

Platelet-Rich Plasma in Orthopaedic Surgery: Where do we stand in 2017?

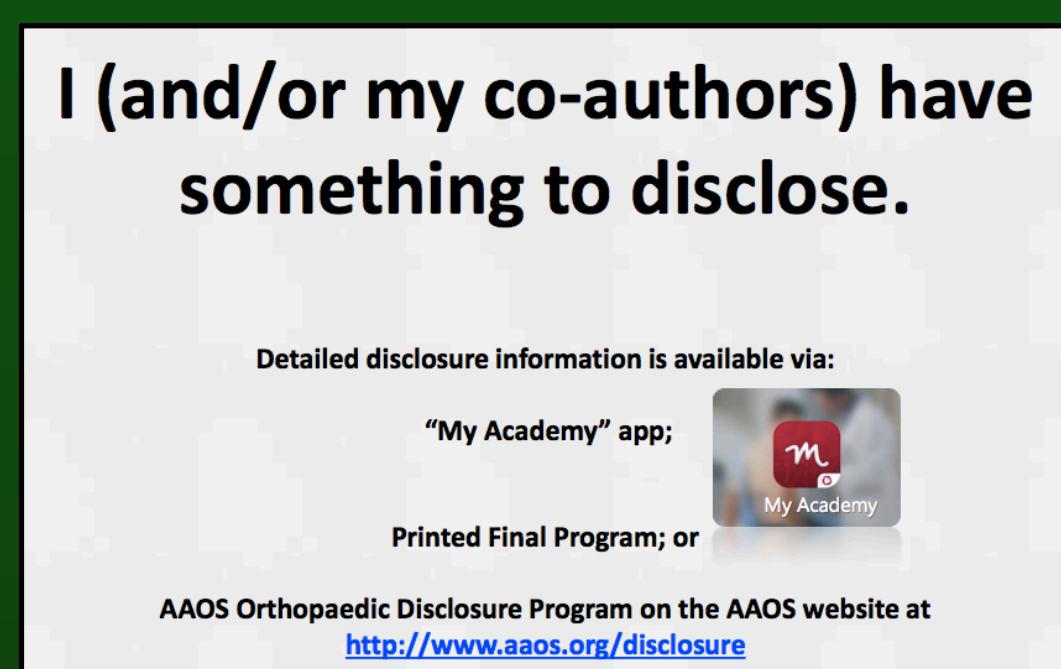
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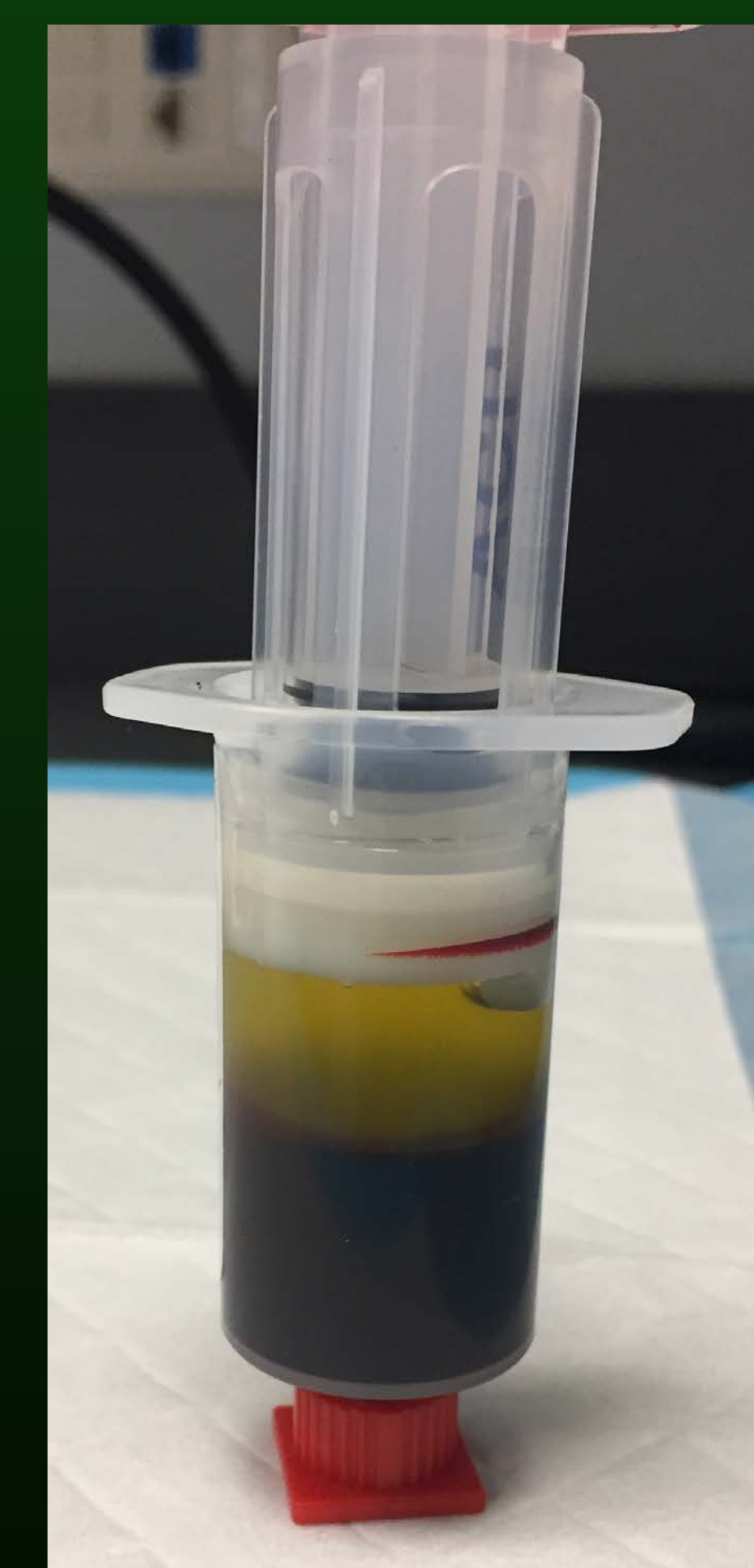
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Disclosures



What is Platelet-Rich Plasma?

- According to the Red Cross, PRP by definition contains a minimum of 200,000 platelets/ μ L
- PRP contains over 300 different molecules including platelets, plasma, leukocytes, and erythrocytes
- PRP has drawn significant interest from the orthopaedic community for its potential ability to enhance tissue repair, augment cellular migration & proliferation, and promote matrix deposition in a variety of tissues including tendons, ligaments, muscle, cartilage, and bone
- Concentrations of various cell types, including leukocytes, growth factors, and bioactive molecules remain unknown and are different based on the patient's venous blood status (e.g. packed cell volume, hydration, medications), method of preparation (e.g. single v. double spin, propriety system selected), and the tissue it is implanted to (e.g. joints, tendon, ligament)



Proposed Benefits

1. Ease of administration in clinical practice
2. Minimal risks
3. Anti-inflammatory effects
4. Stimulation of native chondrocyte, MSC & synovium proliferation
5. Nociceptive effects in symptomatic osteoarthritis
6. Effective adjunct to particular surgical procedures to enhance tissue regeneration

Plasma	
Proteins	Albumin, globulins, fibrinogen, complement, clotting factors
Electrolytes	Sodium, potassium, calcium
Hormones	IGF-1, estrogens, progesterone, androgens, ACTH, HGH
Biomarkers	COMP, CD11b, Protein C, microRNA, osteocalcin, osteonectin
Platelets	
Alpha granules	Adhesive proteins, clotting factors (e.g. Factor V, vWF, fibrinogen), growth factors (PDGF, TGF- β 1, IGF1, VEGF, bFGF, EGF, HGF, PF4, PDAF), angiogenic factors (e.g. angioágenin), antiangiogenic factors, proteases (e.g. MMP-9, MMP-2), necrotic factors (e.g. TNF α , TNF β)
Dense bodies	Calcium, neurotransmitters (e.g. serotonin), ADP
Lysosomes	Lysosomal enzymes
Leukocytes	
Neutrophils Primary Granules	Myeloperoxidase, acid hydrolases, defensins, serine proteases
Neutrophils Secondary Granules	Collagenase, lactoferrin, cathelicidin, bactericidal phagocytins, lysozyme
Neutrophils Tertiary Granules	Gelatinase and proteases
Monocytes	Growth factors (e.g. TGF β , VEGF, FGF, PDGF), cytokines (e.g. IL-1, 6)
Eosinophils	Plasminogen, cytokines (ILs), growth factors (e.g. VEGF, TGF α , TGF β)
Basophils	Histamine, proteases, heparin, leukotrienes
Erythrocytes	
	ATP, nitric oxide, hydrogen sulfide, hemoglobin, free radicals

The Effect of Different PRP preparations on Cell lines			
	LP SS PRP	LP DS PRP	LR PRP
Osteoblasts	Increased cell proliferation and growth factors	Increased cell proliferation and growth factors	No difference in cell proliferation, increased growth factors
Tenocytes	Increased cell proliferation and growth factors	Increased cell proliferation and growth factors	Increased cell proliferation and growth factors, but less than leukocyte poor
Myocytes	Increased cell proliferation and growth factors	Increased cell proliferation and growth factors	No difference in cell proliferation, increased growth factors

LP SS PRP – leukocyte poor single spun PRP, LP DS PRP – leukocyte poor double spun PRP, LR PRP – leukocyte rich high platelet concentration PRP. Growth factors examined were PDGF and TGF B

Comparison of PRP Systems

Manufacturer	Device	Whole blood volume	Procedure	Centrifuge Time	mL of PRP	Average WBC (k/ μ L)	Average Platelet Count (k/ μ L)
Arthrex	Angel 2% HCT	52mL	Double spin	17 minutes	2.9 \pm 0.5	11.0 \pm 4.5	2064 \pm 526
Arthrex	Angel 7% HCT	52mL	Double spin	17 minutes	3.5 \pm 0.7	16.9 \pm 4.4	2310 \pm 524
Emcyte	GenesisCS	54mL	Single Spin	10 minutes	6.0 \pm 0.0	20.6 \pm 3.9	1129 \pm 264
Harvest	SmartPRP	54mL	Double Spin	14 minutes	7.0 \pm 0.0	22.9 \pm 4.3	1508 \pm 406
Arteriocyte	Magellan	52mL	Double Spin	17 minutes	5.3 \pm 1.6	19.8 \pm 177	1989 \pm 1225
Biomet	GPS III	54mL	Single Spin	15 minutes	6.1 \pm 0.2	27.3 \pm 7.1	1343 \pm 670

PRP & Ligament Injury

Basic Science Evidence

- Increases collagen content with increased gene expression of COL1A1 and COL3A1
- Improves collagen organization
- Increases ligament cell viability, differentiation and expression of genes implicated in promoting ECM synthesis
- Ligaments (e.g. ACLs and MCLs) treated with PRP may have improved biomechanical properties (e.g. stiffness, max load to failure) compared to controls

Clinical Evidence

- Limited clinical evidence on PRP effects on native ligament tissue
- Early PRP after ACL reconstruction may accelerate or lead to earlier ACL graft healing
 - Sanchez et al. - 37 second look arthroscopies after ACL reconstructions with autogenous hamstring grafts +/- PRP
 - PRP group had significantly better graft remodeling, new connective tissue enveloping the graft, larger graft thickness, and increased synovial coverage



PRP & Muscles

Basic Science Evidence

- PRP found to increase myocyte proliferation, upregulate expression of stem cell markers in human muscle derived progenitor cells, and increase early cell differentiation
- Conflicting evidence regarding PRPs influence on biomechanical strength of muscle, collagen organization, muscle fibrosis, and muscle regeneration
 - Delos et al. found in their gastrocnemius injured rat model that local PRP did not impact isometric torque strength
- Leukocyte & platelet-poor plasma or leukocyte poor PRP depleted of TGF-B1 and myostatin** subjected to an additional spin to remove platelets is more effective in stimulating myoblast differentiation than traditional leukocyte poor PRP

Clinical Evidence

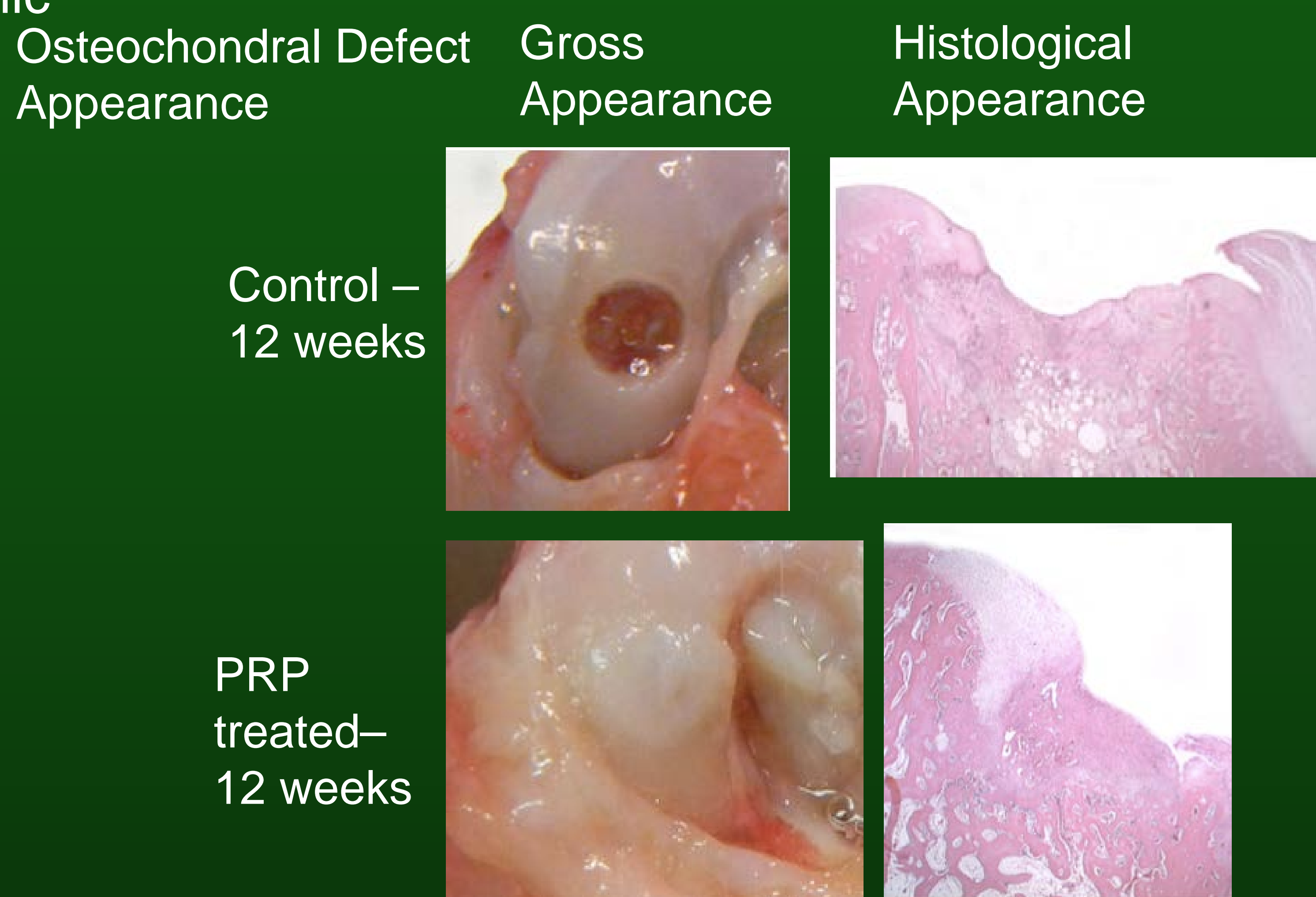
- Most studies low quality, retrospective
- Several RCTs have demonstrated that autologous PRP with rehab leads to shortened RTS (up to 2 weeks) compared to rehab alone for Grade II muscle injury
- PRP has also been shown to have nociceptive effects when compared to control for muscle injuries
- Limited research on influence of PRP on recurrence rate, however recent RCT by Rossi et al. found no difference in recurrence between PRP + rehab and rehab alone at 2 years

PRP, Cartilage, & Osteoarthritis

Basic Science Evidence

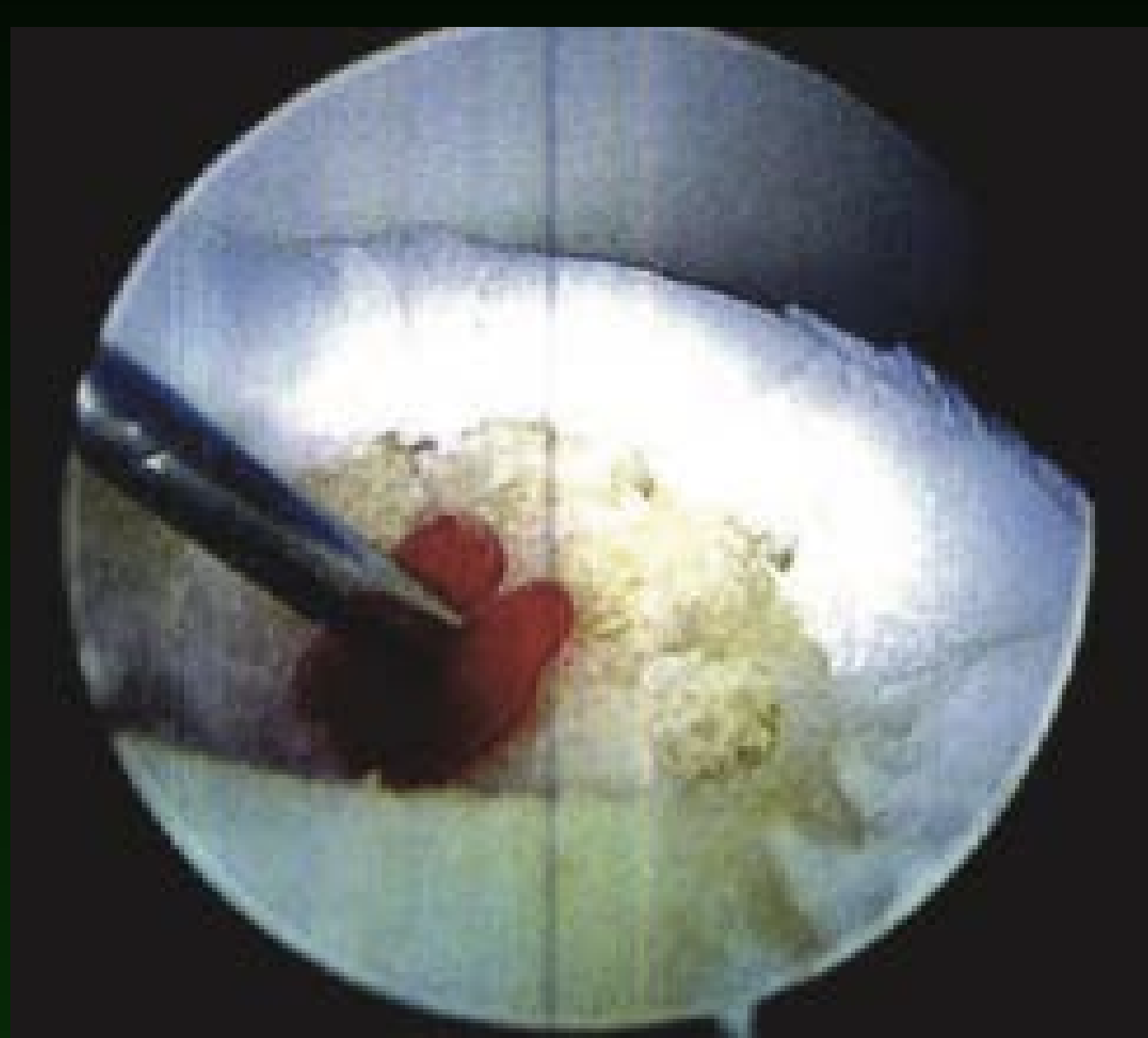
- PRP increases chondrocyte proliferation & viability
- May also increase proteoglycan, glycosaminoglycan, and hyaluronic acid production, as well as type II collagen deposition
- Associated with increased MSC migration & chondrogenic differentiation
- Purported systemic role within a joint by modifying levels of circulating catabolic cytokines
- Conflicting *in vivo* evidence on PRP's impact on healing of osteochondral defects, donor sites, and as an adjunct to cartilage restoration procedures
- In OA, PRP has been found to have a nociceptive & anti-inflammatory role that may modulate the disease

Platelet-Rich Plasma May Improve Osteochondral Donor Site Healing in a Rabbit Model Smyth et al. *Cartilage* 2015



CLINICAL ROLE OF PRP

- Limited evidence on PRP alone for focal cartilage defects
 - Most studies evaluate PRP in combination with other biologics such as BMAC
- Significant variability in the literature regarding outcomes of PRP for OA with no conclusion
- Clinical studies on PRP for OA, generally have found younger more active patients with lower grade degenerative changes, Kellgren Lawrence (KL) grade 0 - 2, see greater functional improvement and decrease in pain



Arthroscopic image of the intra-articular administration following microfracture for an osteochondral lesion of the talus

Kellgren Lawrence Grades of Osteoarthritis	Radiographic Features
Grade 0	No radiographic features of OA
Grade I	Doubtful narrowing of joint space and possible osteophytic lipping
Grade II	Definite osteophytes and possible narrowing of joint space
Grade III	Moderate multiple osteophytes, definite narrowing of joint space, and some sclerosis and possible deformity of bone ends
Grade IV	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends

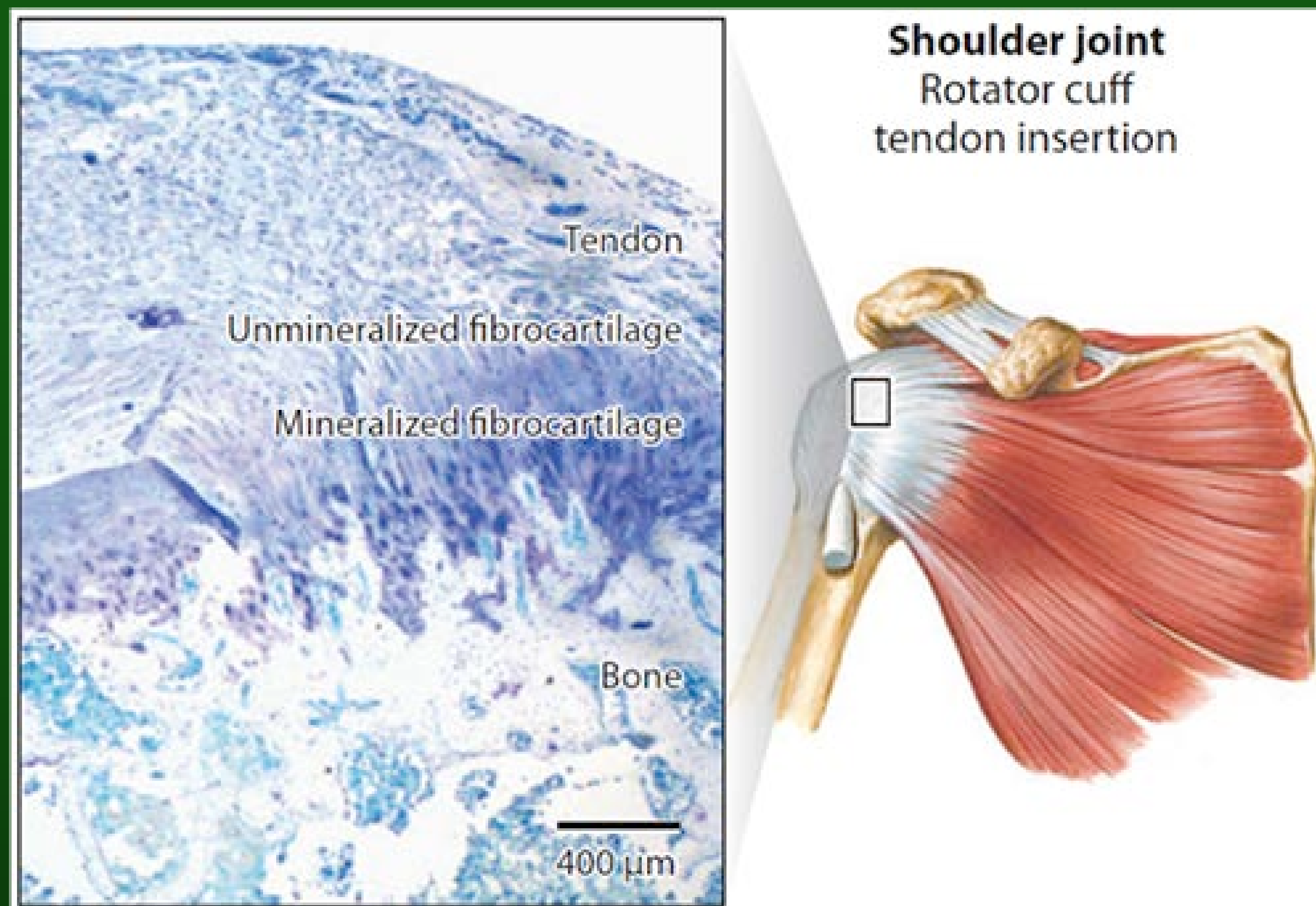
CLINICAL EVIDENCE

- First FDA sanctioned RCT on PRP for OA recently published
 - PRP is safe and resulted in functional outcome scores that improved 78% compared to 7% in the placebo control group at 1 year
- Recent RCT by Cole et al. found PRP leads to lower pain scores and higher functional outcomes at 1 year compared to HA
- Current level of evidence ranges from Level I – Level IV
 - Many studies demonstrate improvement in PROs starting at 2 months and maintained at 12 months compared to controls
 - Double spin v. single spin does not appear to result in differences in patient satisfaction (76.4% v. 80.6%)
 - Significantly better response to PRP at 6 months in patients with degenerative chondropathy KL grade 0 compared to KL grade III or IV
 - Unclear if multiple PRP injections, interval between injections, injection volume, number of spin cycles used to prepare PRP, and the use of an activating agent influence clinical outcomes

PRP & Tendon Pathology

Basic Science Evidence

- Tendon healing is dynamic with inflammation, cellular proliferation, & tissue remodeling
- Multiple *in vitro* & *in vivo* studies have found PRP improves tenocyte proliferation and increases concentration of important growth factors (e.g. TGF- α , bFGF)
- Preclinical studies suggest that leukocyte poor PRP is most effective because leukocytes increase inflammation in tenocytes, this is controversial.
- Some studies have also demonstrated that tendons treated with PRP histologically show earlier healing and increased organization as well as increased mechanical strength (load to failure)



Clinical Evidence

- High level clinical evidence on use of PRP for tendon pathology is sparse, inconsistent, and controversial
- Warth et al performed a meta analysis of eleven Level 1 and 2 studies that looked at PRP augmentation of arthroscopic repair of full-thickness rotator cuff repairs
 - No difference in outcome score improvements with PRP treatment compared to control
 - Some studies have shown a lower retear rate in small to medium tears at 1-2 years with unknown clinical significance
 - Current literature had high risk for selection, performance, and attrition biases and were only powered to detect large differences in outcomes
- Variable outcomes with the use of PRP for chronic tendinopathy
 - Several RCTs on Achilles tendinopathy have found no improvement in PROs when comparing PRP to saline
 - Dragoo et al. found in a RCT comparing dry needling and standardized eccentric exercises with and without PRP for chronic patellar tendinopathy that PRP accelerates recovery at 12 weeks, but the benefit dissipates over time

Challenges with PRP & Future Directions

LIMITATIONS OF CURRENT EVIDENCE

- Variability in preparation methods
- Underreporting of platelet, leukocyte and growth factor concentrations
- Many studies uncontrolled, retrospective, with small sample size
- Poor correlation of *in vivo* animal models with clinical models
- Type & location of injury is variable
- Many confounding variables with variability in control groups
- Outcomes are often subjective and not defined *a priori*
- Profound selection, detection, attrition, and reporting biases
- Lack of concomitant data with other biologic augmentation techniques

Areas for Future Investigation

Host

- Determining ideal host (e.g. age, medical co-morbidities)
- Understanding variations in venous blood (e.g. RBC & platelet counts) and how they affect PRP preparation

Preparation

- Understand variations in cell & growth factor concentrations
- Standardized tissue- and injury specific dosing protocol
- Creation of customizable PRP systems

Delivery

- Determine optimal method of delivery for particular tissues or injuries (e.g. intra-articular, fibrin glue, enriched scaffold)
- Determine optimal timing & frequency in addition to dose-response

Research

- Minimum reporting requirements for PRP studies (e.g. cell & growth factor concentration)
- Standardized tissue specific outcome measures
- Determine ceiling effect

CONCLUSIONS

- PRP is a promising therapeutic agent for orthopaedic soft tissue injuries, but a better understanding of underlying biology & physiology of these pathologies will help identify appropriate clinical targets for PRP
- Need to establish optimal host (e.g. health status), preparation system, concentration, delivery vehicle & timing, and outcome measures for tissue-specific pathologies
- Long term will need preparation systems that allow for these customizations to optimize PRP effectiveness
- PRP is very expensive (up to \$2000) and need cost-effectiveness data
- Need for comparative effectiveness data with evidence-based interventions and Level I data

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