RFA coblation

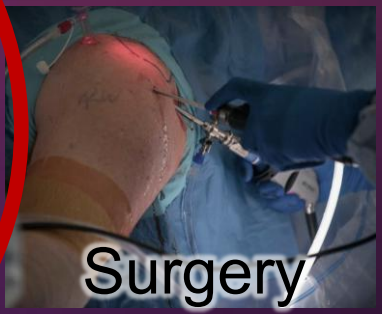
Ultrasonic debridement/
Vacuum-assisted PNT

Prolotherapy

Shockwave therapy

MFAT

BMAC



RFA = radiofrequency ablation; BMAC = bone marrow aspirate concentrate.

When to Consider Orthobiologics

Patients who

- Failed conservative management

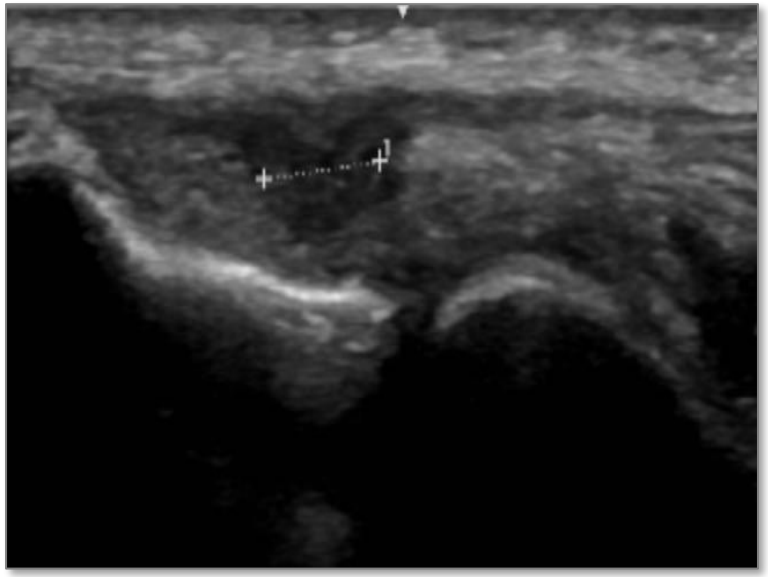
  AND

- Contraindication TO Surgery
- Buying time until definitive treatment is more appropriate
- Patient preference

Patients in the orthopedic treatment gap

Matching the Treatment to the Underlying Tendon Pathology

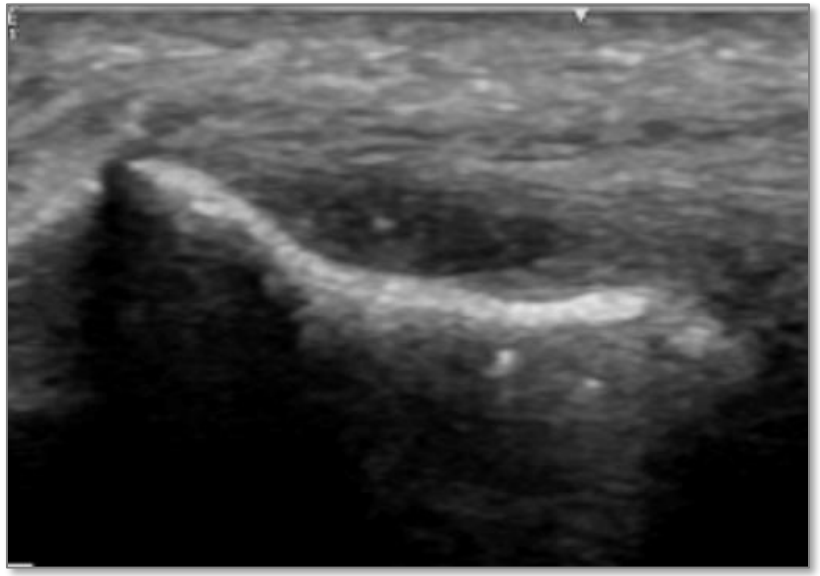
Matching the Treatment to the Underlying Tendon Pathology



Lateral epicondylitis due to a high-grade common extensor tear

Matching the Treatment to the Underlying Tendon Pathology

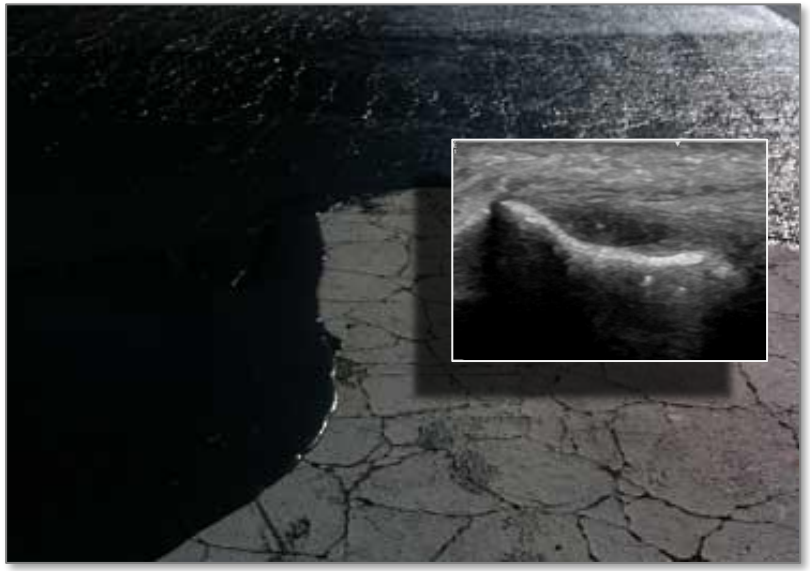
Lateral epicondylitis due to a high-grade common extensor tear



Lateral epicondylitis due to a tendinopathy of the common extensor tear

Matching the Treatment to the Underlying Tendon Pathology

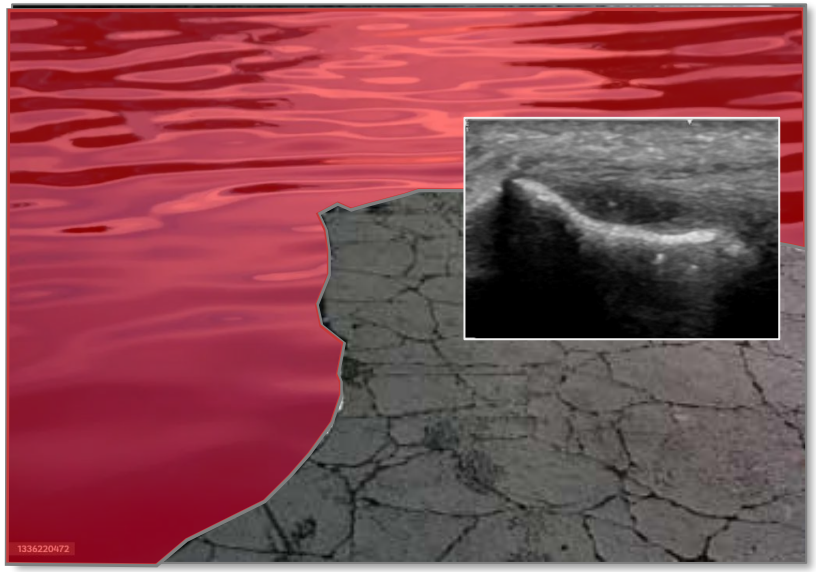
Lateral epicondylitis due to a high-grade common extensor tear



Lateral epicondylitis due to a tendinopathy of the common extensor tear

Matching the Treatment to the Underlying Tendon Pathology

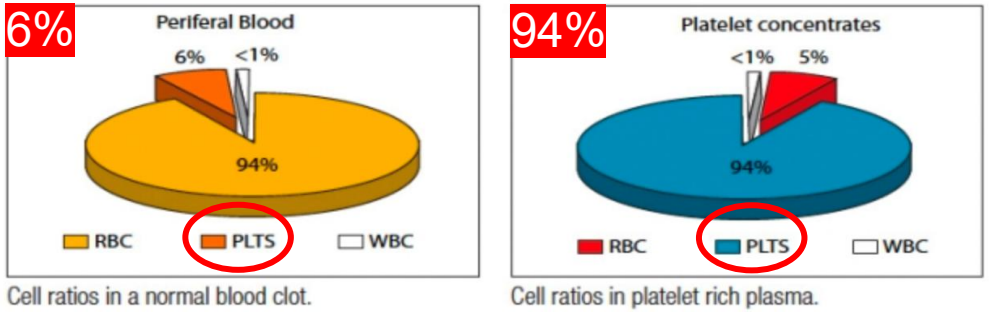
Lateral epicondylitis due to a high-grade common extensor tear



Lateral epicondylitis due to a tendinopathy of the common extensor tear

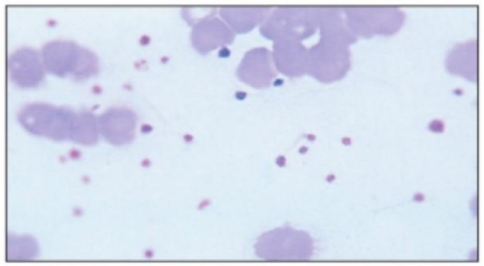
What, Exactly, Is PRP?

FDA definition of PRP: An autologous blood product with a higher concentration of platelets than baseline values

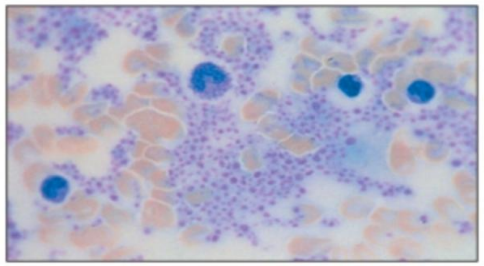


Cell ratios in a normal blood clot.

Cell ratios in platelet rich plasma.



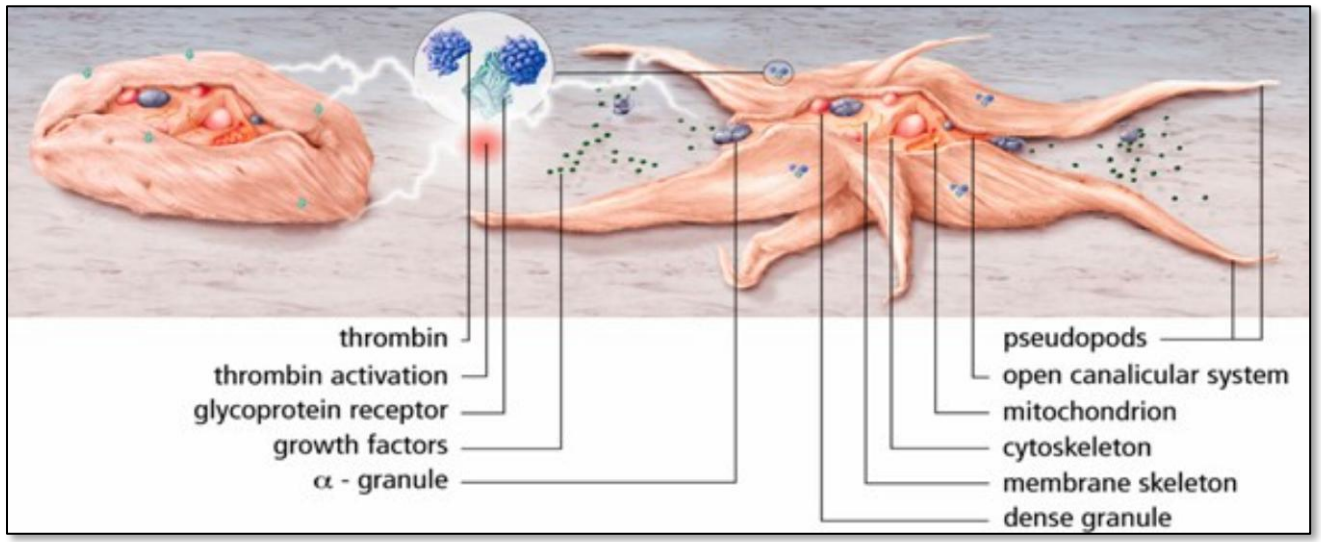
Peripheral blood smear in normal blood.



Peripheral blood smear of platelet rich plasma.

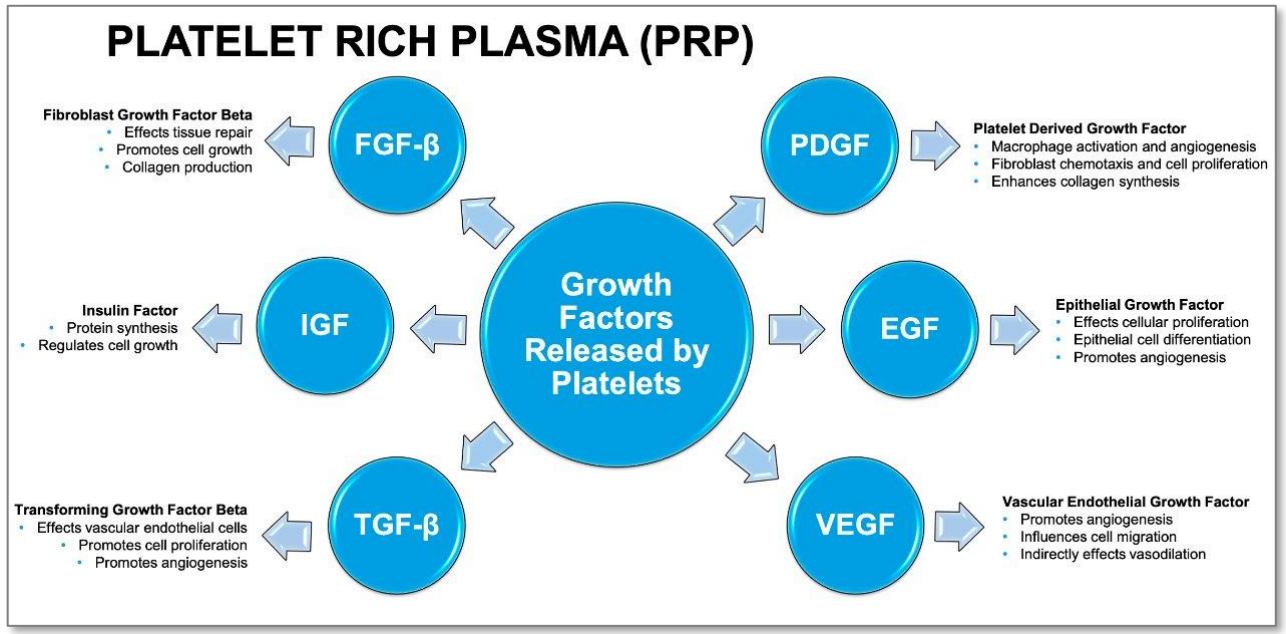
Figure 1. Difference between whole blood and platelet-rich prolotherapy. Top left, cell ratios in a normal blood clot. Top right, cell ratios in platelet-rich plasma. Bottom left, peripheral blood smear in normal blood. Bottom right, peripheral blood smear of platelet-rich plasma.
PLTS, platelets; RBC, red blood cells; WBC, white blood cells

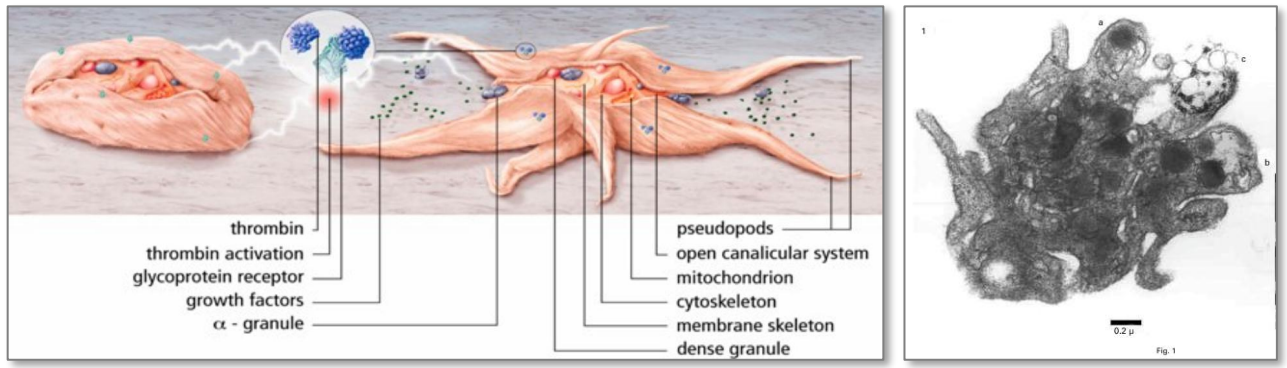
Platelet Counts
- Whole blood 150-400,000 mm^3
- FDA defn PRP >250,000 mm^3



Alderman D, Alexander R. *Pract Pain Manag*. 2011;11(8).

What, Exactly, Is PRP?





PRP contains cocktail of cytokines and growth factors to promote/restart the healing cascade

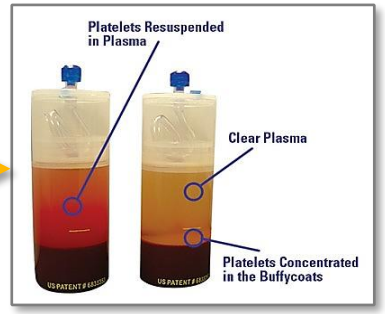
Aim is to deliver a concentrated pool of platelets to the site of injury that then release proregenerative growth factors (GFs) and cytokines

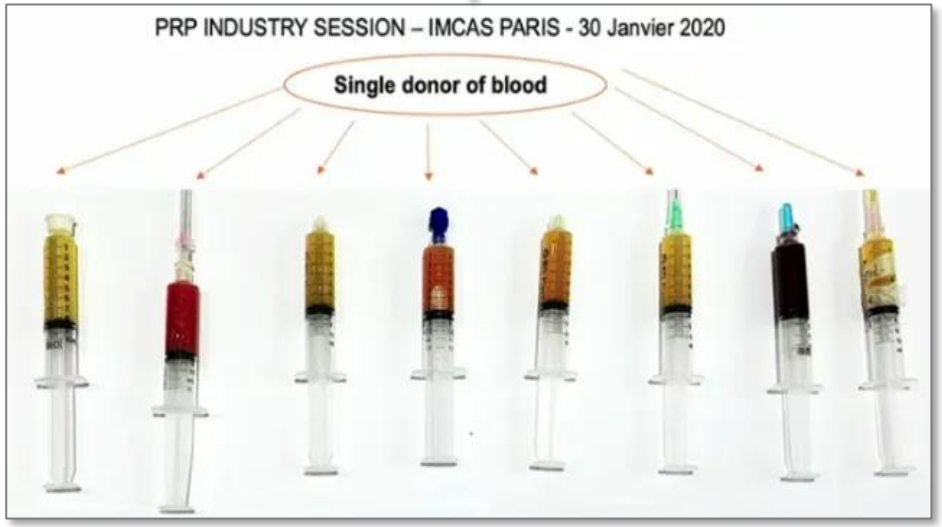
GFs released by platelets have been shown to have proregenerative functions *in vitro*, including

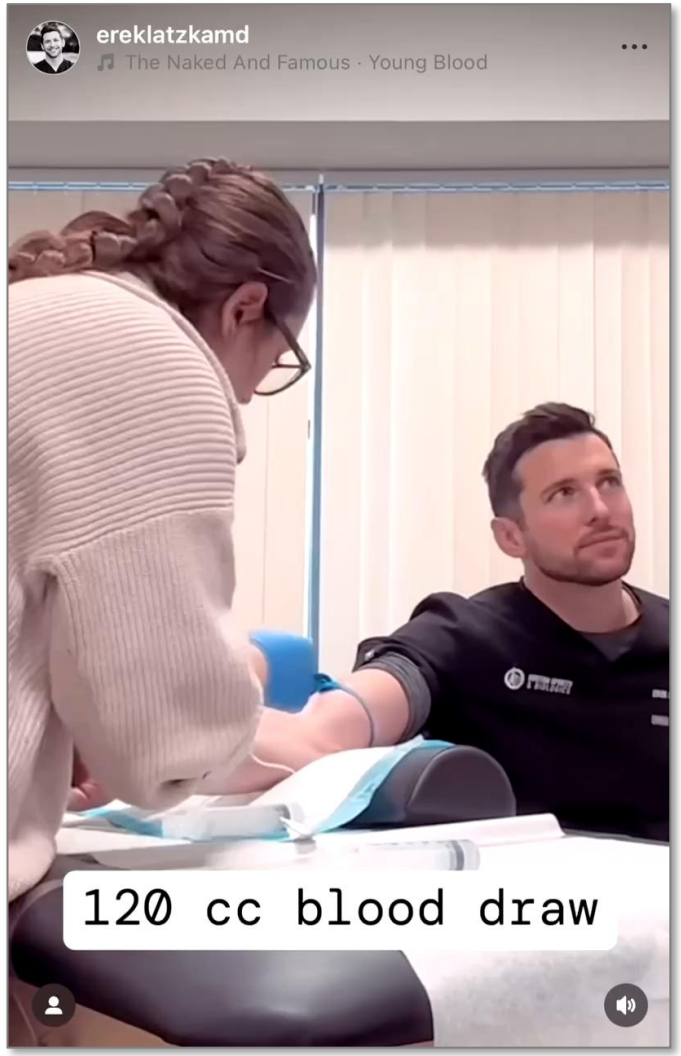
- Promoting stem and progenitor cell Proliferation and recruitment
- Modulating inflammatory responses
- Stimulating angiogenesis

GF = growth factor.

How Is PRP Made?





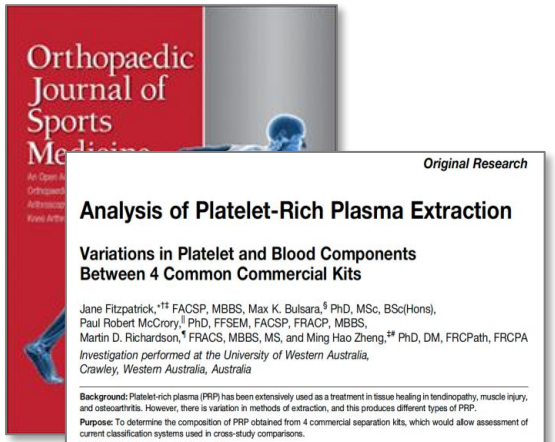


Not All PRP Is the Same

Variables Affecting Efficacy

- **Preparation/technique**
  - **Platelet count**
  - Bioformulation/leukocyte count
  - Platelet activation
  - Local anesthetic (decreased function/aggregation)
  - # of injections (1,2,3)
  - Diagnostic accuracy
  - Procedural accuracy (guidance)
- **Others**
  - Age, sex
  - Medications: NSAIDs, aspirin
  - Drugs: Tobacco (increased platelet aggregation), alcohol (reduced activation)
  - Diet: Saturated fat/sugar (increased aggregation), caffeine (reduced activation)
  - Comorbidities
  - Stress (hormones increase aggregation and factor release)
  - Recent exercise

Variability in PRP



Original Research

Analysis of Platelet-Rich Plasma Extraction

Variations in Platelet and Blood Components Between 4 Common Commercial Kits

Jane Fitzpatrick,*†‡ FACSP, MBBS, Max K. Bulsara,§ PhD, MSc, BSc(Hons), Paul Robert McCrory,‖ PhD, FFSEM, FACSP, FRACP, MBBS, Martin D. Richardson,¶ FRACS, MBBS, MS, and Ming Hao Zheng,†# PhD, DM, FRCPath, FRCPA

Investigation performed at the University of Western Australia, Crawley, Western Australia, Australia

Background: Platelet-rich plasma (PRP) has been extensively used as a treatment in tissue healing in tendinopathy, muscle injury, and osteoarthritis. However, there is variation in methods of extraction, and this produces different types of PRP.

Purpose: To determine the composition of PRP obtained from 4 commercial separation kits, which would allow assessment of current classification systems used in cross-study comparisons.

Study Design: Controlled laboratory study.

Methods: Three normal adults each donated 181 mL of whole blood, some of which served as a control and the remainder of which was processed through 4 PRP separation kits: GPS III (Biomet Biologics), Smart-Prep2 (Harvest Terumo), Magellan (Arteriocyte Medical Systems), and ACP (Device Technologies). The resultant PRP was tested for platelet count, red blood cell count, and white blood cell count, including differential in a commercial pathology laboratory. Glucose and pH measurements were obtained from a blood gas autoanalyzer machine.

Results: Three kits taking samples from the "buffy coat layer" were found to have greater concentrations of platelets (3-6 times baseline), while 1 kit taking samples from plasma was found to have platelet concentrations of only 1.5 times baseline. The same 3 kits produced an increased concentration of white blood cells (3-6 times baseline); these consisted of neutrophils, leukocytes, and monocytes. This represents high concentrations of platelets and white blood cells. A small drop in pH was thought to relate to the citrate used in the sample preparation. Interestingly, an unexpected increase in glucose concentrations, with 3 to 6 times greater than baseline levels, was found in all samples.

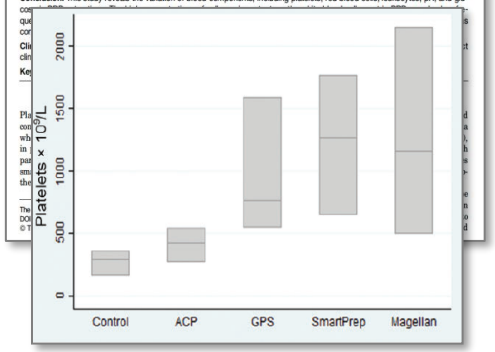
Conclusion: This study reveals the variation of blood components, including platelets, red blood cells, leukocytes, pH, and glu-

TABLE 1
Commercially Available Kits for the Production of Platelet Products[a]

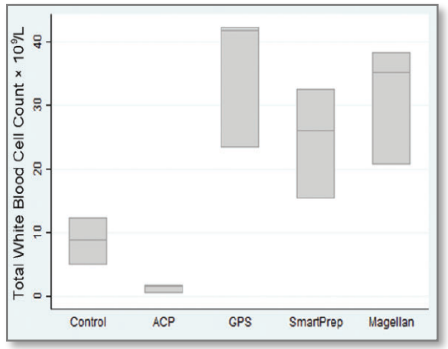
Device Name	Company	Name of Product	Comments
GPS III	Biomet	Platelet-rich plasma	Tested
SmartPrep2	Harvest	Platelet-rich plasma	Tested
Magellan	Arteriocyte Medical	Platelet-rich plasma	Tested
Angel	Sorin	Platelet-rich plasma	Not available for testing
CS	Genesis	Platelet-rich plasma	Not available for testing
ACP	Arthrex	Autologous conditioned plasma	Tested
PRFM Fibrinet System	Cascade	Platelet-rich fibrin	Not tested, fibrin membrane
PRF and Vivostat	Choukroun's	Platelet-rich fibrin	Not tested, fibrin membrane
BMAC	DePuy	Platelet-rich plasma and stem cells	Not tested, bone marrow
Cell saver–based systems Electa, Haemonetics, CATS, BRAT	Several	Pure platelets	Not tested, volume required >200 mL
Caption	Not yet marketed	Pure platelets	Not tested, not available
Total	12 companies		4 tested

[a]Table derived from Engebretson et al.[16]

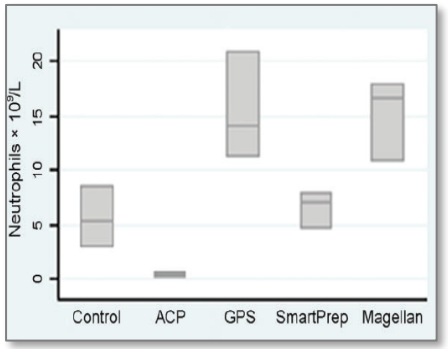
Different PRP systems utilize different preparation protocols and can produce different neutrophil, lymphocyte, and monocyte cell ratios



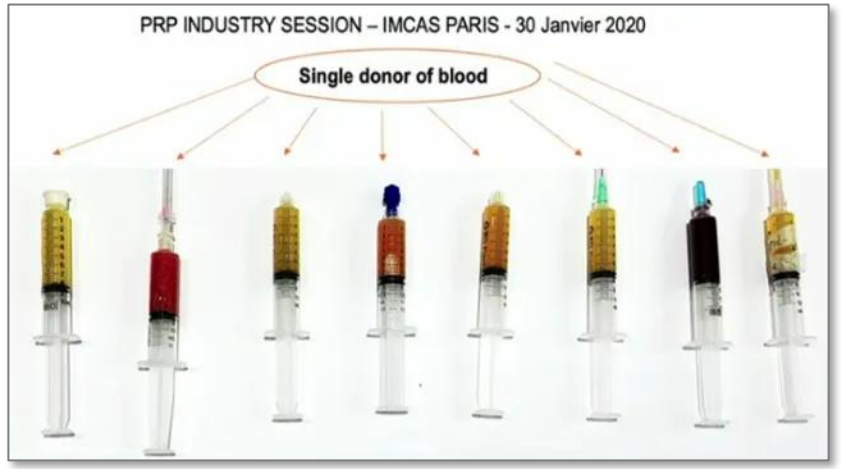
Platelets



WBC

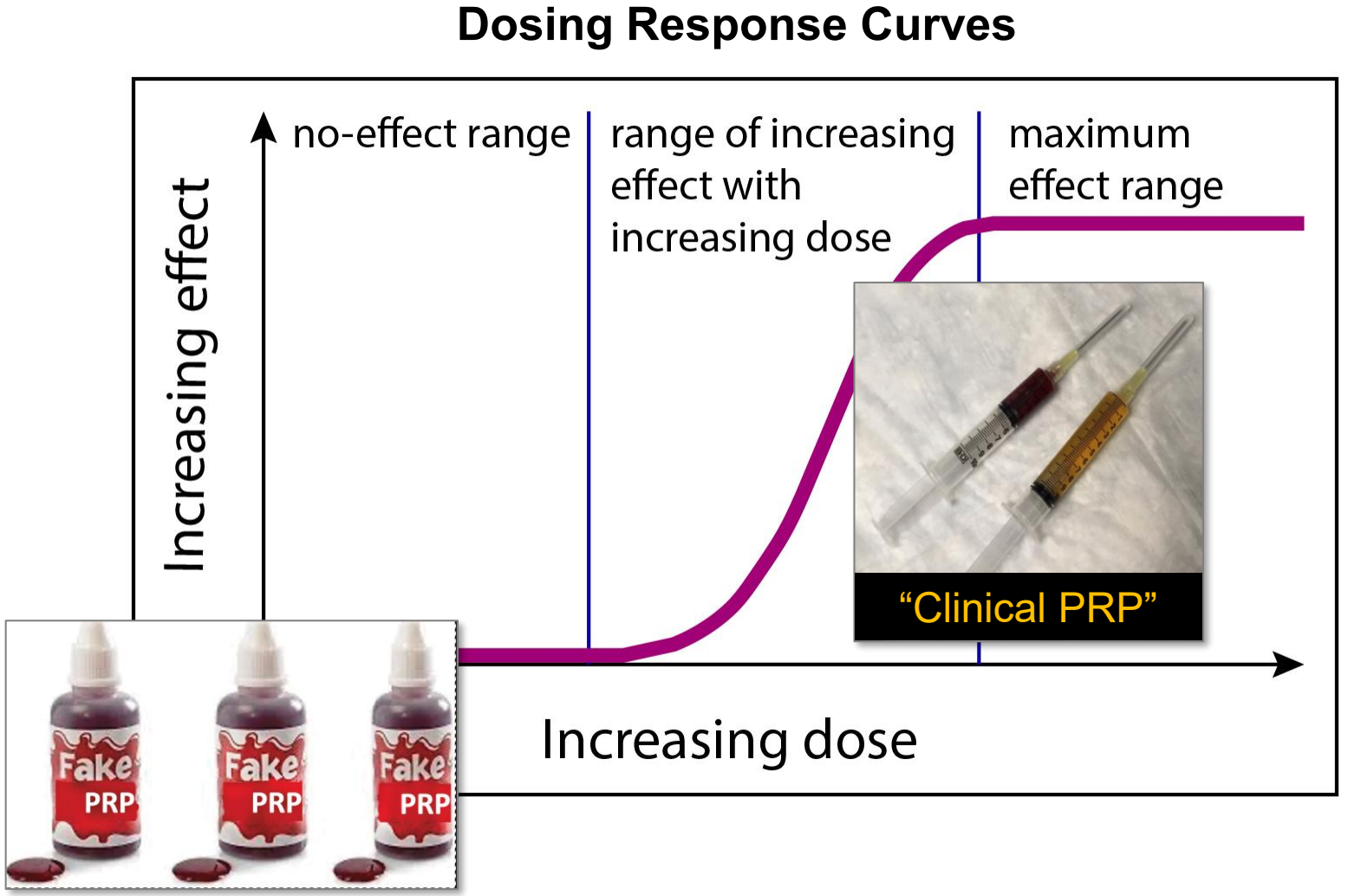


Neutrophil



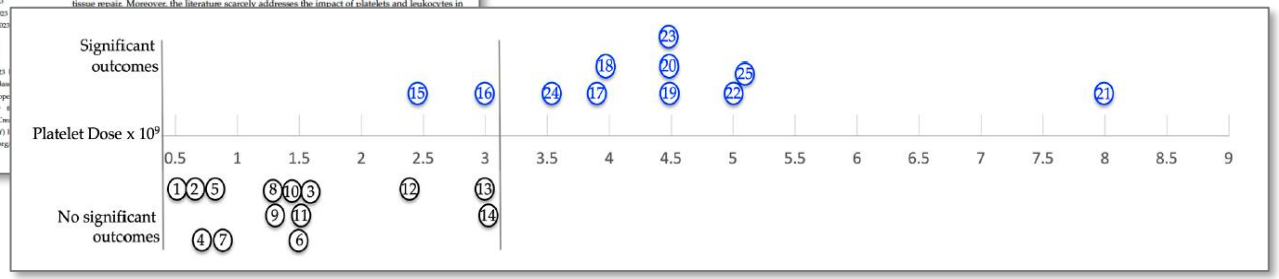
Fitzpatrick J, et al. *Ortho J Sports Med* 2017;5(1):2325967116675272.

Dosing PRP


Dosing Response Curves
Increasing effect
no-effect range
range of increasing effect with increasing dose
maximum effect range
"Clinical PRP"
Fake PRP
Fake PRP
Fake PRP
Increasing dose

Dosing of PRP for Soft Tissue Pathology

Study Identifier	PRP Application	PRP Dose × 10^9 Platelets	Bioformulation LP/LR
	Non-significant outcomes		
1	Rotator cuff repair	0.55	LP
2	Lateral epicondylitis	0.60	LP
3	Rotator cuff repair	1518	LP
4	Patella tendinopathy	0.663	LP
5	Hamstring tendinopathy	0.750	LP
6	Rotator cuff repair	0.701	LP
7	Achilles tendinopathy	0.875	LP
8	Shoulder soft tissue	1312	LR
9	Achilles tendinopathy	1313	LP
10	Achilles tendinopathy	1462	LR
11	Rotator cuff repair	1575	LP
12	Achilles tendinopathy	2430	LR
13	Lateral epicondylitis	3037	LR
14	Achilles tendinopathy	3125	LR
	Significant outcomes		
15	Lateral epicondylitis	2454	LR
16	Rotator cuff repair	3000	LR
17	Lateral epicondylitis	3877	LR
18	Ulnar collateral ligament	3900	LR
19	Lateral epicondylitis	4500	LR
20	Lateral epicondylitis	4500	LR
21	Rotator cuff surgical repair	8100	LR
22	Patellar tendinopathy	5100	LR
23	ACL repair	4500	LR
24	Plantar fasciitis	3500	LP
25	Rotator cuff repair	5.275	LR



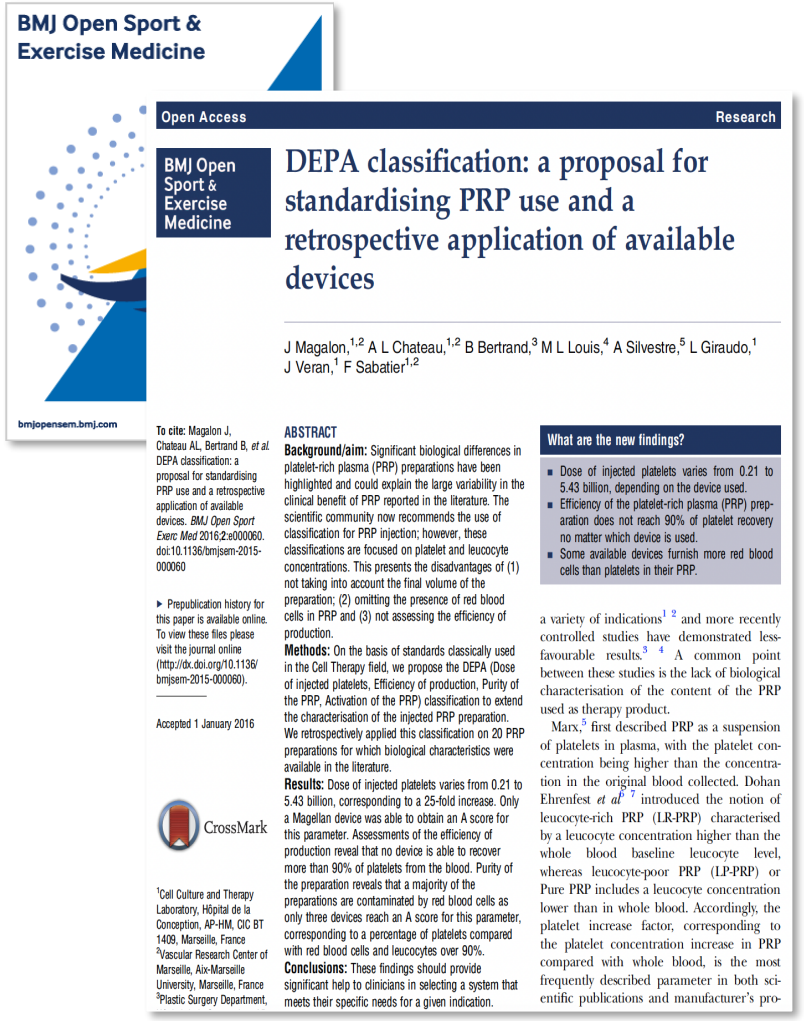
Everts (2023)

Narrative review

- Overview of some significant and non-significant treatment outcomes following PRP applications in soft tissue MSK disorders with emphasis on platelet dose and bioformulation
- Studies 1-14 (black) were not significantly different when compared with control groups (platelet doses were less than $1.5x10^9$ platelets)
- Studies 15-25 (blue) demonstrated a positive outcome (platelet dose was generally higher than $3.2x10^9$)

Everts PA, et al. *Biomedicines.* 2023;11(7):1922.

Dosing of PRP for Soft Tissue Pathology



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DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices

J Magalon,[1,2] A L Chateau,[1,2] B Bertrand,[3] M L Louis,[4] A Silvestre,[5] L Giraudo,[1] J Veran,[1] F Sabatier[1,2]

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To cite: Magalon J, Chateau AL, Bertrand B, *et al*. DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices. *BMJ Open Sport Exerc Med* 2016;2:e000060. doi:10.1136/bmjsem-2015-000060

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Accepted 1 January 2016

ABSTRACT

Background/aim: Significant biological differences in platelet-rich plasma (PRP) preparations have been highlighted and could explain the large variability in the clinical benefit of PRP reported in the literature. The scientific community now recommends the use of classification for PRP injection; however, these classifications are focused on platelet and leucocyte concentrations. This presents the disadvantages of (1) not taking into account the final volume of the preparation; (2) omitting the presence of red blood cells in PRP and (3) not assessing the efficiency of production.

Methods: On the basis of standards classically used in the Cell Therapy field, we propose the DEPA (Dose of injected platelets, Efficiency of production, Purity of the PRP, Activation of the PRP) classification to extend the characterisation of the injected PRP preparation. We retrospectively applied this classification on 20 PRP preparations for which biological characteristics were available in the literature.

Results: Dose of injected platelets varies from 0.21 to 5.43 billion, corresponding to a 25-fold increase. Only a Magellan device was able to obtain an A score for this parameter. Assessments of the efficiency of production reveal that no device is able to recover more than 90% of platelets from the blood. Purity of the preparation reveals that a majority of the preparations are contaminated by red blood cells as only three devices reach an A score for this parameter, corresponding to a percentage of platelets compared with red blood cells and leucocytes over 90%.

Conclusions: These findings should provide significant help to clinicians in selecting a system that meets their specific needs for a given indication.

What are the new findings?

- Dose of injected platelets varies from 0.21 to 5.43 billion, depending on the device used.
- Efficiency of the platelet-rich plasma (PRP) preparation does not reach 90% of platelet recovery no matter which device is used.
- Some available devices furnish more red blood cells than platelets in their PRP.

a variety of indications[1 2] and more recently controlled studies have demonstrated less-favourable results.[3 4] A common point between these studies is the lack of biological characterisation of the content of the PRP used as therapy product.

Marx,[5] first described PRP as a suspension of platelets in plasma, with the platelet concentration being higher than the concentration in the original blood collected. Dohan Ehrenfest *et al*[6 7] introduced the notion of leucocyte-rich PRP (LR-PRP) characterised by a leucocyte concentration higher than the whole blood baseline leucocyte level, whereas leucocyte-poor PRP (LP-PRP) or Pure PRP includes a leucocyte concentration lower than in whole blood. Accordingly, the platelet increase factor, corresponding to the platelet concentration increase in PRP compared with whole blood, is the most frequently described parameter in both scientific publications and manufacturer's pro-

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[2]Vascular Research Center of Marseille, Aix-Marseille University, Marseille, France
[3]Plastic Surgery Department,

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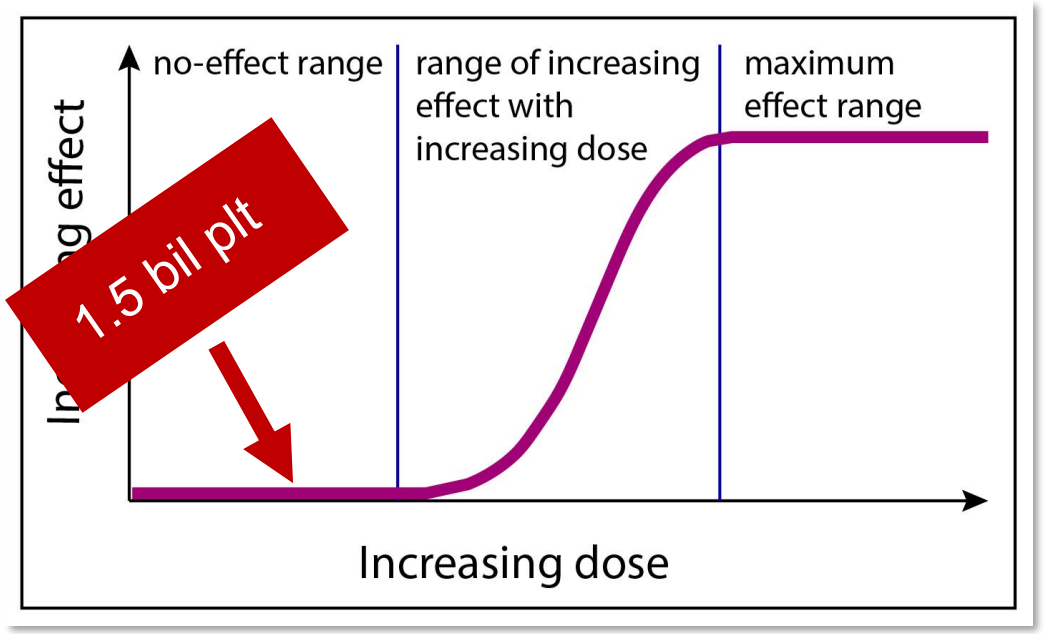

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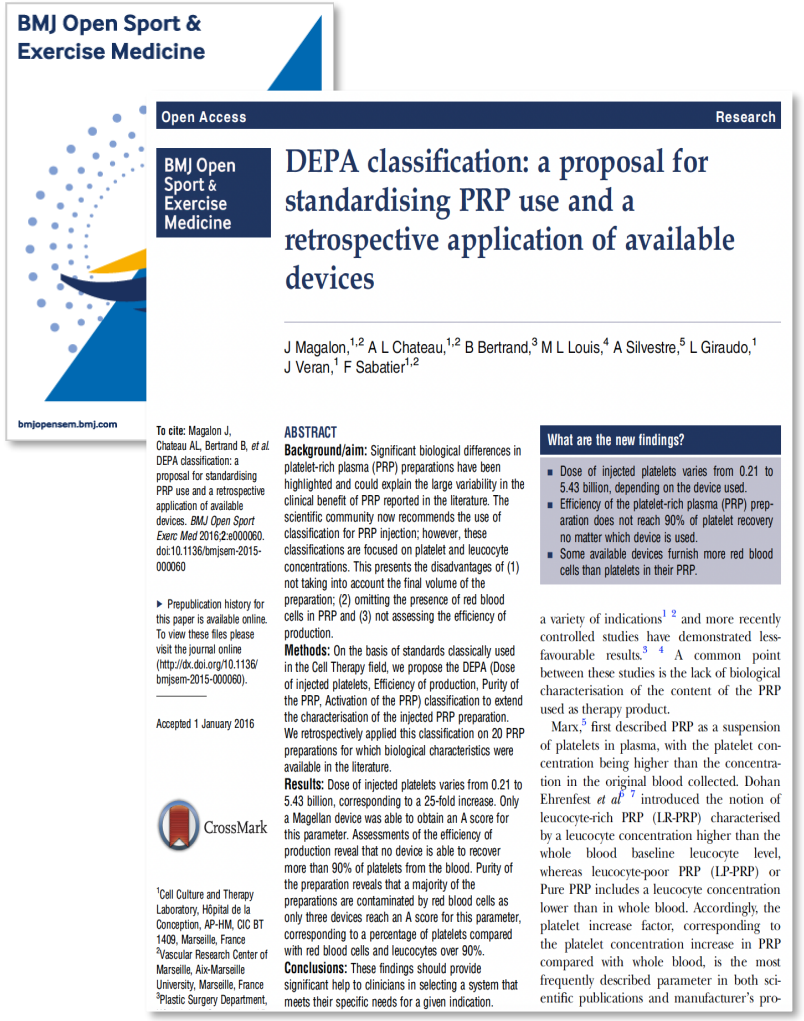
Dosing of PRP for Soft Tissue Pathology



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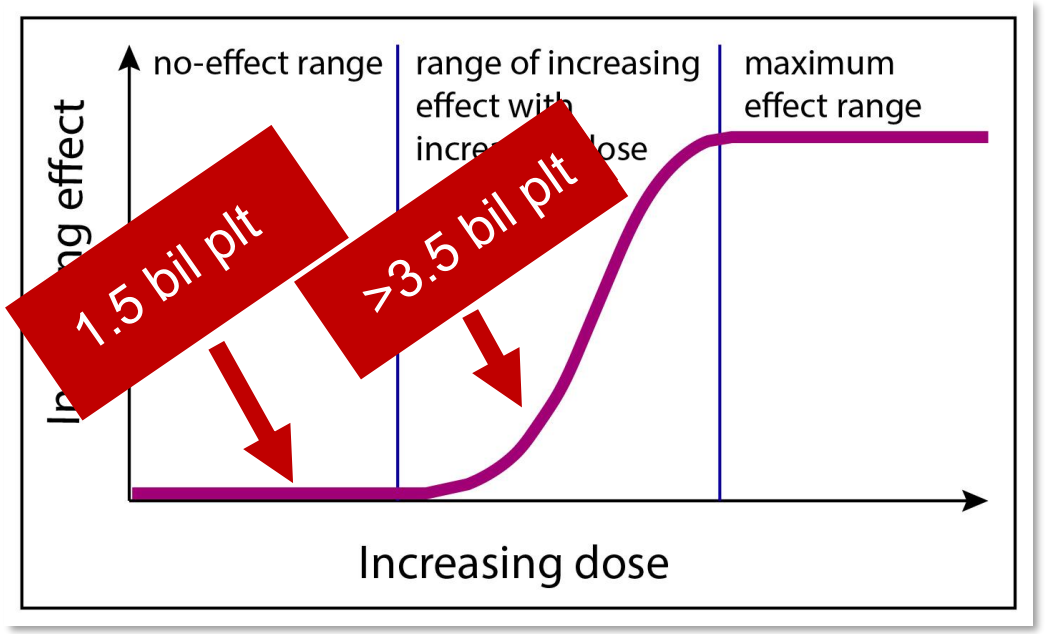

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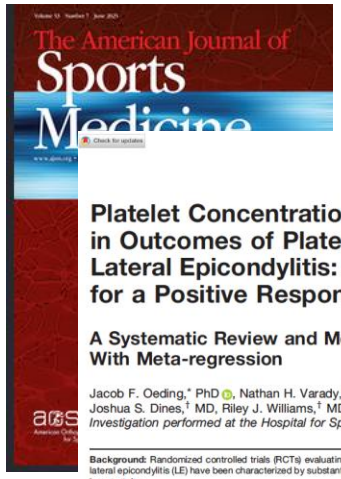


Clinical Sports Medicine Update

Platelet Concentration Explains Variability in Outcomes of Platelet-Rich Plasma for Lateral Epicondylitis: A High Dose Is Critical for a Positive Response

A Systematic Review and Meta-analysis With Meta-regression

Jacob F. Oeding,* PhD, Nathan H. Varady,†‡ MD, MBA, Caden J. Messer,§ BS, Joshua S. Dines,† MD, Riley J. Williams,† MD, and Scott A. Rodeo,† MD
Investigation performed at the Hospital for Special Surgery, New York, New York, USA

Background: Randomized controlled trials (RCTs) evaluating the efficacy of platelet-rich plasma (PRP) for the management of lateral epicondylitis (LE) have been characterized by substantial variability in reported outcomes. The source of this heterogeneity is uncertain.

Purpose: To determine the effect of estimated platelet concentration on the efficacy of PRP for the management of LE.

Study Design: Systematic review and meta-analysis; Level of evidence, 2.

Methods: All RCTs evaluating the efficacy of PRP in managing LE were identified. RCTs were classified according to whether the study documented a platelet concentration factor of PRP representing a greater than 3-fold increase over whole blood or a supraphysiological platelet dose (high-dose vs low-dose PRP). The primary outcome was the mean difference (MD) in the visual analog scale (VAS) score at latest follow-up. Random-effects and mixed-effects meta-analyses were performed, and meta-regression was used to evaluate whether differences in outcomes after treatment with PRP could be explained by differences in the concentration of PRP used.

Results: Overall, 13 RCTs with a total of 791 patients were included in this analysis, with 5 that utilized low-dose PRP and 8 that used high-dose PRP. Meta-analysis of VAS scores reported by studies that used high-dose PRP resulted in an MD of −1.31 (95% CI, −1.87 to −0.75) in favor of PRP over all alternative treatment strategies ($P < .001$). Meta-analysis of VAS scores reported by studies that used low-dose PRP resulted in an MD of 0.08 (95% CI, −0.51 to 0.68), suggesting no difference in the effect between PRP and all alternative treatment strategies ($P = .79$). The platelet concentration factor of PRP used in each RCT was found to be strongly predictive of the VAS score at final follow-up in meta-regression ($P < .001$), with 58.5% of the heterogeneity in the outcomes of PRP between studies explained by the platelet concentration factor alone.

Conclusion: The platelet concentration of PRP may play a significant role in the outcomes of patients with LE. A direct linear relationship was observed between the platelet concentration factor of PRP used and the magnitude of patient-reported symptom relief after the management of LE with PRP. Clinicians should ensure a supraphysiological platelet concentration when preparing PRP for the management of LE.

Keywords: platelet-rich plasma; PRP; lateral epicondylitis; tennis elbow; dose; concentration

Lateral epicondylitis (LE), or tennis elbow, is a common cause of elbow pain in adults aged 35 to 55 years, affecting up to 3% of adults and causing characteristic pain and tenderness over the lateral epicondyle.[34] While several causes have been proposed, the underlying pathophysiology is thought to be related to cumulative microscopic tendon injuries, most commonly of the extensor carpi radialis brevis tendon. Although extensive infiltrates of classic inflammatory/immune cells are not typically seen in tissue biopsy specimens from patients with LE, it is well established that there is "molecular inflammation" in tendinopathy, with increased gene expression for a number of inflammatory cytokines.[4,30] Tissue damage promotes the release of

The American Journal of Sports Medicine
1–8
DOI: 10.1177/03635465241303716

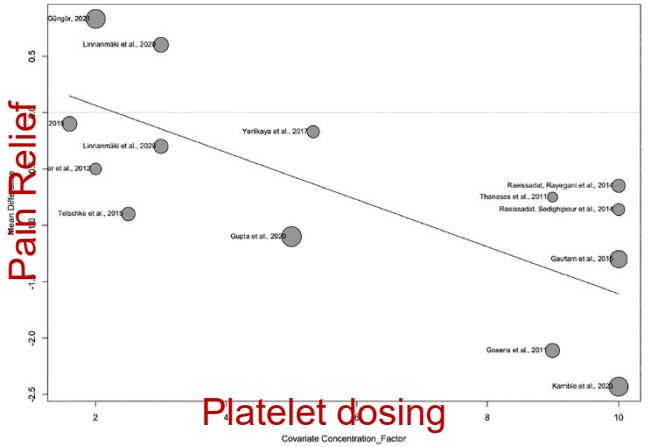


Figure 3. Meta-regression results with platelet concentration factor as the covariate of interest. The treatment effect for each study is plotted on the y-axis versus the platelet concentration factor on the x-axis. The size of each circle is inversely proportional to the variance of the estimated treatment effect. Platelet concentration factor was found to be significantly associated with the visual analog scale (VAS) score at final follow-up ($P < .001$), with 58.5% of the heterogeneity in outcomes accounted for by the platelet concentration factor alone.

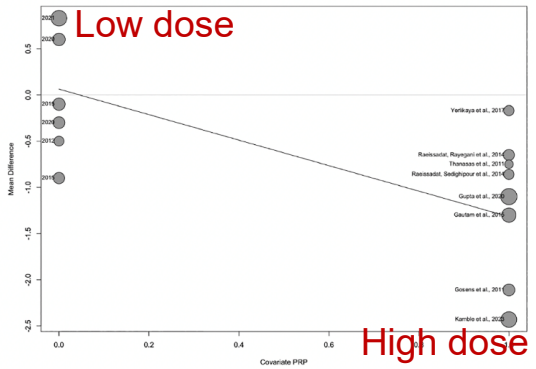


Figure 4. Meta-regression results with a binary platelet-rich plasma (PRP) composition variable corresponding to low-dose versus high-dose PRP as the covariate of interest. The treatment effect for each study is plotted on the y-axis versus the type of PRP (0, low-dose PRP; 1, high-dose PRP) on the x-axis. The size of each circle is inversely proportional to the variance of the estimated treatment effect. This binary variable corresponding to whether each study utilized high-dose PRP (ie, "true" PRP) or low-dose PRP was found to be significantly associated with the visual analog scale (VAS) score at final follow-up ($P < .001$), with 54.1% of the heterogeneity in outcomes accounted for by this variable alone.

Oeding, et al. (2025)

Systematic review/meta-analysis

- RCTs evaluating the efficacy of PRP in managing lateral epicondylitis based on platelet concentration factor
  - >3x increase over whole blood = high-dose
  - <3x increase = low-dose PRP

Results

- 13 RCTs (791 patients)
  - 5 that utilized low-dose PRP
  - 8 used high-dose PRP

Outcomes

- The platelet concentration factor was found to be strongly predictive of outcomes
- A direct linear relationship was observed between the plt concentration and magnitude symptom relief

Oeding JF, et al. *Am J Sports Med.* 2025 Jan 27:3635465241303716.

Dosing of PRP for Osteoarthritis

Berrigan, et al. (2024)

Systematic review of RCT, PRP vs control for KOA

Design

- Inclusion criteria
  - Documented plt count, concentration or dose and >6-month outcome scores

Results

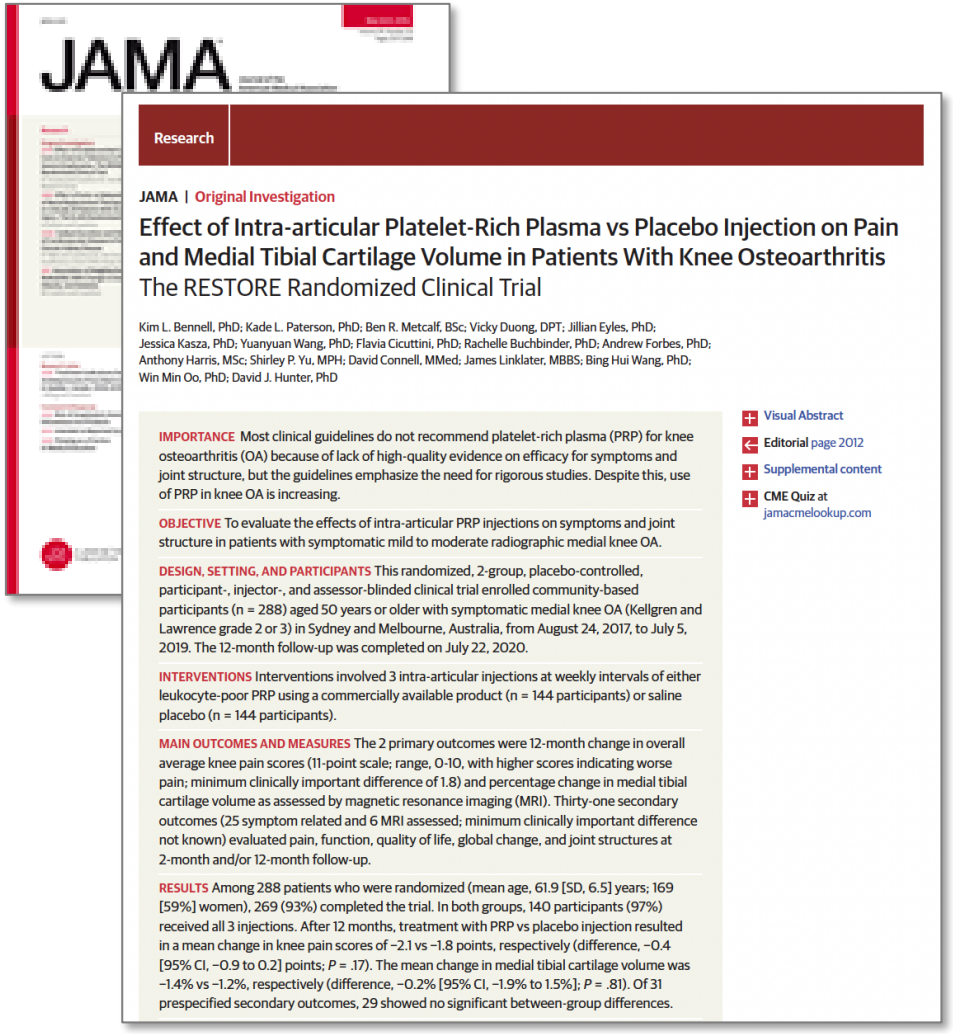
- 29 studies (31 study arms)
- Positive results (n=28) – avg plt dose was 5.5 billion
- Negative results (n=3) – mean avg plt dose was 2.3 billion

Conclusion

- Improved clinical outcomes may be related to a greater platelet dose

Berrigan WA, et al. *Arthroscopy.* 2024;Mar 19:S0749-8063(24)00206-8.

Dosing of PRP for Osteoarthritis



JAMA

Research

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

IMPORTANCE Most clinical guidelines do not recommend platelet-rich plasma (PRP) for knee osteoarthritis (OA) because of lack of high-quality evidence on efficacy for symptoms and joint structure, but the guidelines emphasize the need for rigorous studies. Despite this, use of PRP in knee OA is increasing.

OBJECTIVE To evaluate the effects of intra-articular PRP injections on symptoms and joint structure in patients with symptomatic mild to moderate radiographic medial knee OA.

DESIGN, SETTING, AND PARTICIPANTS This randomized, 2-group, placebo-controlled, participant-, injector-, and assessor-blinded clinical trial enrolled community-based participants (n = 288) aged 50 years or older with symptomatic medial knee OA (Kellgren and Lawrence grade 2 or 3) in Sydney and Melbourne, Australia, from August 24, 2017, to July 5, 2019. The 12-month follow-up was completed on July 22, 2020.

INTERVENTIONS Interventions involved 3 intra-articular injections at weekly intervals of either leukocyte-poor PRP using a commercially available product (n = 144 participants) or saline placebo (n = 144 participants).

MAIN OUTCOMES AND MEASURES The 2 primary outcomes were 12-month change in overall average knee pain scores (11-point scale; range, 0-10, with higher scores indicating worse pain; minimum clinically important difference of 1.8) and percentage change in medial tibial cartilage volume as assessed by magnetic resonance imaging (MRI). Thirty-one secondary outcomes (25 symptom related and 6 MRI assessed; minimum clinically important difference not known) evaluated pain, function, quality of life, global change, and joint structures at 2-month and/or 12-month follow-up.

RESULTS Among 288 patients who were randomized (mean age, 61.9 [SD, 6.5] years; 169 [59%] women), 269 (93%) completed the trial. In both groups, 140 participants (97%) received all 3 injections. After 12 months, treatment with PRP vs placebo injection resulted in a mean change in knee pain scores of −2.1 vs −1.8 points, respectively (difference, −0.4 [95% CI, −0.9 to 0.2] points; $P = .17$). The mean change in medial tibial cartilage volume was −1.4% vs −1.2%, respectively (difference, −0.2% [95% CI, −1.9% to 1.5%]; $P = .81$). Of 31 prespecified secondary outcomes, 29 showed no significant between-group differences.

Visual Abstract
Editorial page 2012
Supplemental content
CME Quiz at jamacmelookup.com

RESTORE Trial
Bennell, et al. (2021)

RCT, double blind, placebo-controlled trial of PRP vs saline (placebo) for mild-moderate medial knee OA (n=288)

Design

- 3 weekly IA-injection
- Low dose PRP (5mL injected)
  - Dose: 5mL x 325 x $10^3/mm^3$ = 1.625 billion platelets

Results

- No significant difference in symptoms or cartilage volume

Conclusion

- These findings do not support use of PRP for the management of knee OA

Bennell KL, et al. *JAMA.* 2021 Nov 23;326(20):2021-2030.

Dosing of PRP for Osteoarthritis

BMJ Open Sport & Exercise Medicine

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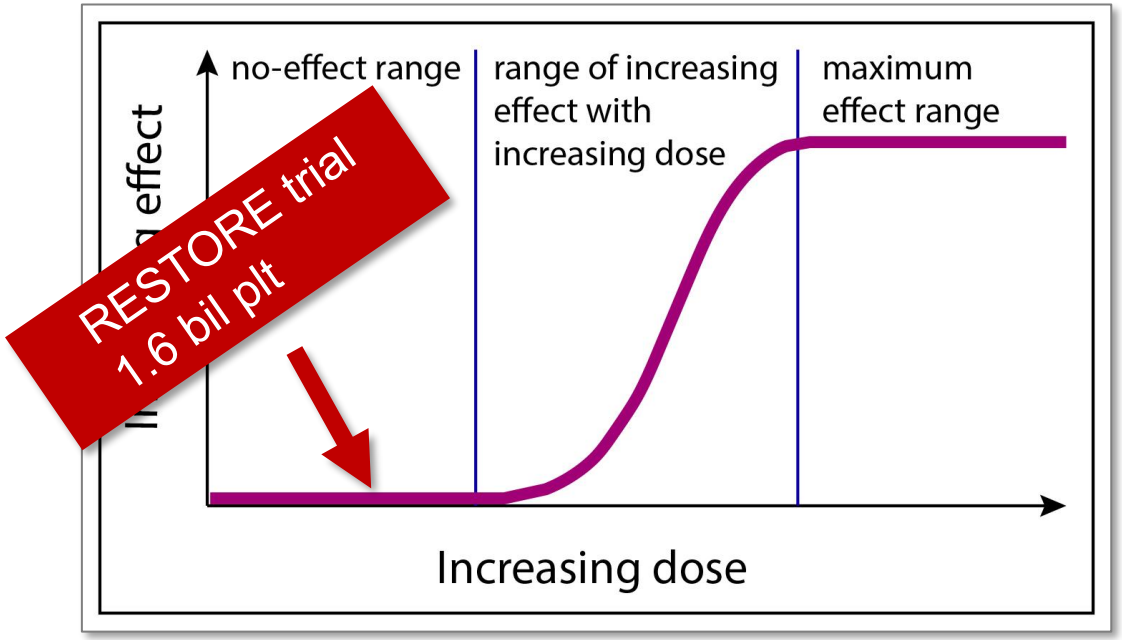
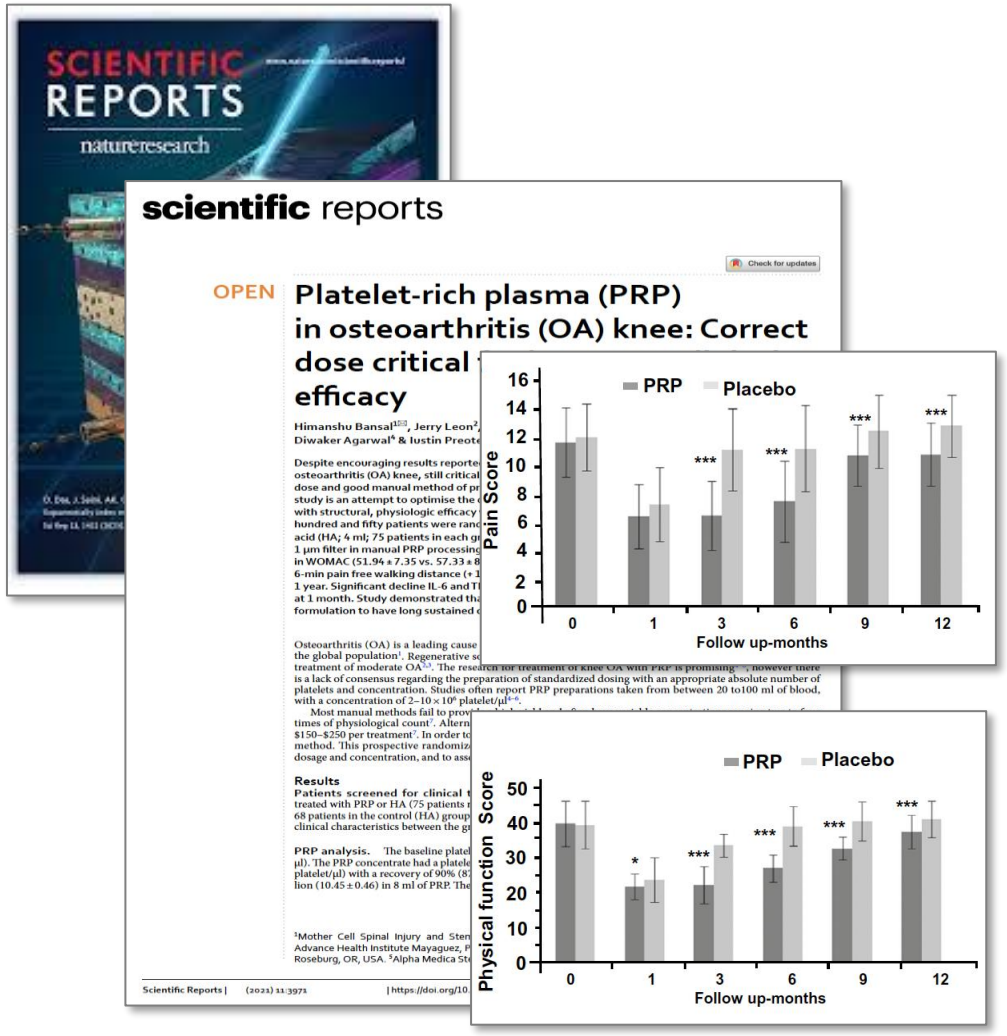


Magalon J, et al. *BMJ Open Sport Exerc Med.* 2016;Feb 4;2(1):e000060.

Dosing of PRP for Osteoarthritis



Bansal, et al. (2021)

RCT HA vs high-dose PRP (>10bil plt) for knee OA (n=150)

Design

- HA (n=75) vs PRP (n=75)
  - PRP 10.5 billion in 8mL PRP
- Follow up 1 yr

Results

- Significant improvement in WOMAC, IKDC and pain-free walking
- Improvement persisted in PRP group vs HA group at 1 yr
- Cartilage thickness unchanged in 82.8% of PRP patients vs 61.7% of HA patients; remaining patients lost thickness

Conclusion

- Dose of 10 billion platelets in 8 ml of PRP improves functional outcomes and protects the articular cartilage from further wear

Bansal H, et al. *Sci Rep.* 2021;11(1):3971.

Dosing of PRP for Osteoarthritis

Knee Surgery, Sports Traumatology, Arthroscopy
https://doi.org/10.1007/s00167-022-06887-7

KNEE

Intra-articular injections of platelet-rich plasma decrease pain and improve functional outcomes than sham saline in patients with knee osteoarthritis

Jiabao Chu[1,7] · Weifeng Duan[1] · Ziqiang Yu[2,3] · Tao Tao[4] · Jie Xu[5] · Qianli Ma[6] · Lingying Zhao[2,3] · Jiong Jiong Guo[1,2]

Received: 14 October 2021 / Accepted: 10 January 2022

Abstract

Purpose To compare the long-term clinical efficacy provided by intra-articular injections of either Pure Platelet-rich Plasma (P-PRP) or sham saline to treat knee osteoarthritis (KOA).

Methods This prospective, parallel-group, double-blind, multi-center, sham-controlled randomized clinical trial recruited participants with KOA from orthopedic departments at nine public hospitals (five tertiary medical centers, four secondary medical units) starting January 1, 2014, with follow-up completed on February 28, 2021. Participants were randomly allocated to interventions in a 1:1 ratio. Data were analyzed from March 1, 2021, to July 15, 2021. Three sessions (1 every week) of P-PRP or sham saline injected by physicians. The primary outcome was the Western Ontario and McMaster Universities Arthritis Index (WOMAC) at 3, 6, 12, 24, 60 months of follow-up. Secondary outcomes included the International Knee Documentation Committee (IKDC) subjective score, visual analogue scale (VAS) score, intra-articular biochemical marker concentrations, cartilage volume, and adverse events. Laboratory of each hospital analyzed the content and quality of P-PRP.

Results 610 participants (59% women) with KOA who received three sessions of P-PRP ($n = 308$, mean age 53.91 years) or sham saline ($n = 302$, mean age 54.51 years) injections completed the trial. The mean platelet concentration in PRP is 4.3fold (95% confidence interval 3.6–4.5) greater than that of whole blood. Both groups showed significant improvements in IKDC, WOMAC, and VAS scores at 1 month of follow-up. However, only the P-PRP group showed a sustained improvement in clinical outcome measurements at month 24 ($P < 0.001$). There were statistically significant differences between the P-PRP and sham saline groups in all clinical outcome measurements at each follow-up time point ($P < 0.001$). The benefit of P-PRP was clinically better in terms of WOMAC-pain, WOMAC-physical function and WOMAC-total at 6, 12, 24, and 60 months of follow-up. No clinically significant differences between treatments were documented in terms of WOMAC-stiffness at any follow-up. A clinically significant difference favoring P-PRP group against saline in terms of IKDC and VAS scores was documented at 6, 12, 24 and 60 months of follow-up. At 6 months after injection, TNF-α and IL-1β levels in synovial fluid were lower in the P-PRP group ($P < 0.001$). Tibiofemoral cartilage volume decreased by a mean value of 1171 mm^3 in the P-PRP group and 2311 mm^3 in the saline group over 60 months and the difference between the group was statistically significant (intergroup difference, 1140 mm^3, 95% CI − 79 to 1320 mm^3; $P < 0.001$).

Conclusions In this randomized clinical trial of patients with KOA, P-PRP was superior to sham saline in treating KOA. P-PRP was effective for achieving at least 24 months of symptom relief and slowing the progress of KOA, with both P-PRP and saline being comparable in safety profiles.

Keywords Platelet-rich plasma (PRP) · Osteoarthritis · Knee · Pain · Saline

Introduction

Available therapies for patients with mild to severe knee osteoarthritis (KOA) are limited. There is an urgent need for disease-modifying osteoarthritis treatment, which targets the biochemical process of KOA that improves symptoms and inhibits structural disease progression.

Jiabao Chu and Weifeng Duan contributed equally to this article.

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Extended author information available on the last page of the article

Published online: 06 February 2022

Springer

Chu, et al. (2022)

RCT, double blind, multicenter, sham-controlled study

Saline placebo vs high-dose PRP for knee OA (n=610)

Design

- 3 PRP (n= 308) vs saline (n=302), injections 1 wk apart
  - PRP 50mL blood draw, made 5mL PRP with platelet count mean 832.1 x 10^9/L = dose of 4.1 billion
  - WOMAC, IKDC, VAS, biochem markers, and cartilage MRI vol

Results

- PRP greater improvement in pain, function, and biomarkers
- Over 2x greater loss of cartilage in the saline group at 5yr f/u MRI

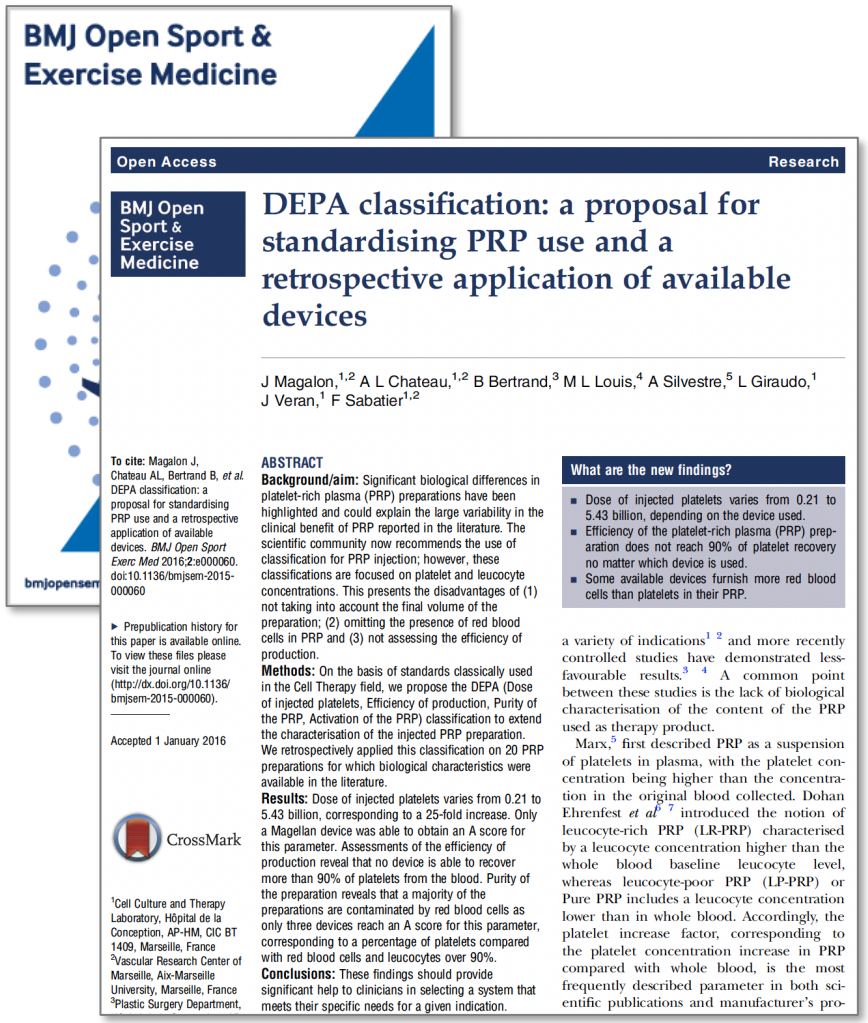
Conclusion

– PRP with a dose of 4.1 billion was superior in treating KOA
  - 24 mo of symptom relief
  - Slowing of the progression of KOA

WOMAC = Western Ontario and McMaster Universities Arthritis Index; IKDC = International Knee Documentation Committee; VAS = visual analogue scale.

Chu J, et al. *Knee Surg Sports Traumatol Arthrosc.* 2022;30(12):4063-4071.

Dosing of PRP for Osteoarthritis



BMJ Open Sport & Exercise Medicine

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DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices

J Magalon,[1,2] A L Chateau,[1,2] B Bertrand,[3] M L Louis,[4] A Silvestre,[5] L Giraudo,[1] J Veran,[1] F Sabatier[1,2]

To cite: Magalon J, Chateau AL, Bertrand B, *et al*. DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices. *BMJ Open Sport Exerc Med* 2016;2:e000060. doi:10.1136/bmjsem-2015-000060

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjsem-2015-000060).

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ABSTRACT

Background/aim: Significant biological differences in platelet-rich plasma (PRP) preparations have been highlighted and could explain the large variability in the clinical benefit of PRP reported in the literature. The scientific community now recommends the use of classification for PRP injection; however, these classifications are focused on platelet and leucocyte concentrations. This presents the disadvantages of (1) not taking into account the final volume of the preparation; (2) omitting the presence of red blood cells in PRP and (3) not assessing the efficiency of production.

Methods: On the basis of standards classically used in the Cell Therapy field, we propose the DEPA (Dose of injected platelets, Efficiency of production, Purity of the PRP, Activation of the PRP) classification to extend the characterisation of the injected PRP preparation. We retrospectively applied this classification on 20 PRP preparations for which biological characteristics were available in the literature.

Results: Dose of injected platelets varies from 0.21 to 5.43 billion, corresponding to a 25-fold increase. Only a Magellan device was able to obtain an A score for this parameter. Assessments of the efficiency of production reveal that no device is able to recover more than 90% of platelets from the blood. Purity of the preparation reveals that a majority of the preparations are contaminated by red blood cells as only three devices reach an A score for this parameter, corresponding to a percentage of platelets compared with red blood cells and leucocytes over 90%.

Conclusions: These findings should provide significant help to clinicians in selecting a system that meets their specific needs for a given indication.

What are the new findings?

- Dose of injected platelets varies from 0.21 to 5.43 billion, depending on the device used.
- Efficiency of the platelet-rich plasma (PRP) preparation does not reach 90% of platelet recovery no matter which device is used.
- Some available devices furnish more red blood cells than platelets in their PRP.

a variety of indications[1 2] and more recently controlled studies have demonstrated less-favourable results.[3 4] A common point between these studies is the lack of biological characterisation of the content of the PRP used as therapy product.

Marx,[5] first described PRP as a suspension of platelets in plasma, with the platelet concentration being higher than the concentration in the original blood collected. Dohan Ehrenfest *et al*[6 7] introduced the notion of leucocyte-rich PRP (LR-PRP) characterised by a leucocyte concentration higher than the whole blood baseline leucocyte level, whereas leucocyte-poor PRP (LP-PRP) or Pure PRP includes a leucocyte concentration lower than in whole blood. Accordingly, the platelet increase factor, corresponding to the platelet concentration increase in PRP compared with whole blood, is the most frequently described parameter in both scientific publications and manufacturer's pro-

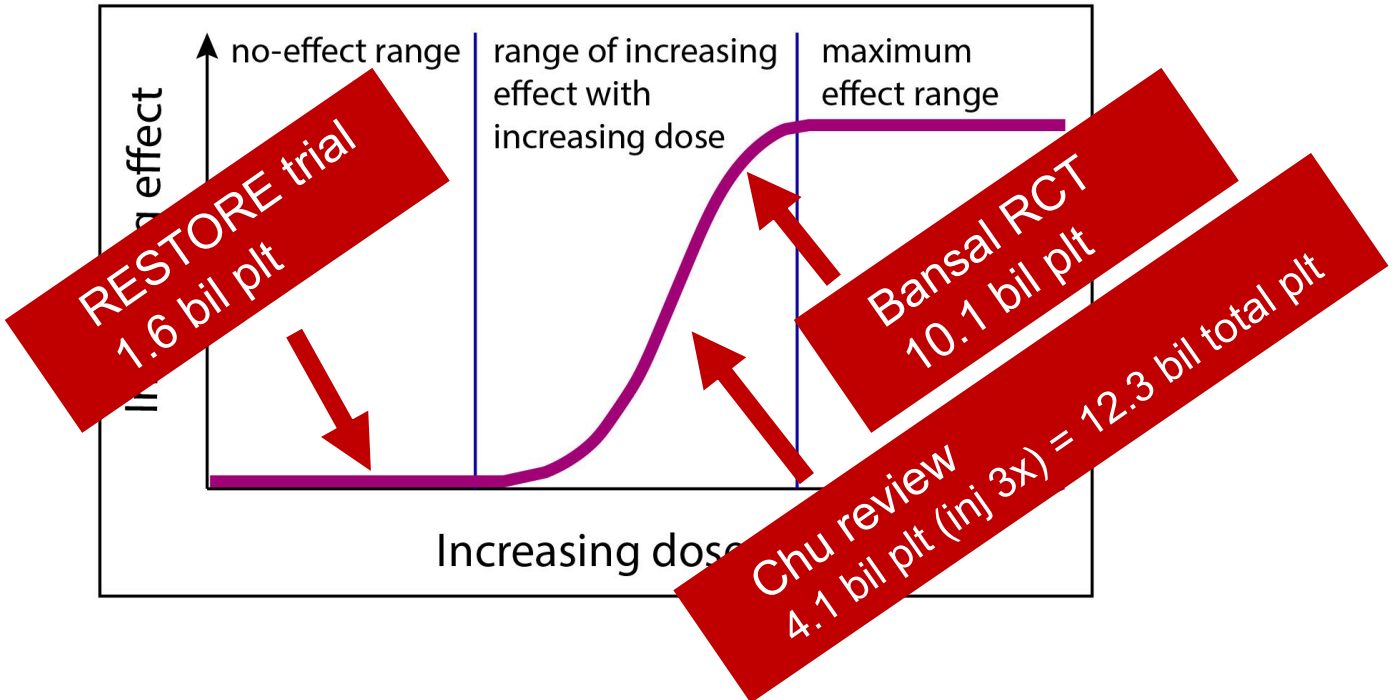
The injected dose of platelets should be measured in billions or millions of platelets and categorized as follows:

A. very high dose of injected platelets of >5 billion

B. high dose of injected platelets, from 3 to 5 billion

C. medium dose of injected platelets, from 1 to 3 billion

D. low dose of injected platelets, <1 billion



Magalon J, et al. *BMJ Open Sport Exerc Med.* 2016;2(1):e000060.

How to Calculate Dosing of PRP

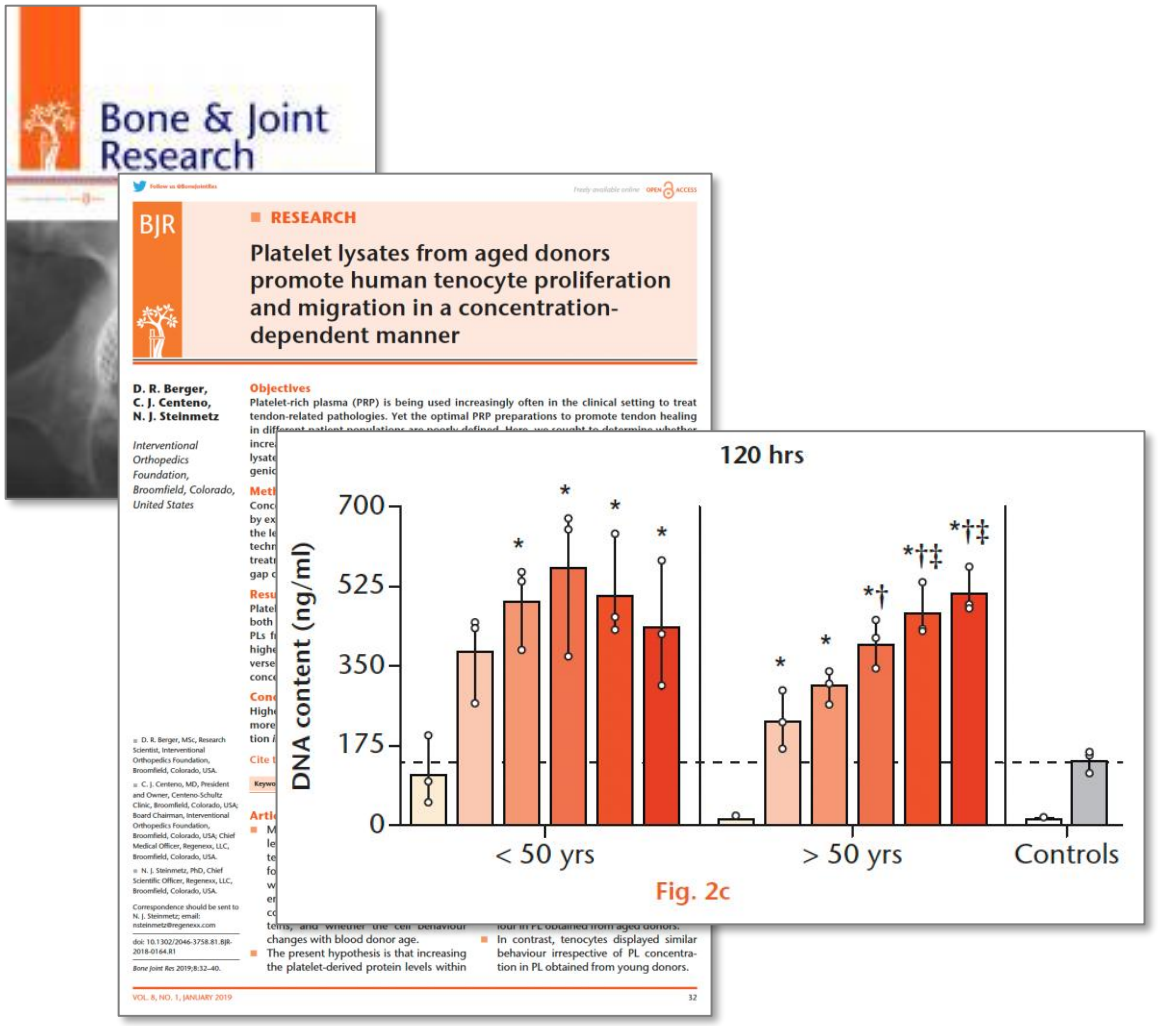
WHAT'S THE MATH?

- Assume a normal PLT # 150-450,000 PLTs/ul
- Assume mean **PLT capture rate** of 70% (yields range 43%-99%)

Blood draw	**Platelet "Dose"**
10mL → 1.5-4.5 billion PLTs x 70% =	**1.05-3.15 billion PLTs**
20mL → 3-9 billion PLTs x 70 % =	**2.1-6.3 billion PLTs**
30mL → 4.5-13.5 billion PLTs x 70% =	**3.15-9.45 billion PLTs**
60mL → 9-26 billion PLTs x 70% =	**6.3-18.9 billion PLTs**

If you're not analyzing PLT #s, a 60mL system should be used at a minimum 120cc better in case yield is <55%

Age and Dosing Considerations for PRP (Tendons)



Berger, et al. (2019)

Basic science

Design

- Varied platelet-derived proteins (from lysed platelets, PL) from both young (<50yr) and aged (>50 yr) donors
- Human tenocytes cultured with varying concentrations of platelet proteins and measured tendon proliferation

Results

- Both age groups showed improved tenocyte proliferation; however, aged donors yielded a dose-response relationship vs no difference in tenocyte behavior in younger donors

Conclusion

- Increasing PRP dosing in older patients increases cell activity, but this doesn't occur in younger patients

Berger DR, et al. *Bone Joint Res.* 2019;8(1):32-40.

But What about Other Cells? The Bioformulation of PRP

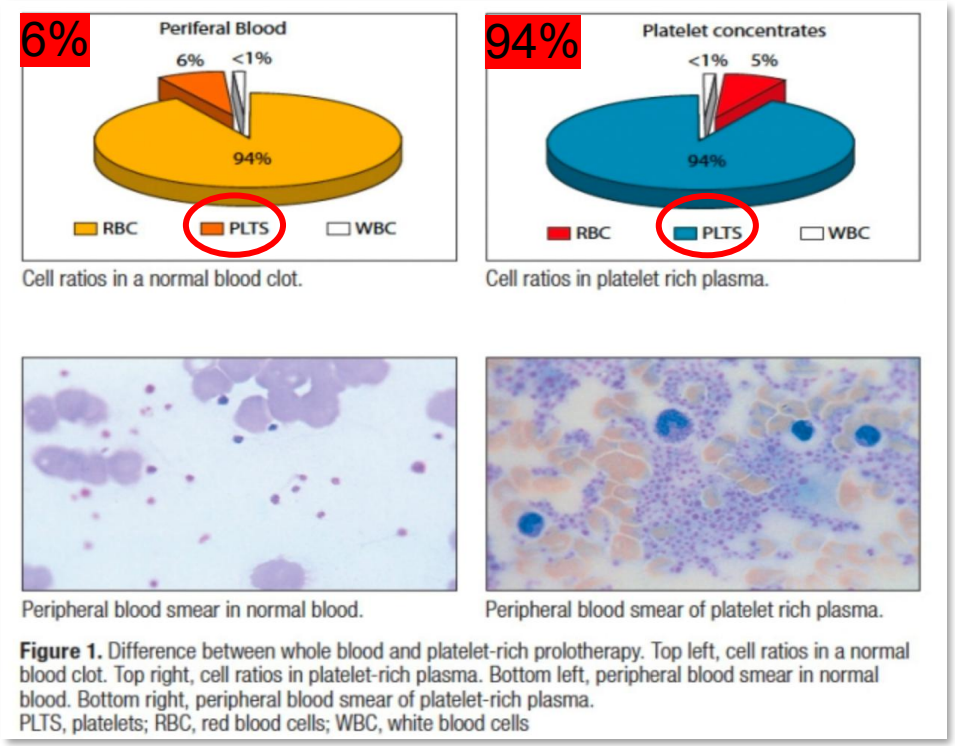
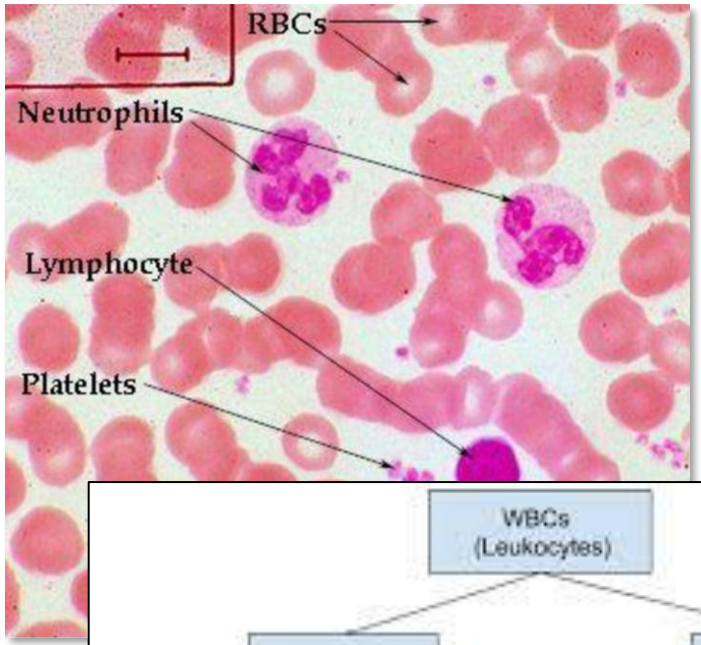
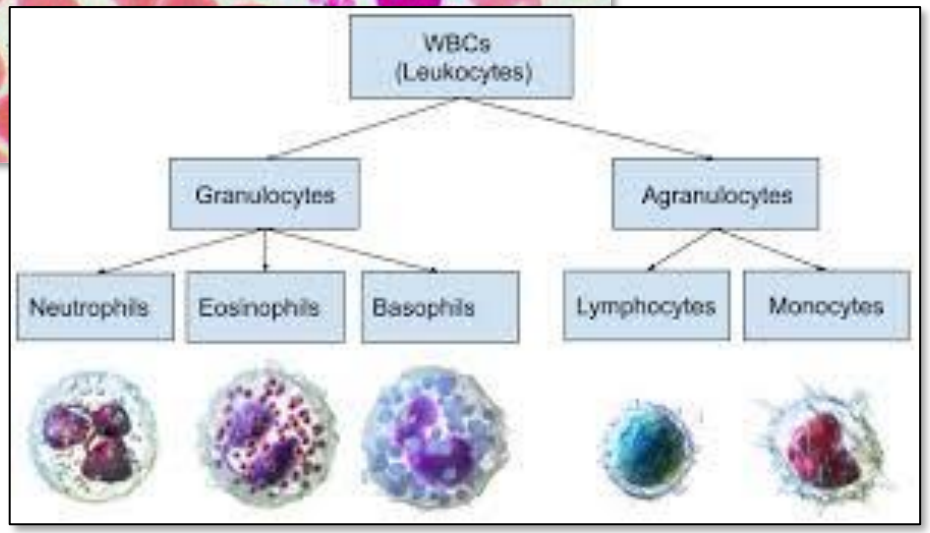
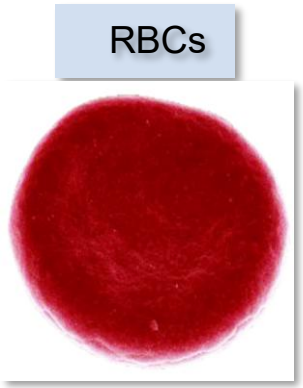


Figure 1. Difference between whole blood and platelet-rich prolotherapy. Top left, cell ratios in a normal blood clot. Top right, cell ratios in platelet-rich plasma. Bottom left, peripheral blood smear in normal blood. Bottom right, peripheral blood smear of platelet-rich plasma.
PLTS, platelets; RBC, red blood cells; WBC, white blood cells

Alderman D, Alexander R. *Pract Pain Manag.* 2011.







Finnoff JT, et al. *Clin J Sport Med.* 2021;31(6):530-541.

Bioformulation of PRP

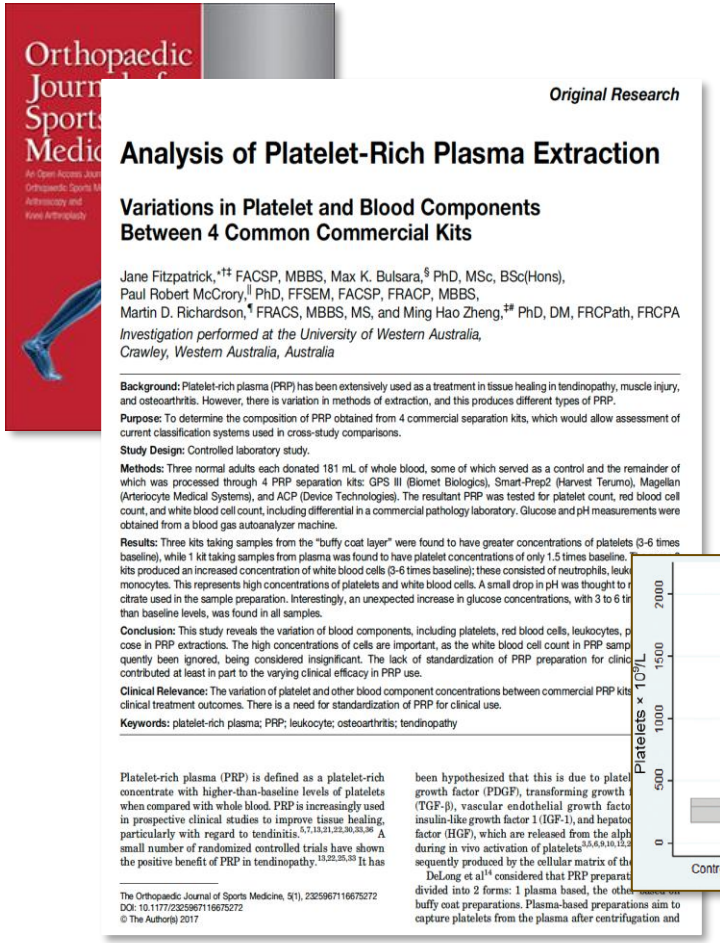
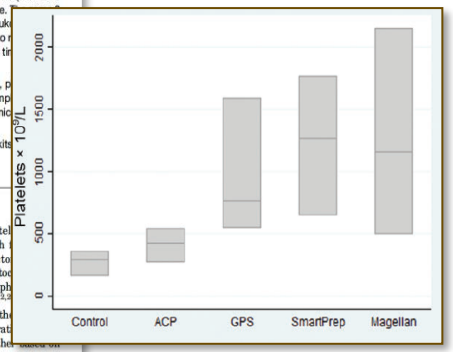


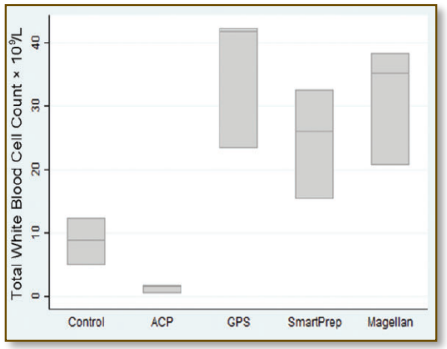
TABLE 1
Commercially Available Kits for the Production of Platelet Products[a]

Device Name	Company	Name of Product	Comments
GPS III	Biomet	Platelet-rich plasma	Tested
SmartPrep2	Harvest	Platelet-rich plasma	Tested
Magellan	Arteriocyte Medical	Platelet-rich plasma	Tested
Angel	Sorin	Platelet-rich plasma	Not available for testing
CS	Genesis	Platelet-rich plasma	Not available for testing
ACP	Arthrex	Autologous conditioned plasma	Tested
PRFM Fibrinet System	Cascade	Platelet-rich fibrin	Not tested, fibrin membrane
PRF and Vivostat	Choukroun's	Platelet-rich fibrin	Not tested, fibrin membrane
BMAC	DePuy	Platelet-rich plasma and stem cells	Not tested, bone marrow
Cell saver–based systems Electa, Haemonetics, CATS, BRAT	Several	Pure platelets	Not tested, volume required >200 mL
Caption	Not yet marketed	Pure platelets	Not tested, not available
Total	12 companies		4 tested

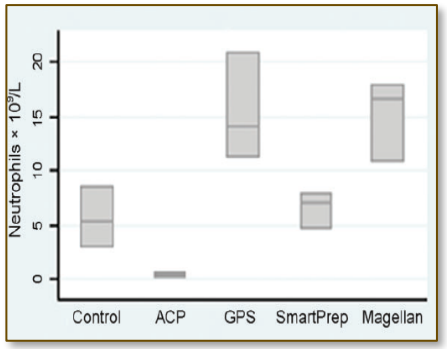
[a]Table derived from Engebretson et al.[16]



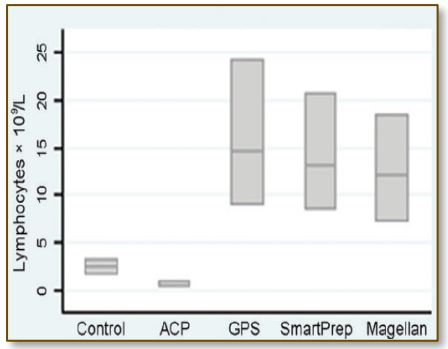
Platelets



WBC



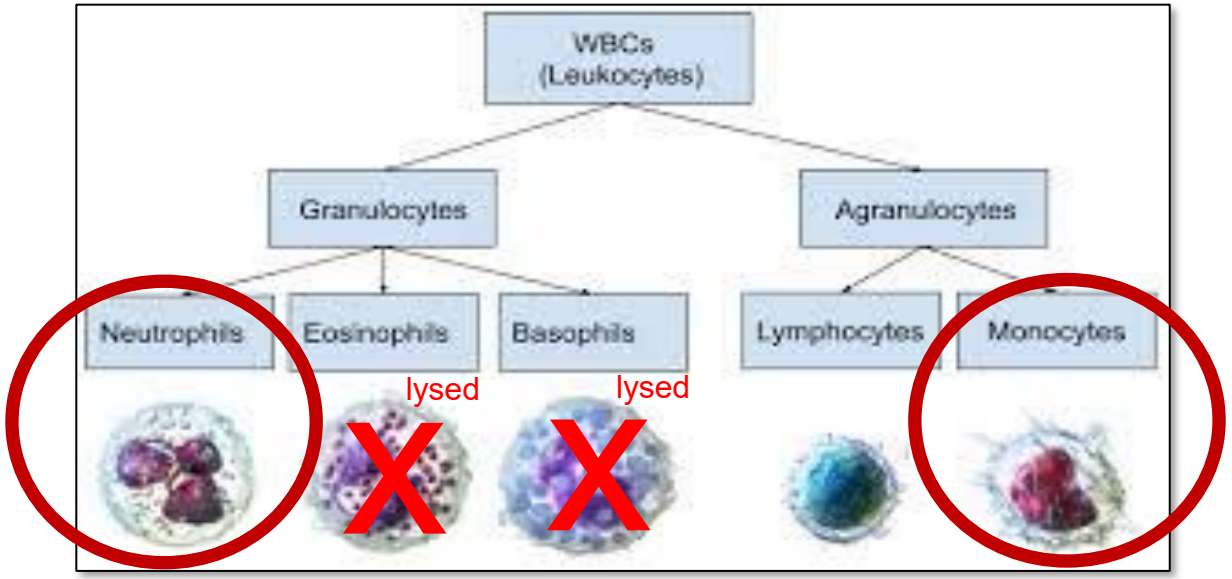
Neutrophil



Lymphocytes

Fitzpatrick J, et al. *Orthop J Sports Med.* 2017;5(1):2325967116675272.

Leukocytes in PRP



Neutrophils increase inflammation stimulate angiogenesis and anti-microbial action destroying/clearing pathogens

Monocytes clear necrotic tissue and produce growth factors that stimulate neovascularization

Everts P, et al. *Int J Mol Sci.* 2020;21(20):E7794.

How Do We Define LR-PRP vs LP-PRP?

Several attempts have been made to characterize and classify PRP, however, no consensus has been reached, and there is no generally accepted standard or classification system in place

6 Classification Systems
Only 3 of 6 Define LR vs LP

Rich: > baseline; poor: < baseline (NR)

Lana et al. (2017)

Leucocyte present: +ve; leucocyte absent: -ve (% of neutrophils)

Mautner et al. (2015)

A: above baseline; B: below or equal to baseline (α: above baseline; β: below or equal to baseline)

DeLong et al. (2012)

LR = leukocyte-rich; LP = leukocyte-poor.
Rossi LA, et al. *Bone Joint J.* 2019;101-B(8):891-896.

How Do We Define LR-PRP vs LP-PRP?

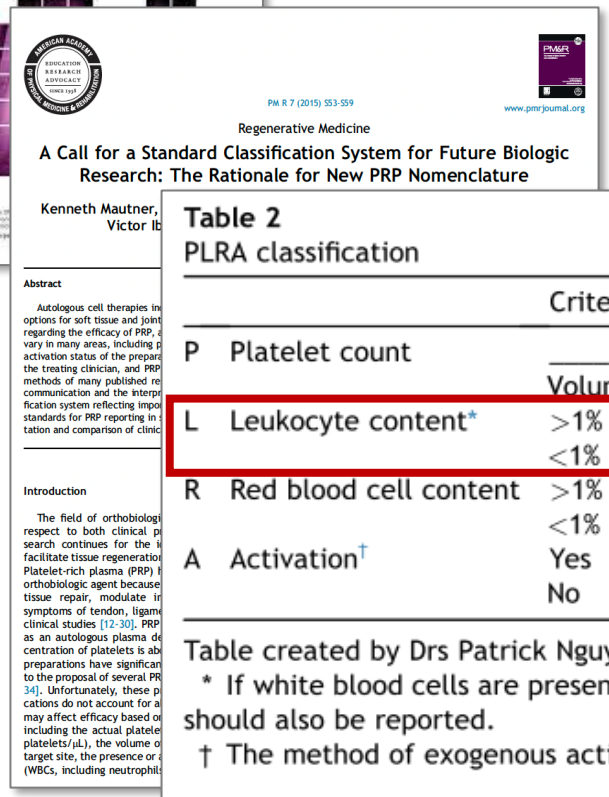
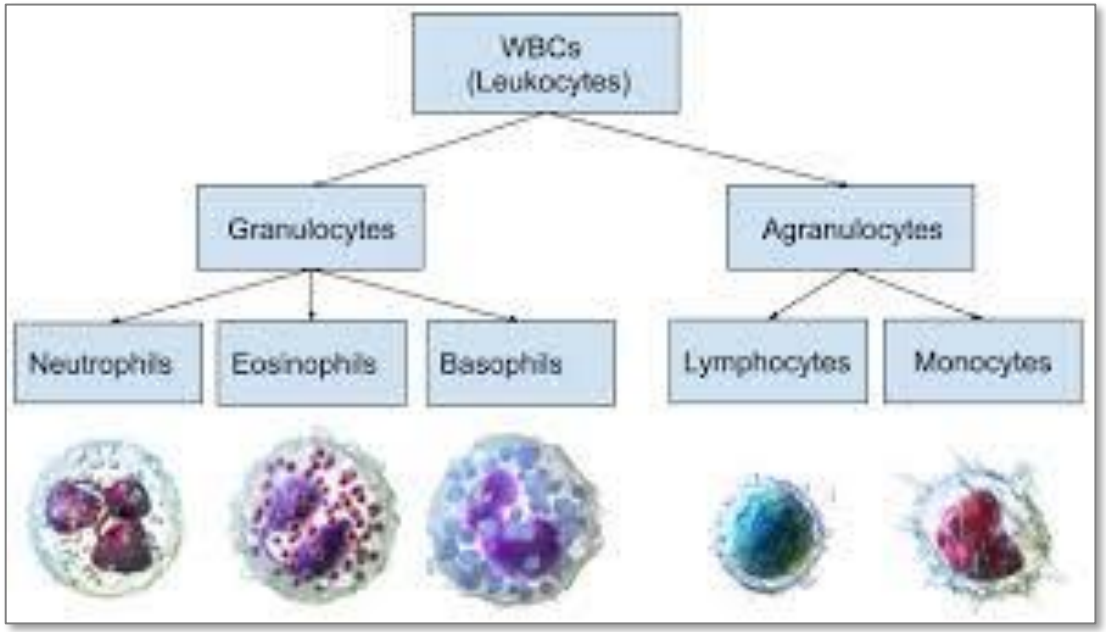


Table 2
PLRA classification

		Criteria	Final Score
		_____ P	_____ M
P	Platelet count	Volume injected	Cells/μL
L	Leukocyte content*	>1%	+
		<1%	–
R	Red blood cell content	>1%	+
		<1%	–
A	Activation†	Yes	+
		No	–

Table created by Drs Patrick Nguyen and Walter Sussman.
* If white blood cells are present (+), the percentage of neutrophils should also be reported.
† The method of exogenous activation should be reported.

LR-PRP and LP-PRP are more specific definitions than the generic PRP definition, but still lacks specific details of the types of leukocytes or their concentrations



Mautner K, et al. *PM&R.* 2015;7(4 Suppl):s53-s59.

LR vs LP-PRP in KOA

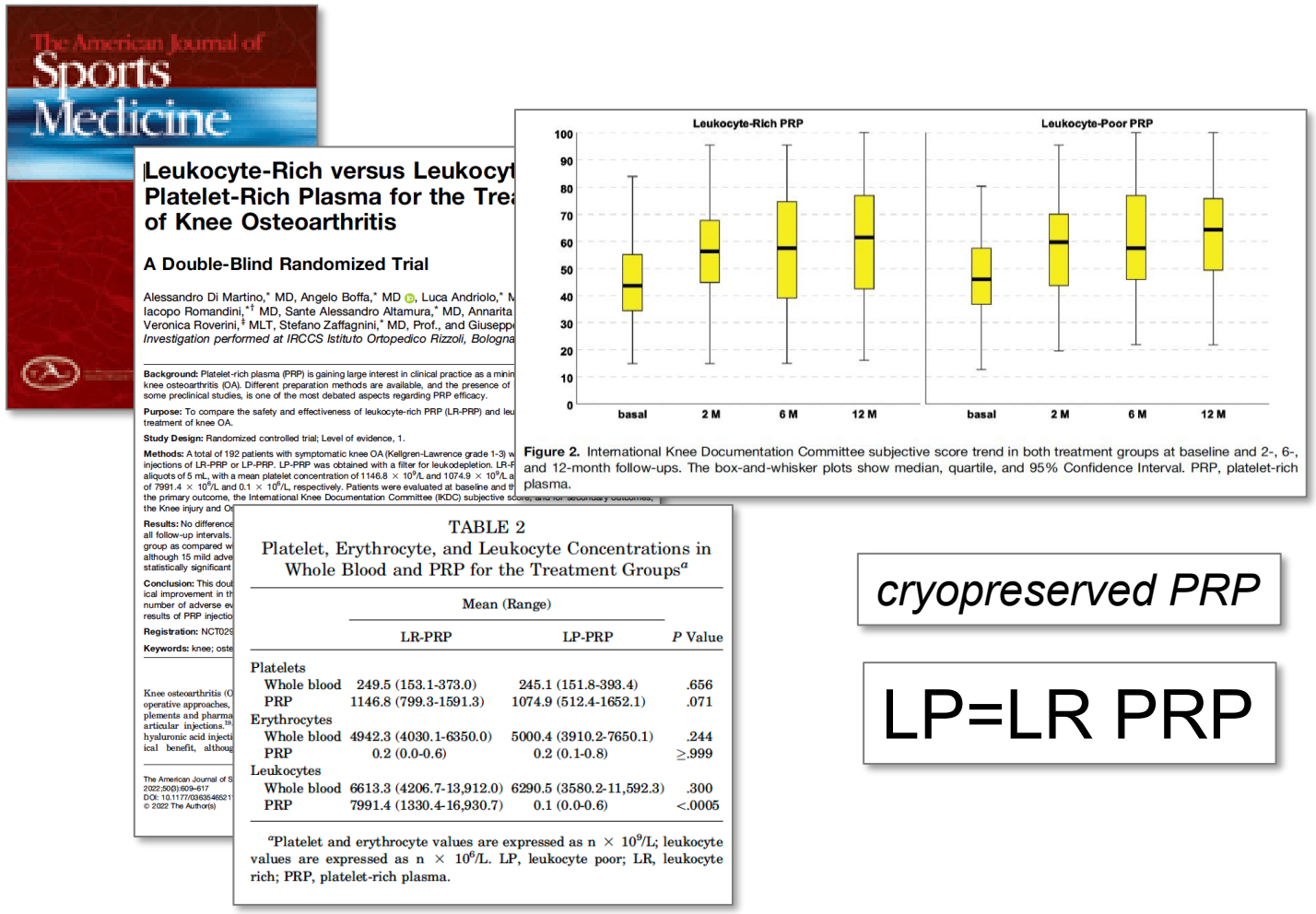


TABLE 2
Platelet, Erythrocyte, and Leukocyte Concentrations in Whole Blood and PRP for the Treatment Groups[a]

	Mean (Range)		
	LR-PRP	LP-PRP	*P* Value
Platelets			
Whole blood	249.5 (153.1-373.0)	245.1 (151.8-393.4)	.656
PRP	1146.8 (799.3-1591.3)	1074.9 (512.4-1652.1)	.071
Erythrocytes			
Whole blood	4942.3 (4030.1-6350.0)	5000.4 (3910.2-7650.1)	.244
PRP	0.2 (0.0-0.6)	0.2 (0.1-0.8)	≥.999
Leukocytes			
Whole blood	6613.3 (4206.7-13,912.0)	6290.5 (3580.2-11,592.3)	.300
PRP	7991.4 (1330.4-16,930.7)	0.1 (0.0-0.6)	<.0005

[a]Platelet and erythrocyte values are expressed as n × 10^9/L; leukocyte values are expressed as n × 10^6/L. LP, leukocyte poor; LR, leukocyte rich; PRP, platelet-rich plasma.

cryopreserved PRP

LP=LR PRP

DiMartino, et al. (2022) RCT

n=192, w/osteoarthritis (OA) KL grade 1-3

- 3-wkly injection cycle of LR- or LP-PRP
- PRP produced using manual method, 300mL of whole blood draw, 2 spin approach, divided into 3 aliquots of 5mL and stored

Results

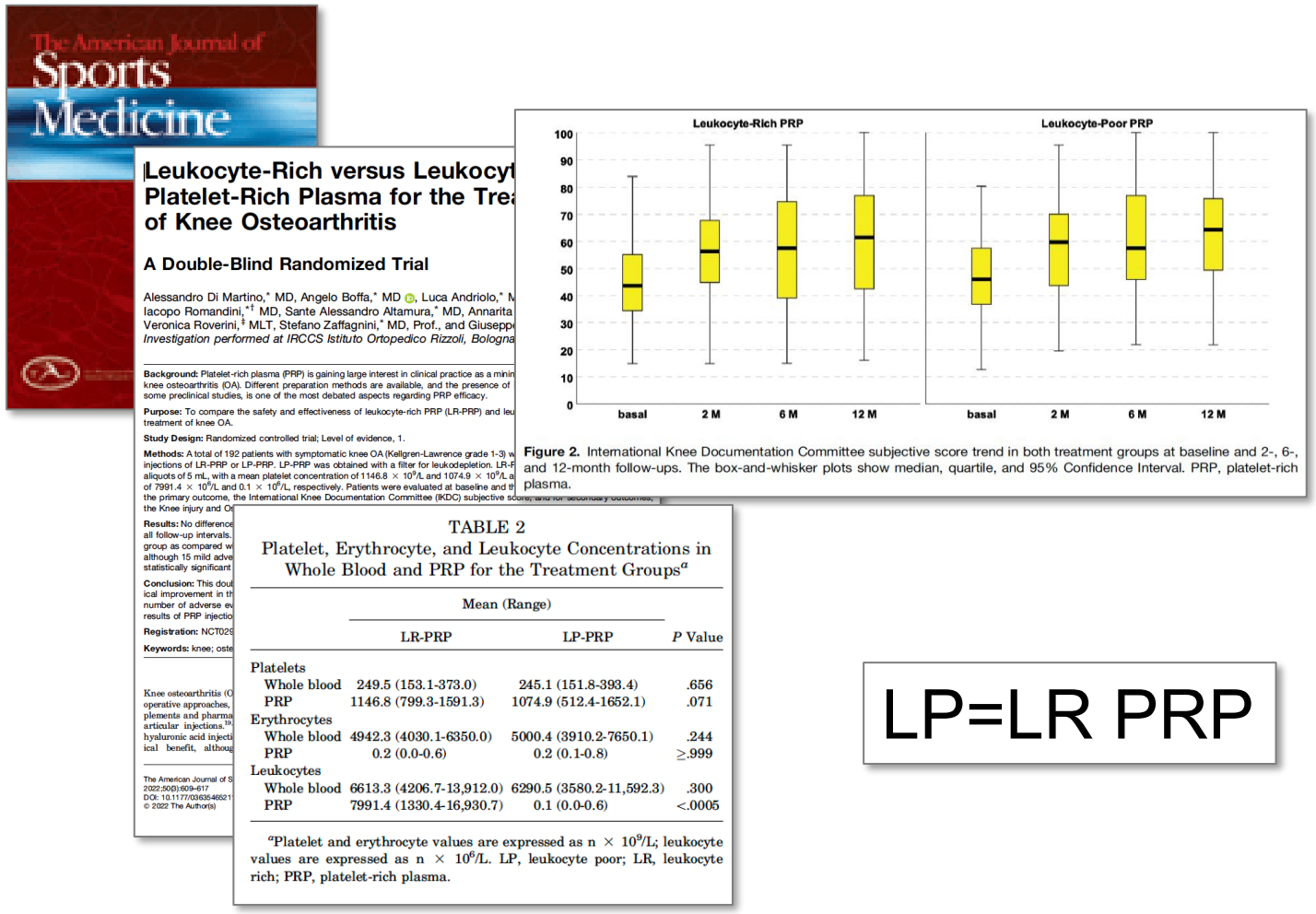
- No difference in clinical scores @ baseline and f/u 2, 6, and 12mo
- LR 12.2% had pain/swelling, LP 4.7%

Outcomes

- Leukocytes did not affect the efficacy of intra-articular PRP injections

DiMartino A, et al. *Am J Sports Med.* 2022;50(3):609-617.

LR vs LP-PRP in KOA



LP=LR PRP

Romandini, et al. (2024) RCT

n=132, w/osteoarthritis (OA) KL grade 1-3

- 3-wkly injection cycle of LR- or LP-PRP
- PRP produced using CPunT system, 50mL of whole blood draw each time, 2 spin system

Results

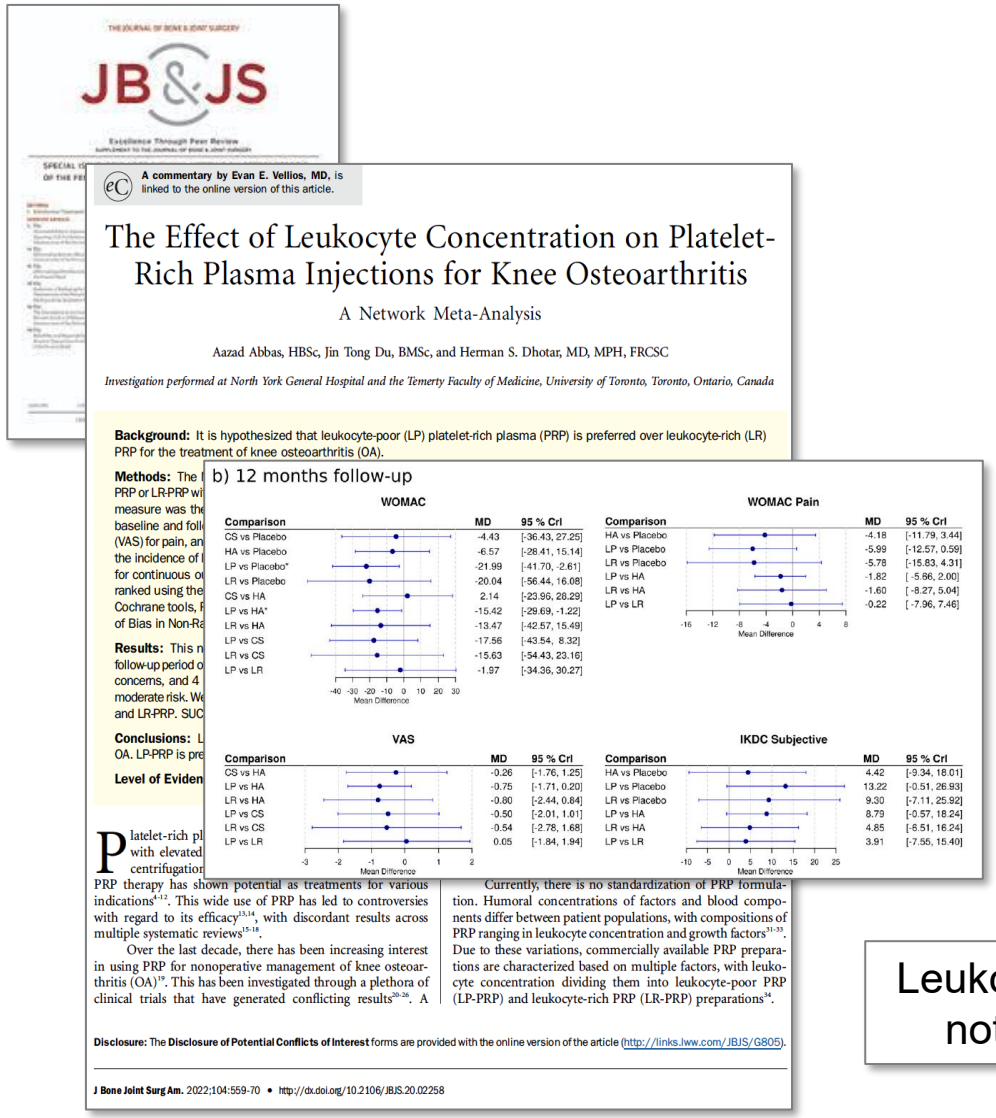
- Subjective and objective outcomes were documented with no differences @ baseline and f/u 2, 6, and 12mo

Outcomes

- Leukocytes did not affect the safety and efficacy of intra-articular PRP injections for the treatment of patients with knee OA

Romandini I, et al. *Am J Sports Med.* 2024;52(13):3212-3222.

Evidence for LR vs LP-PRP in OA


JB&JS

A commentary by Evan E. Vellios, MD, is linked to the online version of this article.

The Effect of Leukocyte Concentration on Platelet-Rich Plasma Injections for Knee Osteoarthritis

A Network Meta-Analysis

Aazad Abbas, HBSc, Jin Tong Du, BMSc, and Herman S. Dhotar, MD, MPH, FRCSC

Investigation performed at North York General Hospital and the Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Background: It is hypothesized that leukocyte-poor (LP) platelet-rich plasma (PRP) is preferred over leukocyte-rich (LR) PRP for the treatment of knee osteoarthritis (OA).

Methods: The

Results: This

Conclusions:

Level of Evidence

b) 12 months follow-up

WOMAC

Comparison	MD	95 % CrI
CS vs Placebo	-4.43	[-36.43, 27.25]
HA vs Placebo	-6.57	[-28.41, 15.14]
LP vs Placebo*	-21.99	[-41.70, -2.61]
LR vs Placebo	-20.04	[-56.44, 16.08]
CS vs HA	2.14	[-23.96, 28.29]
LP vs HA*	-15.42	[-29.69, -1.22]
LR vs HA	-13.47	[-42.57, 15.49]
LP vs CS	-17.56	[-43.54, 8.32]
LP vs CS	-15.63	[-54.43, 23.16]
LP vs LR	-1.97	[-34.36, 30.27]

WOMAC Pain

Comparison	MD	95 % CrI
HA vs Placebo	-4.18	[-11.79, 3.44]
LP vs Placebo	-5.99	[-12.57, 0.59]
LR vs Placebo	-5.78	[-15.83, 4.31]
LP vs HA	-1.82	[-5.86, 2.00]
LR vs HA	-1.60	[-8.27, 5.04]
LP vs LR	-0.22	[-7.96, 7.46]

VAS

Comparison	MD	95 % CrI
CS vs HA	-0.26	[-1.76, 1.25]
LP vs HA	-0.75	[-1.71, 0.20]
LR vs HA	-0.80	[-2.44, 0.84]
LP vs CS	-0.50	[-2.01, 1.01]
LR vs CS	-0.54	[-2.78, 1.68]
LP vs LR	0.05	[-1.84, 1.94]

IKDC Subjective

Comparison	MD	95 % CrI
HA vs Placebo	4.42	[-9.34, 18.01]
LP vs Placebo	13.22	[-0.51, 26.93]
LR vs Placebo	9.30	[-7.11, 25.92]
LP vs HA	8.79	[-0.57, 18.24]
LR vs HA	4.85	[-8.51, 16.24]
LP vs LR	3.91	[-7.55, 15.40]

Mean Difference

Platelet-rich pl
with elevated
centrifugation

PRP therapy has shown potential as treatments for various indications[4-12]. This wide use of PRP has led to controversies with regard to its efficacy[13,14], with discordant results across multiple systematic reviews[15-18].

Over the last decade, there has been increasing interest in using PRP for nonoperative management of knee osteoarthritis (OA)[19]. This has been investigated through a plethora of clinical trials that have generated conflicting results[20-26]. A

Currently, there is no standardization of PRP formulation. Humoral concentrations of factors and blood components differ between patient populations, with compositions of PRP ranging in leukocyte concentration and growth factors[31-33]. Due to these variations, commercially available PRP preparations are characterized based on multiple factors, with leukocyte concentration dividing them into leukocyte-poor PRP (LP-PRP) and leukocyte-rich PRP (LR-PRP) preparations[34].

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/G805).

J Bone Joint Surg Am. 2022;104:559-70 • http://dx.doi.org/10.2106/JBJS.20.02258

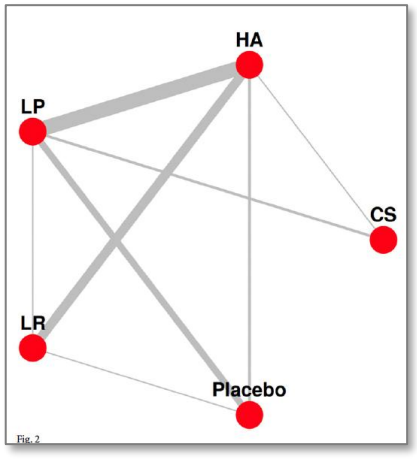


Fig. 2

Leukocyte concentration does not play a significant role

Abbas, et al. (2022)

Systematic Review/Meta-Analysis

n=23 studies included (2,260 patients; 20 RCT, 3 PCS)

Results/Conclusions

- Leukocyte concentration of PRP does not play a significant role in patient-reported outcome for KOA

Abbas A, et al. *J Bone Joint Surg.* 2022;104(6):559-570.

What Is the Ideal Bioformulation of PRP?

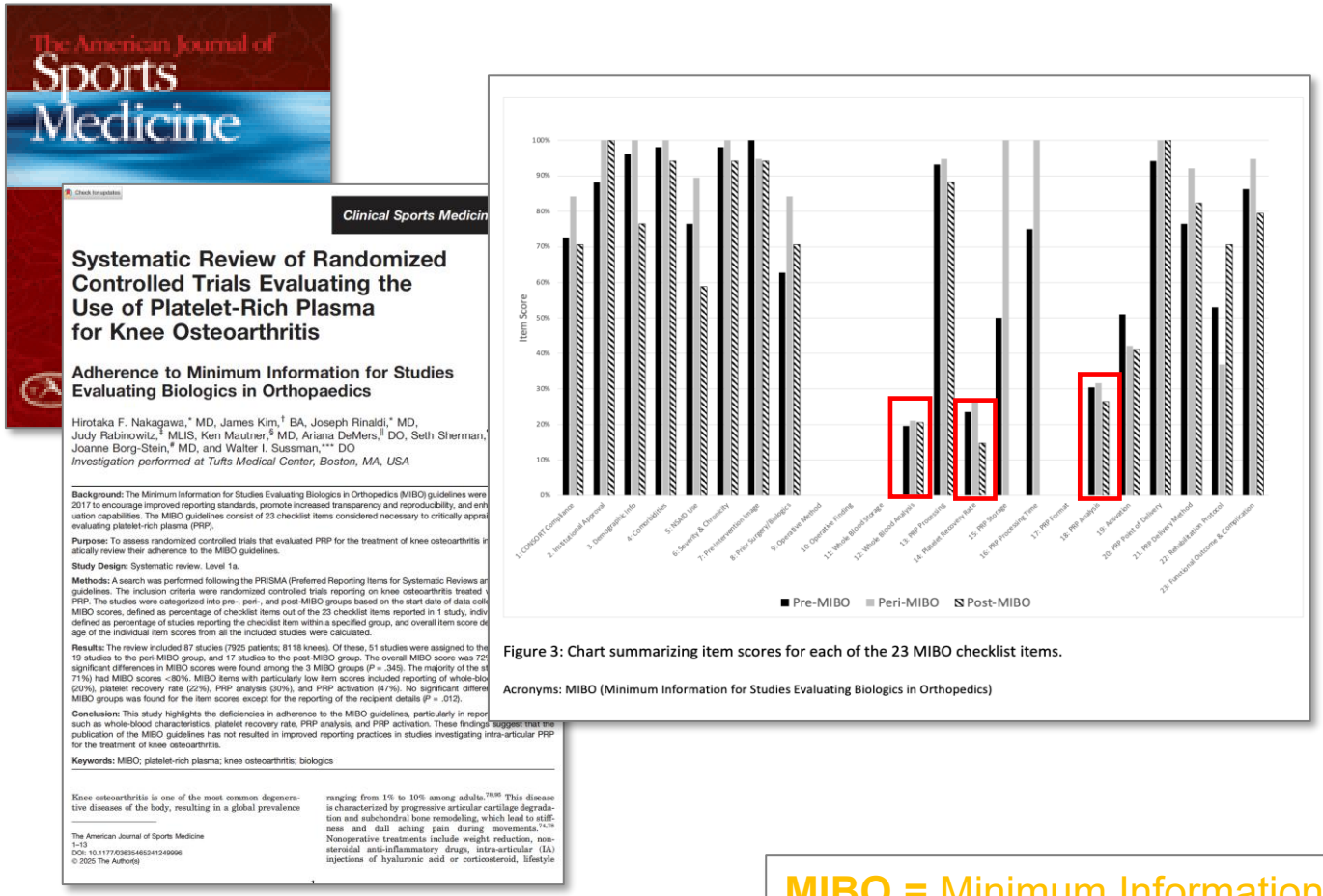


Figure 3: Chart summarizing item scores for each of the 23 MIBO checklist items.

Acronyms: MIBO (Minimum Information for Studies Evaluating Biologics in Orthopedics)

MIBO = Minimum Information for Studies Evaluating Biologics in Orthopaedics

Nakagawa, et al. (2024)

Systematic review of RCTs

Categorized into pre-, peri-, post-MIBO groups

Results

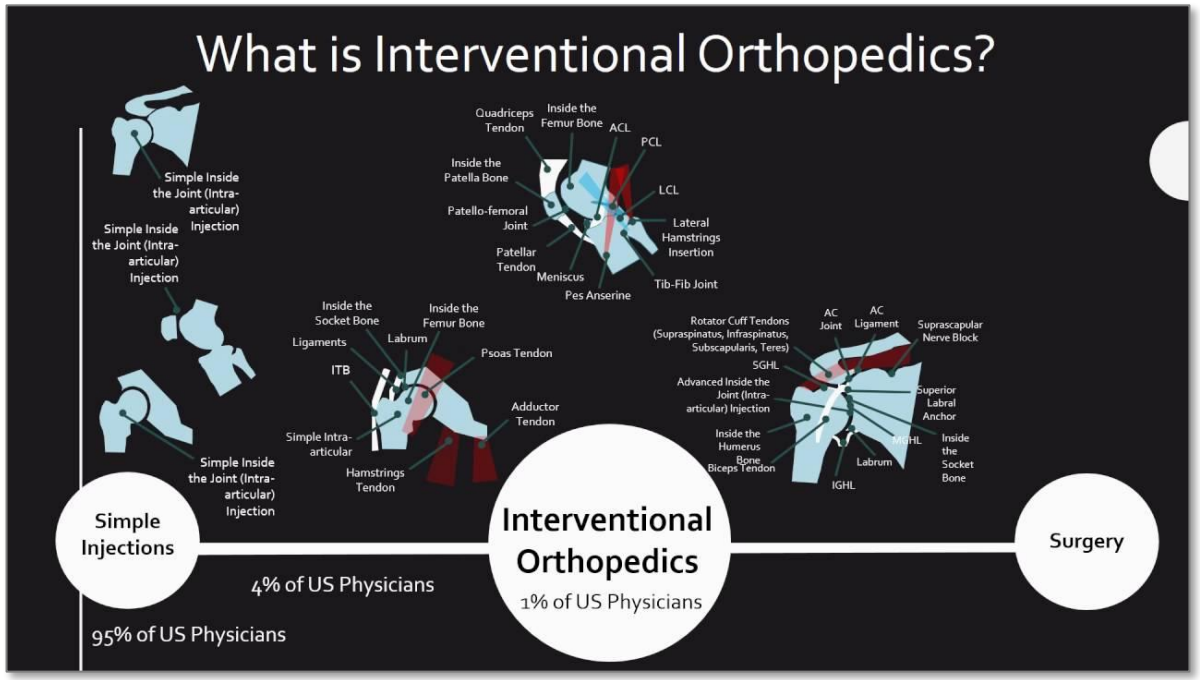
- 87 studies (7925 patients, 8118 knees)
  - Pre-MIBO = 51 studies
  - Peri-MIBO = 19
  - Post-MIBO =17

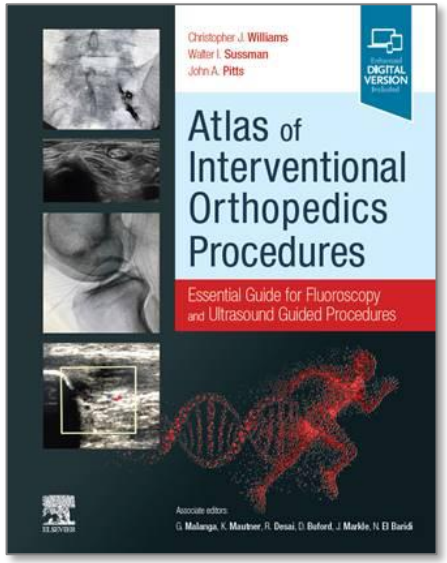
Conclusion

- No statistically significant differences in MIBO scores among groups (p=0.345)
- MIBO items with particularly low item scores included: whole-blood characteristics (20%), platelet recovery rate (22%), PRP analysis (30%)

.Nakagawa HF, et al. *Am J Sports Med.* 2025;53(5):1241-1253.

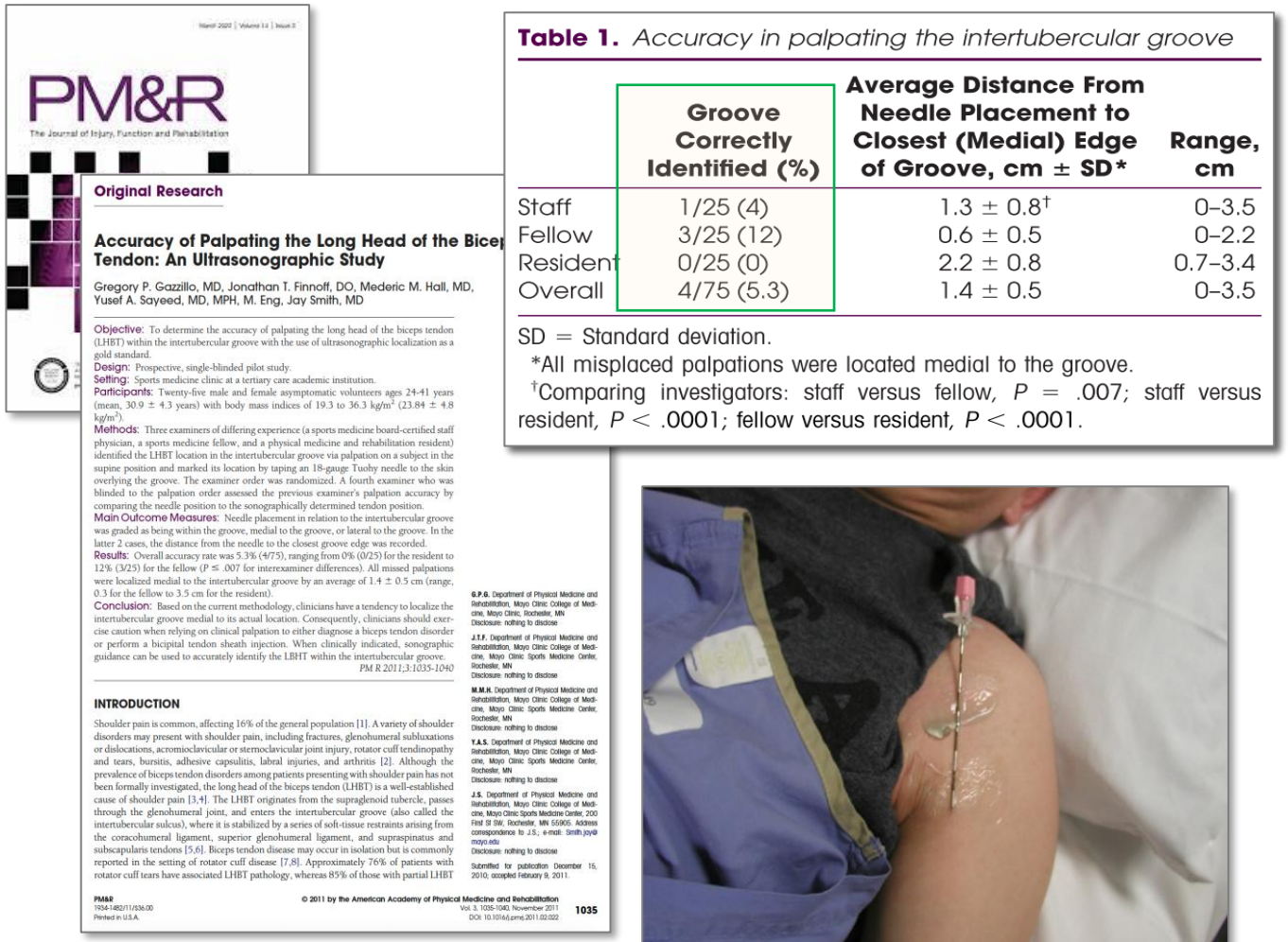
The Role of High-Resolution Ultrasound





Chris Centeno, https://www.youtube.com/watch?v=e6fMXKsELT8

Role of High-Resolution Ultrasound



PM&R

The Journal of Injury, Function and Rehabilitation

Original Research

Accuracy of Palpating the Long Head of the Bicep Tendon: An Ultrasonographic Study

Gregory P. Gazzillo, MD, Jonathan T. Finnoff, DO, Mederic M. Hall, MD, Yusef A. Sayeed, MD, MPH, M. Eng, Jay Smith, MD

Objective: To determine the accuracy of palpating the long head of the biceps tendon (LHBT) within the intertubercular groove with the use of ultrasonographic localization as a gold standard.

Design: Prospective, single-blinded pilot study.

Setting: Sports medicine clinic at a tertiary care academic institution.

Participants: Twenty-five male and female asymptomatic volunteers ages 24-41 years (mean, 30.9 ± 4.3 years) with body mass indices of 19.3 to 36.3 kg/m^2 (23.84 ± 4.8 kg/m^2).

Methods: Three examiners of differing experience (a sports medicine board-certified staff physician, a sports medicine fellow, and a physical medicine and rehabilitation resident) identified the LHBT location in the intertubercular groove via palpation on a subject in the supine position and marked its location by taping an 18-gauge Tuohy needle to the skin overlying the groove. The examiner order was randomized. A fourth examiner who was blinded to the palpation order assessed the previous examiner's palpation accuracy by comparing the needle position to the sonographically determined tendon position.

Main Outcome Measures: Needle placement in relation to the intertubercular groove was graded as being within the groove, medial to the groove, or lateral to the groove. In the latter 2 cases, the distance from the needle to the closest groove edge was recorded.

Results: Overall accuracy rate was 5.3% (4/75), ranging from 0% (0/25) for the resident to 12% (3/25) for the fellow ($P \leq .007$ for interexaminer differences). All missed palpations were localized medial to the intertubercular groove by an average of 1.4 ± 0.5 cm (range, 0.3 for the fellow to 3.5 cm for the resident).

Conclusion: Based on the current methodology, clinicians have a tendency to localize the intertubercular groove medial to its actual location. Consequently, clinicians should exercise caution when relying on clinical palpation to either diagnose a biceps tendon disorder or perform a bicipital tendon sheath injection. When clinically indicated, sonographic guidance can be used to accurately identify the LHBT within the intertubercular groove.

PM R 2011;3:1035-1040

INTRODUCTION

Shoulder pain is common, affecting 16% of the general population [1]. A variety of shoulder disorders may present with shoulder pain, including fractures, glenohumeral subluxations or dislocations, acromioclavicular or sternoclavicular joint injury, rotator cuff tendinopathy and tears, bursitis, adhesive capsulitis, labral injuries, and arthritis [2]. Although the prevalence of biceps tendon disorders among patients presenting with shoulder pain has not been formally investigated, the long head of the biceps tendon (LHBT) is a well-established cause of shoulder pain [3,4]. The LHBT originates from the supraglenoid tubercle, passes through the glenohumeral joint, and enters the intertubercular groove (also called the intertubercular sulcus), where it is stabilized by a series of soft-tissue restraints arising from the coracohumeral ligament, superior glenohumeral ligament, and supraspinatus and subscapularis tendons [5,6]. Biceps tendon disease may occur in isolation but is commonly reported in the setting of rotator cuff disease [7,8]. Approximately 76% of patients with rotator cuff tears have associated LHBT pathology, whereas 85% of those with partial LHBT

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Disclosure: nothing to disclose

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Table 1. *Accuracy in palpating the intertubercular groove*

	Groove Correctly Identified (%)	Average Distance From Needle Placement to Closest (Medial) Edge of Groove, cm ± SD*	Range, cm
Staff	1/25 (4)	1.3 ± 0.8†	0–3.5
Fellow	3/25 (12)	0.6 ± 0.5	0–2.2
Resident	0/25 (0)	2.2 ± 0.8	0.7–3.4
Overall	4/75 (5.3)	1.4 ± 0.5	0–3.5

SD = Standard deviation.
*All misplaced palpations were located medial to the groove.
†Comparing investigators: staff versus fellow, $P = .007$; staff versus resident, $P < .0001$; fellow versus resident, $P < .0001$.

Gazzillo, et al. (2011)

Methods

- 25 volunteers, 3 examiners (SM board-certified staff, fellow, and resident)
- Tape Tuohy needle over location of bicipital groove
- Palpation accuracy confirmed by ultrasound

Results

- Overall accuracy was 5.3%
- Average difference was 1.4cm

Conclusion

- When clinically indicated, sonographic guidance should be used to accurately identify the LHBT

LHBT = long head of the biceps tendon.

Gazzillo GP, et al. *PMR.* 2011;3(11):1035-1040.

The Role of High-Resolution Ultrasound in Orthobiologics

Didactics

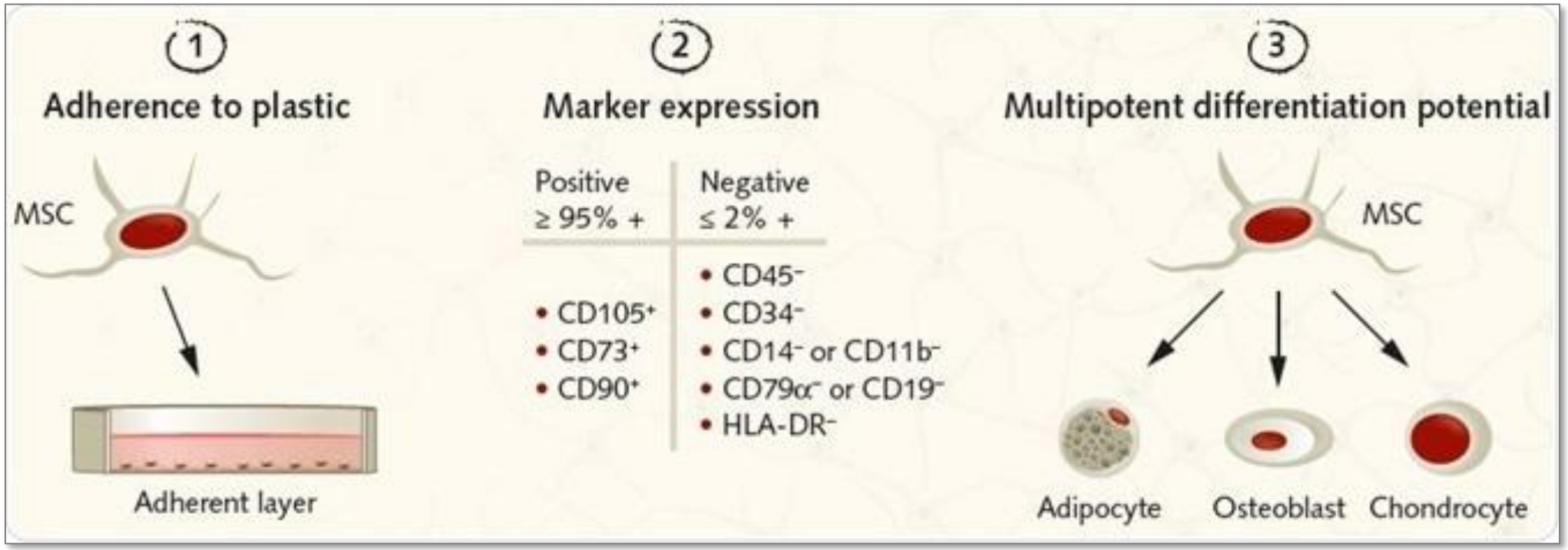
Hands-On Needle Training

Interventional Orthobiologics Foundation

https://interventionalorthobiologics.org/physician-education/

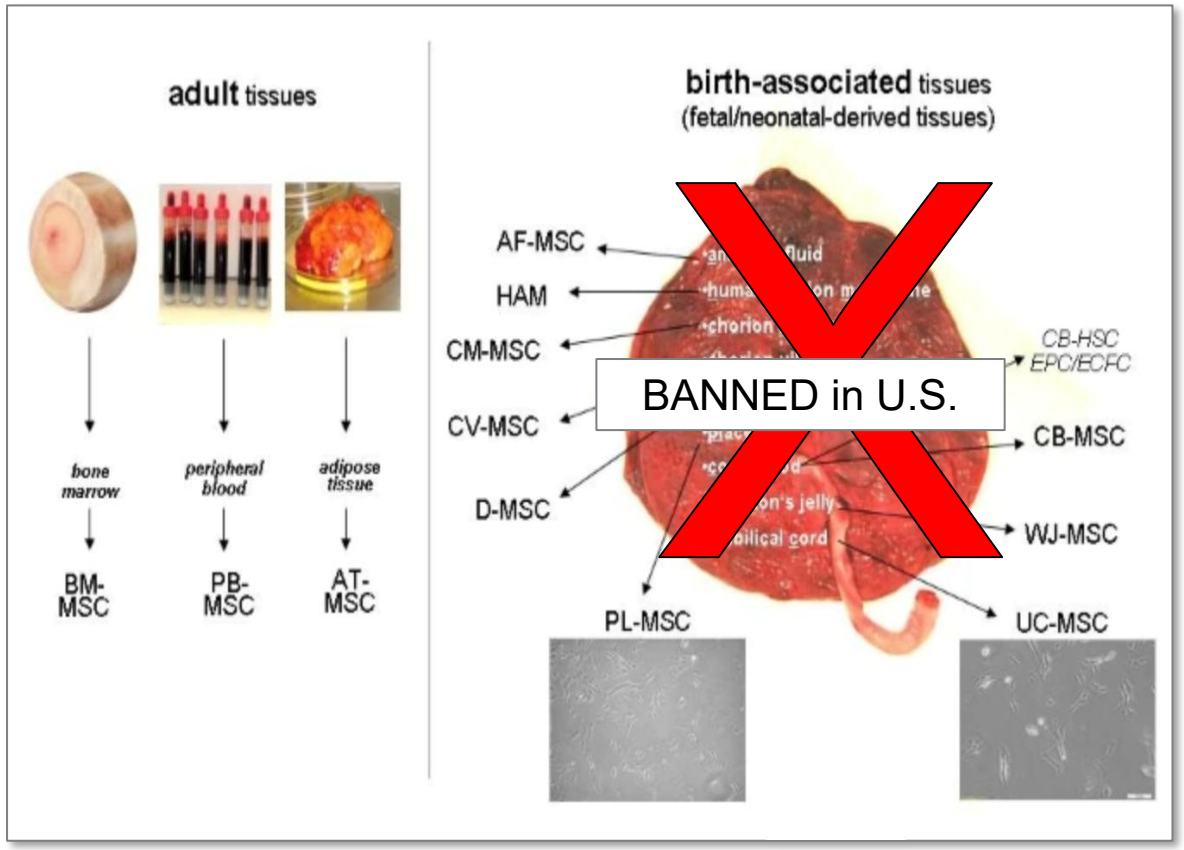
What Is a Stem Cell?

- Stem cells are simply a cellular population with the ability to self-replicate through mitosis to form daughter cell lines



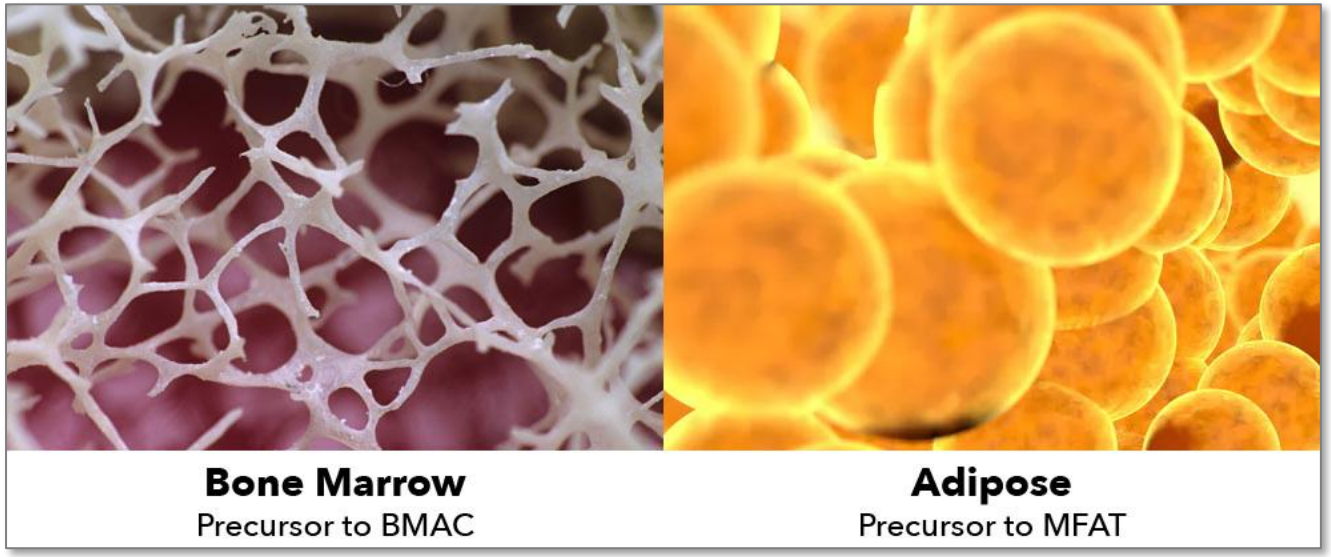
What Is a Stem Cell?

- Stem cells typically are <u>classified based upon their tissue of origin</u>
  - The majority of orthopedic-related stem cell research to date has focused on adult stem cells
  - Embryonic or perinatal stem cells banned by FDA in U.S. in 2021



What Is a Stem Cell?

- The majority of adult mesenchymal stem cell (MSC) products used in orthopedics are obtained from bone marrow tissue or adipose tissue



Both procedures involved

- Cells harvested and prepared at point-of-care in an office setting

MSC = mesenchymal stem cell.

Regulatory Considerations

Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

Guidance for Industry and Food and Drug Administration Staff

For questions on the content of this guidance, contact Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD) at 240-402-8010 or 800-835-4709. For questions about this document concerning products regulated by Center for Devices and Radiological Health (CDRH), contact the CDRH product jurisdiction officer at CDRHProductJurisdiction@fda.hhs.gov. If you need additional assistance with regulation of combination products, contact the Office of Combination Products (OCP) at 301-796-8930.

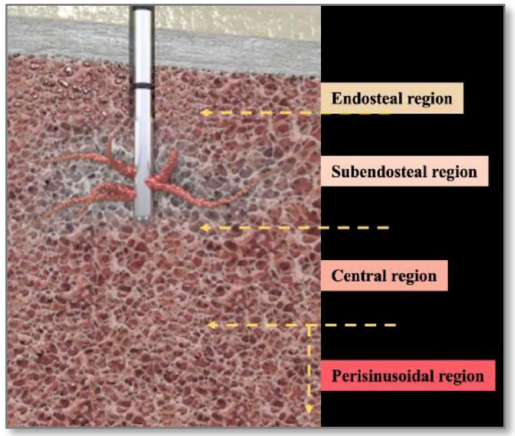
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Office of Combination Products
July 2020

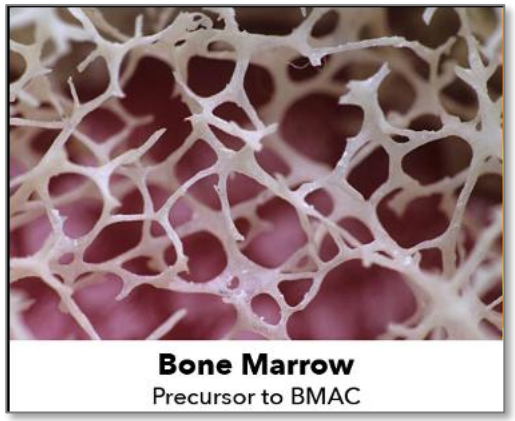
Matching the Treatment to the Underlying Tendon Pathology

BMAC

Rationale for use of BMAC

- BMAC is composed of concentrated MSCs that play a pivotal role in tissue regenerative and repair processes
- Contains stem cells, but stem cell products require incubated BM in plastic culture dishes and identifying and isolating MSCs as colony-forming unit fibroblasts (CFUs)
- Concentrated BM-MSCs synthesize cytokines and trophic mediators and institute a regenerative microenvironment for tissue repair
  - Increase cell-signaling
  - (Neo)angiogenesis
  - Improve cell recruitment
- Total number of BM-MSCs in BMAC is low
  - Estimated to vary between 0.01%-0.02%





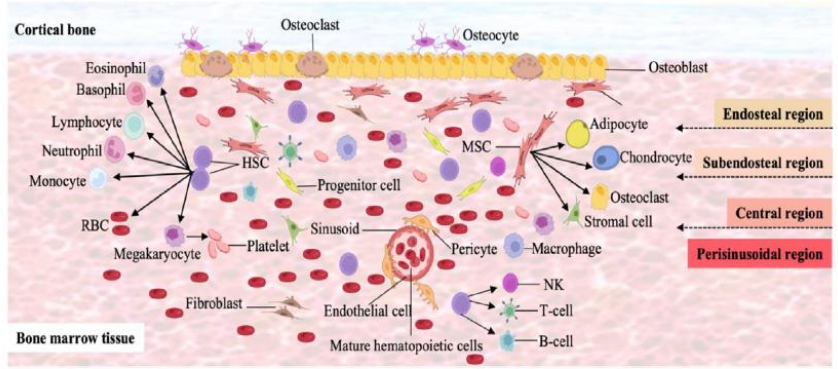
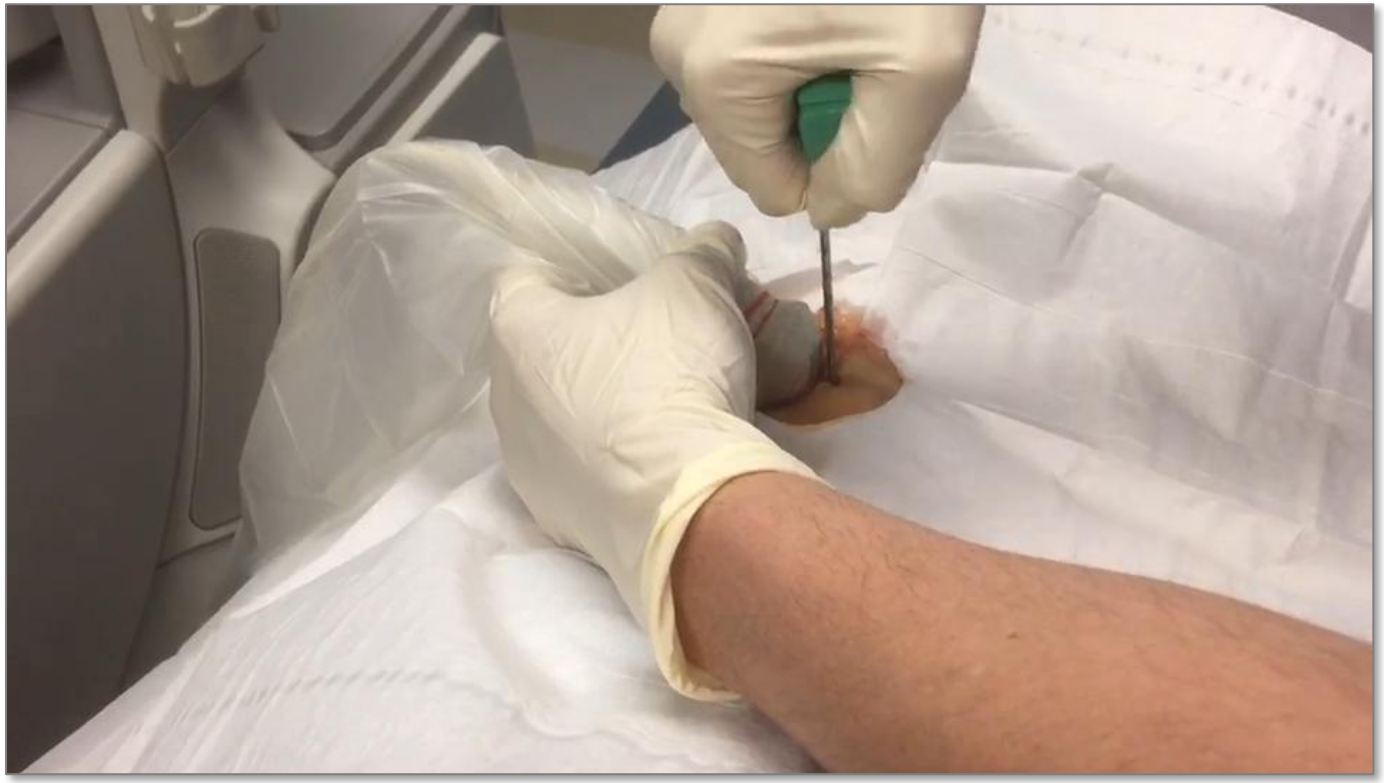


Fig. 1. Impression of the heterogenous cellular content of bone marrow tissue and region segmentation.

The cellular content of BMAC is more complex and distinct compared to PRP

BMAC Harvest

- The iliac crest is the harvest site of preference containing more BM-MSCs compared with other extraction sites



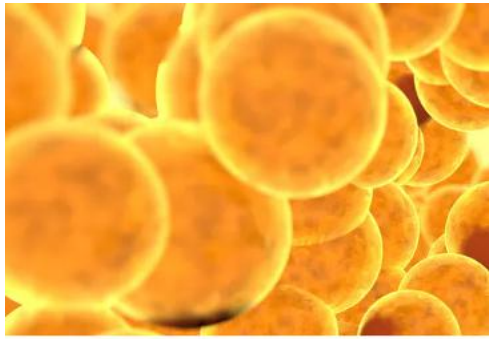
Bone Marrow
Precursor to BMAC

AD-MSC

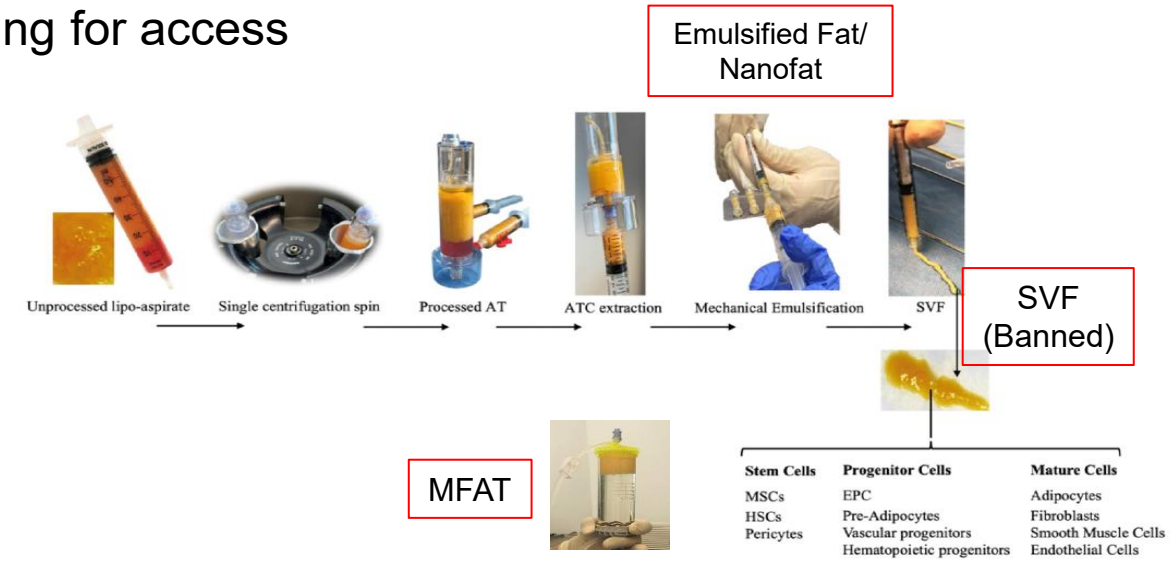
Rationale for use of AD-MSC

- Adipose tissue provides clinicians with 3D multicellular scaffold, including adipose-derived stem cells (ASCs) and stromal cells
- Mediated effects on the reduction of proinflammatory cytokines, chemokines, cellular apoptosis, and collagenases
- The use of adipose tissue in orthobiologics is based on the separation of the stromal vascular stroma contained in ATC, allowing for access to AD-MSCs
- Multiple techniques to process adipose tissue
  - Resized by emulsification or mechanical cutting (allowed by FDA)
  - Enzymatic processing to produce SVF (NOT allowed by FDA)

AD-MSCs constitute as much as 1% of SVF cells compared with 0.001% to 0.002% of BM-MSCs



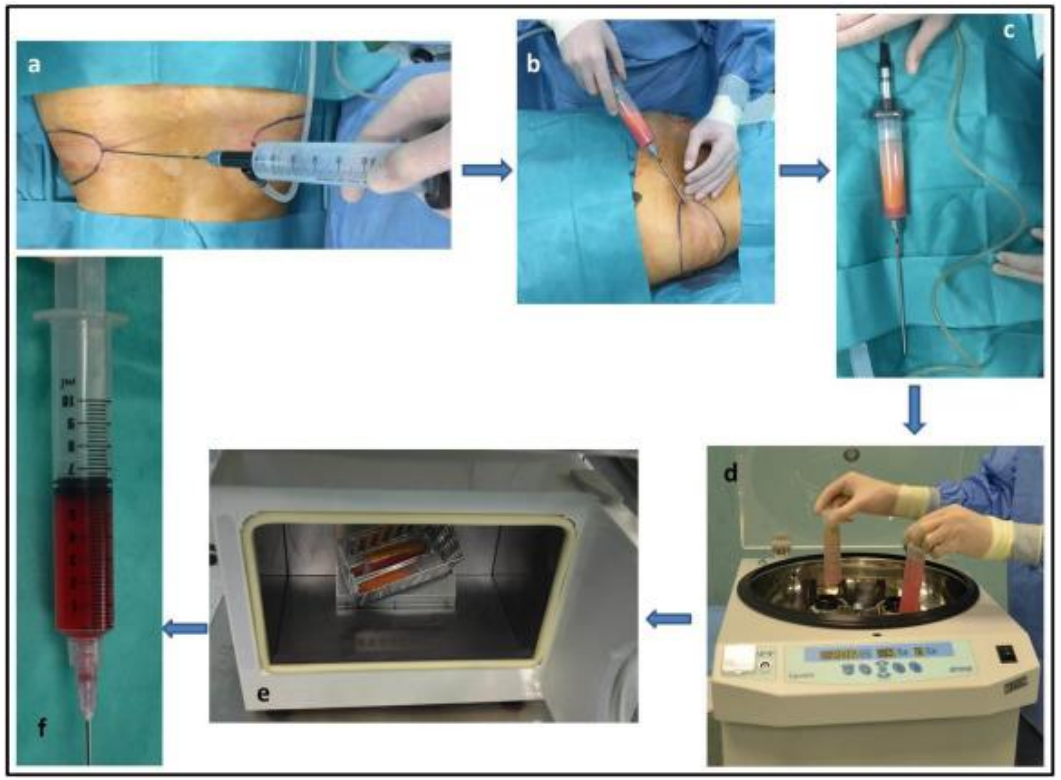
Adipose
Precursor to MFAT



FDA guidelines, enzymatic cellular prepared SVF products are listed in the “more than manipulated” category

AD-MSC = adipose-derived mesenchymal stem cells; ATC = adipose tissue complex; SVF = stromal vascular fraction.

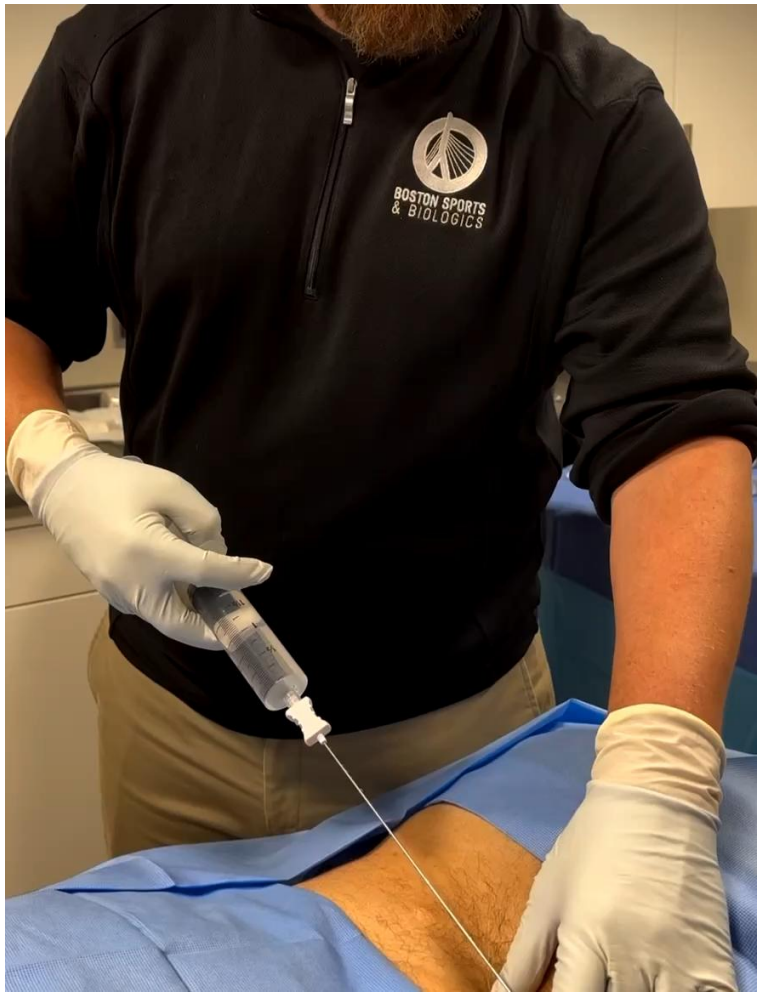
AD-MSC



Harvesting

Rudimentary Processing
- Filtered
- Washed
- Centrifugation

Resizing
- Emulsification
- Cutting (MFAT)



Take-Home Points

Highlights from the American Medical Society for Sports Medicine position statement on responsible use of regenerative medicine and orthobiologics in sports medicine

Shane A Shapiro ,[1] Jonathan T Finnoff,[2,3] Tariq M Awan,[4] Joanne P Borg-Stein,[5] Kimberly G Harmon ,[6] Daniel C Herman,[7] Gerard Malanga,[8,9] Zubin Master ,[10] Kenneth Mautner[11]

Tiered approach to considering orthobiologics for patients with musculoskeletal conditions

Shane A Shapiro ,[1] Zubin Master ,[2] Jennifer R Arthurs,[3] Kenneth Mautner [4]

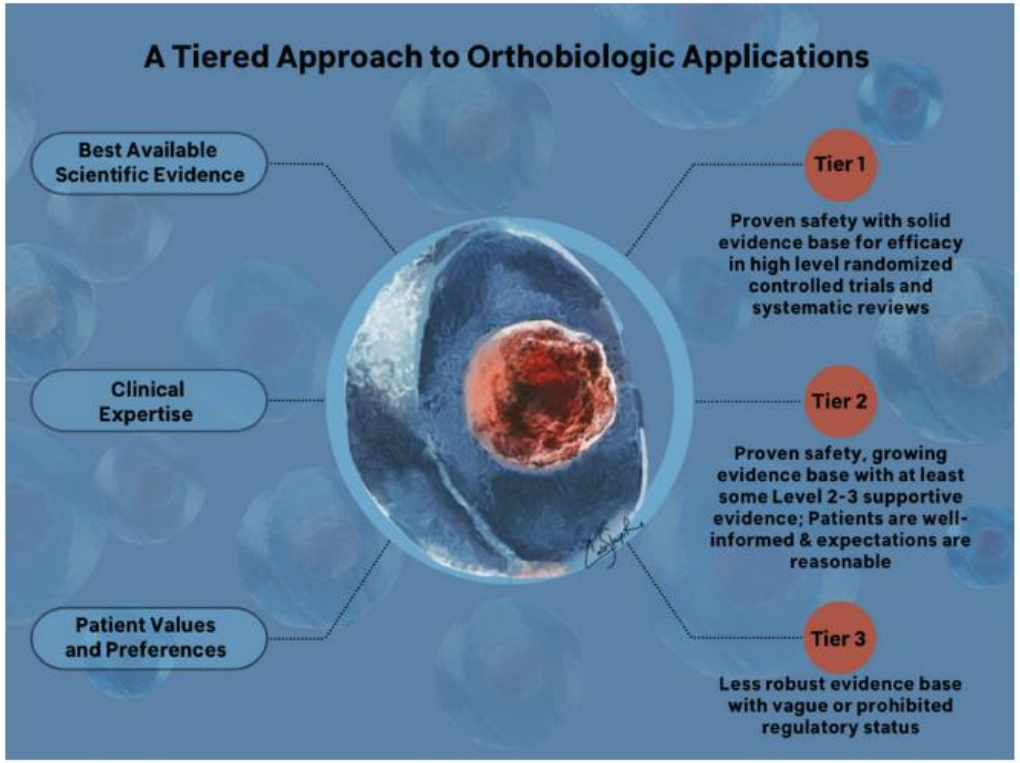


Figure 1 A tiered approach to orthobiologic applications. The ultimate goal of evidence based medicine is to use the best evidence to improve the care of individual patients. However, applying best evidence to clinical practice is not always straightforward. As a result, the best available scientific evidence is often combined with other valuable factors including the clinician's expertise and patient values and perspectives.

Clinical Pearls

- Be careful about comparing studies
  - Not all PRP is the same
  - Different preparations may be better for different conditions
  - Consider other factors: Patient selection, dosing, timing of injection (acute vs chronic phase)

Walter.Sussman@bsbortho.com

Innovations for Active Healing

Thank You