BIOLOGICS IN SPORTS MEDICINE

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DISCLOSURES

- HOUSTON MARATHON COMMITTEE: MEDICAL DIRECTOR
- 2ND.MD: CONSULTANT
- Musculoskeletal Ultrasound Consultants: Owner
- DEMOS MEDICAL PUBLISHING: ROYALTIES

OBJECTIVES

- DISCUSS BIOLOGIC TREATMENTS:
 - PROLOTHERAPY, PRP & DHACM
- REVIEW EVIDENCE FOR THESE TREATMENTS
- PROPOSE A RATIONALE FOR USE
- PRESENT CLINICAL EXAMPLES

PROLOTHERAPY

- Various concentrations of dextrose (5%, 12.5%-25%) injected in small amounts
 Into the regional anatomy of an affected area
- PROLIFERATING EFFECT
- OSMOLAR INJURY AT A CELLULAR LEVEL
 - AN INFLAMMATORY (HEALING) RESPONSE
 - INDUCES TISSUE REMODELING
- TREAT THE REGION; NOT A POINT
- INJECTED AROUND NERVES AND INTO TENDONS, LIGAMENTS AND JOINTS
- TREATMENTS IN SERIES, 4-6 WEEKS APART



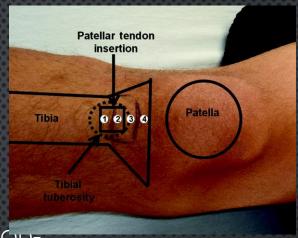
PROLOTHERAPY IN OA

- Topol GA, Podesta LA, Reeves DR, et al. Chondrogenic Effect of Intra-articular Hypertonic-Dextrose (Prolotherapy) in Severe Knee Osteoarthritis. PM R 2016;1:1-11
 - Case series with blinded arthroscopic evaluation pre and post
 - 6 SUBJECTS WITH KL IV MFC CARTILAGE LOSS
 - Intraarticular 12.5% dextrose (10ml) x 4-6 monthly treatments
 - ARTHROSCOPIC, HISTOLOGIC, WOMAC OUTCOME MEASURES
 - CHONDROGENIC EFFECTS

PROLOTHERAPY IN OA

- RABAGO, MILLER, ZAJIERSKA. DEXTROSE PROLOTHERAPY FOR KNEE OSTEOARTHRITIS: RESULTS
 OF A RANDOMIZED CONTROLLED TRIAL. OA RESEARCH SOCIETY 2011
 - SIGNIFICANTLY GREATER IMPROVEMENT IN WOMAC SCORES AT 52 WEEKS IN DEXTROSE PROLOTHERAPY GROUP COMPARED WITH SALINE AND EXERCISE
 - HIGH PATIENT SATISFACTION IN PROLOTHERAPY GROUP

PROLOTHERAPY IN OA

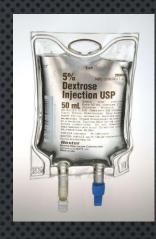


- TOPOL GA ET AL. HYPEROSMOLAR DEXTROSE INJECTION FOR RECALCITRANT OSGOOD-SCHLATTER DISEASE. PEDIATRICS 2011;128:e1121-e1128
 - Dextrose injection over the apophysis and patella tendon was safe and well tolerated and resulted in more rapid and frequent achievement of unaltered sport and asymptomatic sport
- Rabago D, Patterson JJ, Mundt M, et al. Dextrose Prolotherapy for Knee
 Osteoarthritis: A Randomized Controlled Trial. Annals of Family Medicine May/June
 2013
- Jahanigiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial. J Orthopaedic Science 2014
- Vora A, Borg-Stein et al. Regenerative Injection Therapy for Osteoarthritis: Fundamental Concepts and Evidence-Based Review. PM R 2012; 4:S104-S109

PROLOTHERAPY IN TENDINOPATHY

- TOPOL GA, REEVES DK, HASSANEIN KM. EFFICACY OF DEXTROSE PROLOTHERAPY IN ELITE MALE KICKING-SPORT ATHLETES WITH CHRONIC GROIN PAIN. ARCH PHYS MED REHABIL 2005;86: 697-702.
 - 72 ELITE ATHLETES
 - MONTHLY INJECTIONS OF 12.5% DEXTROSE ABDOMINAL AND ADDUCTOR ATTACHMENTS
 - RETURN TO SPORT OCCURRED IN AVERAGE OF 3 MOS.
 - OUTCOME MEASURE AT 0 AND AVG 26 MONTHS POST
 - AVG VAS: 82% IMPROVED / AVG NIRSCHL: 78% IMPROVED

PERI-NEURAL INJECTION THERAPY

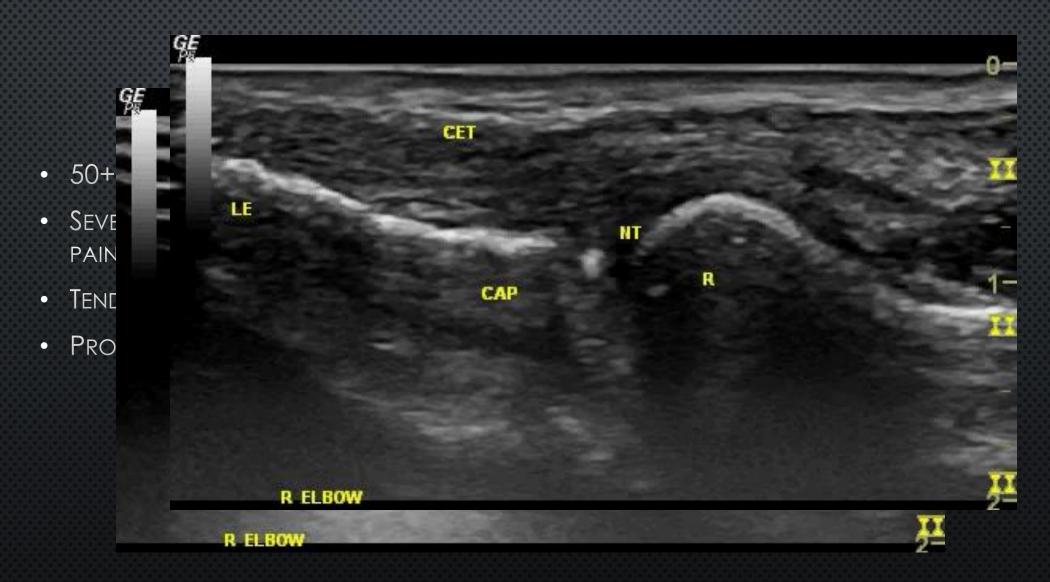


- Lyftogt J. Subcutaneous prolotherapy treatment of refractory knee, shoulder and lateral elbow pain. Australian Musculoskeletal Medicine. 2005
 - TREATMENT FOCUSES ON TREATMENT OF NEUROGENIC PAIN AND INFLAMMATION FROM THE SMALL SENSORY PEPTIDERGIC NERVES
 - Multiple small injections along the path of tender superficial nerves, in areas of fascial constriction, with a small amount of 5% dextrose (or mannitol)
 - THIS BLOCKS THE TRPV-1 OR CAPSACIN RECEPTOR ON THE NERVE.



Anterior Femoral Nerves and CCI's

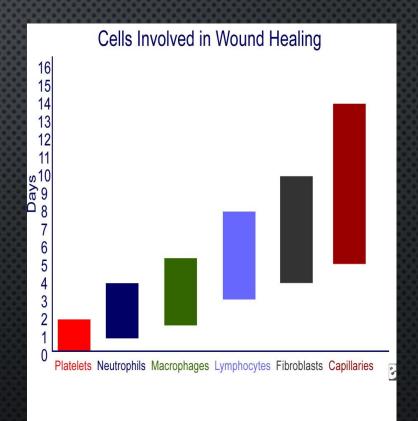
PROLOTHERAPY: CLINICAL EXAMPLE



SUMMARY

- PROLOTHERAPY IS SAFE, INEXPENSIVE AND EFFECTIVE
- ROBUST EVIDENCE IN TENDINOPATHY AND OA
- Requires superior command of anatomy and injection skills
- RESULTS ARE SLOW BUT PROGRESSIVE

- PLATELETS ARE THE FIRST CELLS TO ARRIVE AT THE SITE OF INJURY
- RESPONSIBLE FOR INITIATION OF HEALING CASCADE
- A-GRANULES AND DENSE GRANULES



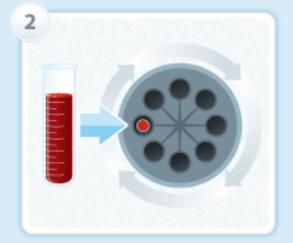
- PRP CAN STIMULATE PRODUCTION & RECRUITMENT OF GROWTH FACTORS
 AND STEM CELLS TO PROMOTE ANGIOGENESIS, EXTRACELLULAR MATRIX
 PRODUCTION AND COLLAGEN FORMATION
 - ACTIVATED BY THROMBIN
 - CHANGE SHAPE AND ADHERE TO TISSUES
 - ALPHA & DENSE GRANULES WITHIN PLATELETS RELEASE GROWTH FACTORS AND CYTOKINES

PROCESS OF PRP THERAPY



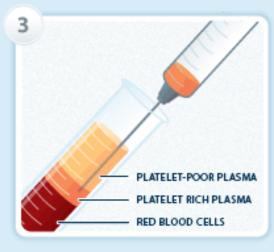
Collect blood

30-60ml of blood is drawn from the patient's arm.



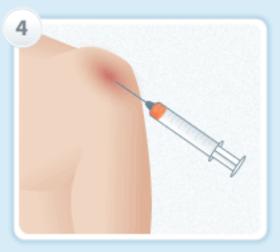
Separate the platelets

The blood is then placed in a centrifuge. The centrifuge spins and separates the platelets from the rest of the blood components.



Extract platelet-rich plasma

Extract 3-6ml of platelet-rich plasma.



Inject injured area with PRP

Using the concentrated platelets, we increase the growth factors up to eight times, which promotes temporary relief and stops inflammation.

- SAMPSON S, GERHARDT M, MANDELBAUM B. PLATELET RICH PLASMA INJECTION GRAFTS FOR MUSCULOSKELETAL INJURIES: A REVIEW. CURR REV MUSCULOSKELET MED
- SUPERNATANT OF WHOLE BLOOD RESULTING IN A CONCENTRATED AMOUNT OF PLATELETS
- PLATELETS >>> CLOTTING.
- PLATELETS RELEASE: BIOACTIVE PROTEINS RESPONSIBLE FOR ATTRACTING MACROPHAGES,
 MESENCHYMAL STEM CELLS, AND OSTEOBLASTS
 - PROMOTES REMOVAL OF NECROTIC TISSUE,
 - ENHANCES TISSUE REGENERATION AND HEALING.

Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg. 2004 Nov;114(6):1502–8

- PLATELET-DERIVED GROWTH FACTOR (PDGF)
 - STIMULATES CELL REPLICATION
 - Promotes angiogenesis
 - PROMOTES EPITHELIALIZATION
 - PROMOTES GRANULATION TISSUE FORMATION
- TRANSFORMING GROWTH FACTOR (TGF)
 - PROMOTES FORMATION OF EXTRACELLULAR MATRIX
 - REGULATES BONE CELL METABOLISM

- VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)R
 - PROMOTES ANGIOGENESIS
 - EPIDERMAL GROWTH FACTOR (EGF) PROMOTES CELL DIFFERENTIATION AND STIMULATES
 - RE-EPITHELIALISATION, ANGIOGENESIS AND COLLAGENASE
 - ACTIVITY
- FIBROBLAST GROWTH FACTOR (FGF)
 - PROMOTES PROLIFERATION OF ENDOTHELIAL CELLS AND FIBROBLASTS
 - STIMULATES ANGIOGENESIS

- VARIETY OF PREPARATIONS:
 - L-PRP (LEUCOCYTE RICH)
 - P-PRP (LEUCOCYTE POOR)
 - PLASMA RICH GROWTH FACTORS (PGRF)
 - PLATELET LYSATE
 - AUTOLOGOUS CONDITIONED PLASMA
- NO CLEAR EVIDENCE FOR WHAT IS BEST
 - NGUYEN, BORG-STEIN ET AL, PM R, MARCH 2011, 226-211
 - EHRENFEST ET AL, 2008, TRENDS IN BIOTECHNOLOGY, 158-167





PLATELET LYSATE

- SERUM WITH GROWTH FACTORS
- PRP IN WHICH THE PLATELETS HAVE BEEN ACTIVATED ("LYSED")
 - THROUGH UNFREEZING PROCESS OR MECHANICAL "LYSIS"
 - WILL CAUSE MORE IMMEDIATE RELEASE OF GF'S
 - CONCENTRATION OF INDIVIDUAL GF'S CAN BE UNPREDICTABLE
 - MAY WORK AS "NATURAL CORTICOSTEROID"
 - MAY NOT HAVE THE SAME REGENERATIVE POTENTIAL AS PRP

PRP VARIABLES

- Buffering
- ACTIVATION
- SINGLE VS MULTIPLE INJECTIONS
- TIMING OF INJECTIONS FOR ACUTE OR CHRONIC CONDITIONS
- NSAIDs
- POST PROCEDURE REHABILITATION
- NOTHING SUBSTANTIATED



PRP CLASSIFICATION

• Mautner K, Malanga, GA, Smith J, et al. A Call for a Standard Classification System for Future Biologic research: the Rationale for New PRP Nomenclature

		Criteria		
Р	Platelet count	P Volume Injected	M Concentration/ uL	
L.	Leukocyte Concentration 1	>1%	+	
		<1%	-	
R	Red Blood Cell Concentration	> 1%	+	
		< 1%	-	
A	Activation ²	Yes	+	
		No	-	

	Р	L	R	А
Final Score				

¹ If WBC are present (+) the % of neutrophils should also be reported. ² The method of exogenous activation should be reported

EVIDENCE: MUSCLES

- REURINK NEJM 2014:
 - PRP (ACP) NO BETTER THAN SALINE FOR RTP (42 DAYS AVG)
- HAMID ET AL. AJSM 2014
 - L+PRP MAY REDUCE RECOVERY TIME IN HAMSTRING INJURIES
- HAMILTON ET AL.
 - PRP NO BETTER THAN REHAB; BUT BETTER THAN PPP IN HAMSTRING INJURIES FOR RTP
- DRAGOO J. AOSSM MEETING 2016
 - L+ PRP BETTER THAN L- PRP IN ACUTE HAMSTRING INJURIES.
 - NEITHER BETTER THAN REHAB

EVIDENCE: TENDONS

- FILARDO, KON, ET AL. PLATELET RICH PLASMA INJECTIONS FOR THE TREATMENT OF REFRACTORY ACHILLES TENDINOPATHY: RESULTS AT 4 YEARS. BLOOD TRANSFUSION 2014 ++
 - 27 SUBJECTS, 34 TENDONS, MID PORTION ACHILLES TENDINOPATHY
 - 3 INTRA-TENDINOUS PRP INJECTIONS
 - EVALUATED AT BASELINE, 2, 6 AND 54 MONTHS
 - IMPROVED THROUGH 6 MONTHS, STABLE AT 4.5 YEARS USING VISA-A
 - TEGNER SCORES INDICATED ONGOING FUNCTIONAL RECOVERY
 - Longer duration of symptoms pretreatment predicted a slower return to function.

EVIDENCE: TENDINOPATHY

- Mishra A, Pavelko T. Treatment of Chronic Elbow Tendinosis with Buffered Plateletrich Plasma. Am J Sports Med 2006; 34:1774-1778
 - Prospective cohort of 15 pts. LE, 93% improved at 1 yr.
- PEERBOOMS J, SLUMER J ET AL. POSITIVE EFFECT OF AN AUTOLOGOUS PLATELET CONCENTRATE IN LATERAL EPICONDYLITIS IN A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL: PLATERLET-RICH PLASMA VERSUS CORTICOSTEROID INJECTION WITH 1-YEAR FOLLOW-UP. AM J SPORTS MED 2010; 38:255-262
 - RCT of LE, 100 subjects PRP vs Corticosteroid, 1 yr FU PRP superior in duration of improvement, 73% vs 49%
- FILARDO G, KON E ET AL. USE OF PLATELET-RICH PLASMA FOR THE TREATMENT OF REFRACTORY JUMPER'S KNEE. INT ORTHOP 2010; 34:909-915
 - PROSPECTIVE CONTROLLED TRIAL, 15 PTS WITH PAT. TEND.
 - PRP IMPROVED IN ALL MEASURES

EVIDENCE: TENDINOPATHY

- DE VOS R, WEIR A ET AL. PLATELET-RICH PLASMAINJECTION FOR CHRONIC ACHILLES TENDINOPATHY- A RANDOMIZED CONTROLLED TRIAL. JAMA 2010; 303:144-149
 - STRATIFIED BLOCK RCT OF 54 PTS WITH ACHILLES TEND. BOTH PRP AND SALINE IMPROVED (BOTH USED ECCENTRICS)
- MAUTNER K, COLBERG R ET AL. OUTCOMES AFTER ULTRASOUND GUIDED PLATELET-RICH PLASMA INJECTIONS FOR CHRONIC TENDINOPATHY: A MULTICENTER, RETROSPECTIVE REVIEW. PM R 2013; 5:169-175
 - Retrospective, cross sectional survey of 180 pts., multi-center, variety of tendons
 - 68% reported no pain during activities

EVIDENCE: BLOOD VS PRP

- CREANEY L, WALLACE A, CURTIS M, CONNELL D. GROWTH FACTOR-BASED THERAPIES
 PROVIDE ADDITIONAL BENEFIT BEYOND PHYSICAL THERAPY IN RESISTANT ELBOW
 TENDINOPATHY: A PROGRESSIVE, SINGLE—BLIND, RANDOMIZED TRIAL OF AUTOLOGOUS BLOOD
 VERSUS PLATELET RICH PLASMA INJECTIONS
- At 6 MONTHS:
 - 66% SUCCESS RATE IN PRP GROUP >> 10% CONVERTED TO SURGERY
 - 72%SUCCESS RATE IN ABI GROUP >> 20% CONVERTED TO SURGERY

EVIDENCE: BLOOD

- EDWARDS S, CALANDRUCCIO J. AUTOLOGOUS BLOOD INJECTIONS FOR REFRACTORY LATERAL EPICONDYLITIS. J HAND SURG MARCH 2003, 272-278
- Connell D, Ali K et al. Ultrasound-Guided Autologous Blood Injection for Tennis Elbow. Skeletal Radiol 2006; 35:371-377
- Suresh S, Ali K et al. Medial Epicondylitis: Is Ultrasound Guided Autologous Blood Injection an Effective treatment. Br J Sports Med 2006; 40:935-939
- James S, All K et al. Ultrasound Guided Dry Needling and Autologous Blood Injection for Patellar Tendinosis. BR J Sports Med 2007; 41:518-521

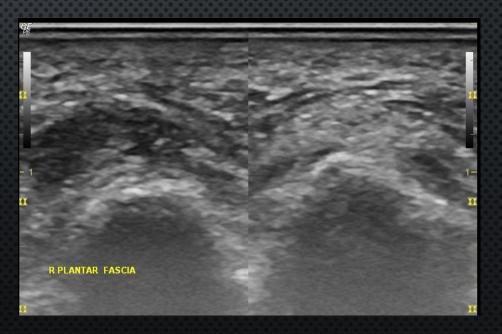
TENOTOMY FOR TENDINOPATHY

- FINNOFF ET AL, PM R, OCTOBER 2011, 900-911
 - N=41,US GUIDED TENOTOMY FOLLOWED BY PRP. 83% SATISFACTION, PAIN SCORE REDUCTIONS
- McShane J, Nazarian L et al; Sonographically Guided Percutaneous
 Tenotomy for Treatment of Common Extensor Tendinosis in the Elbow: Is
 A Corticosteroid Really Necessary. JUM 2008; 27:1137-1144
- McShane J, Nazarian L et al; Sonographically Guided Percutaneous Tenotomy for Treatment of Common Extensor Tendinosis in the Elbow. JUM 2006; 25:1281-1289

PRP: CLINICAL EXAMPLE

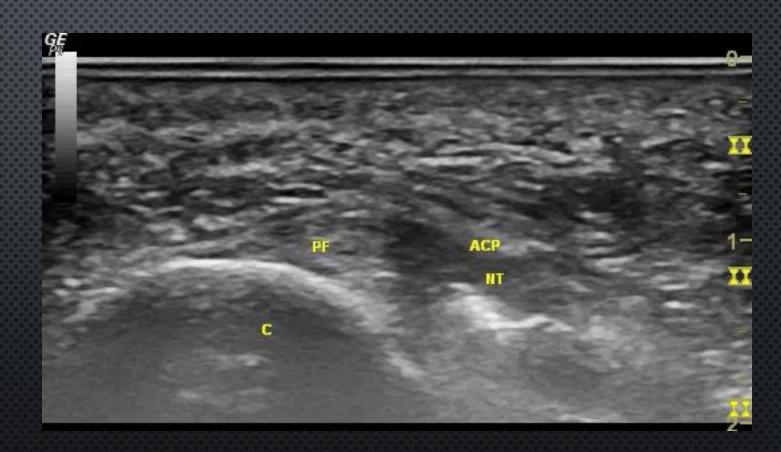
- 40 YO FEMALE DISTANCE RUNNER
- ACUTE PLANTAR FASCIA TEAR





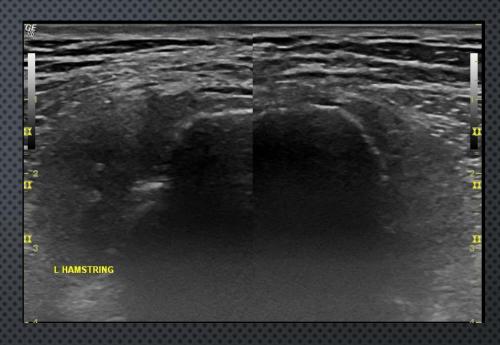
PRP: CLINICAL EXAMPLE

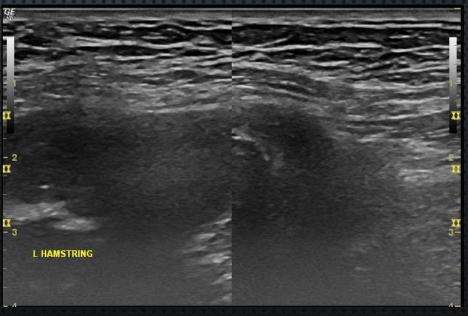
- WALKING BOOT X 2 WEEKS
- PT FOR LOADING PROGRESSION
- GRADUAL PROGRESSION OF WALKING TO RUNNING

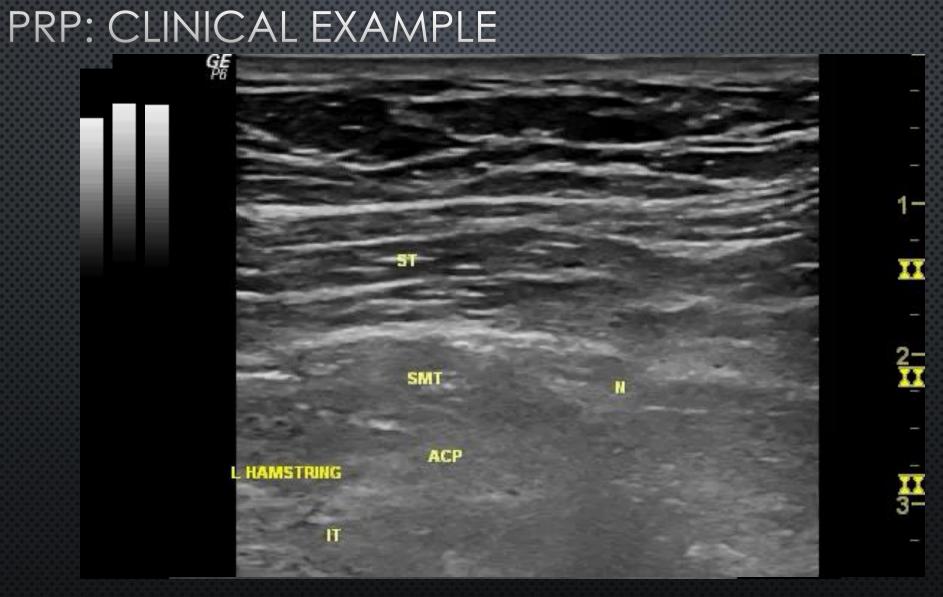


PRP: CLINICAL EXAMPLE

- 42 YO FEMALE RUNNER
- 10 months of L hamstring origin pain
- REDUCED RUNNING







SUMMARY: MUSCLE AND TENDON

- PRP for muscle injury recovery does not appear to offer advantage over traditional therapy
- PRP FOR TENDINOPATHY APPEARS TO BE USEFUL PARTICULARLY FOR THE ELBOW
 - Successful studies use <u>LR-PRP</u>
 - NEED MONTHS FOR OUTCOMES FROM EVEN A SINGLE INJECTION
- WHOLE BLOOD HAS + EFFECTS FOR TENDON HEALING ALSO
- TENOTOMY HAS CLINICAL BENEFIT FOR TENDINOPATHY WITH OR WITHOUT SALINE (PLACEBO)
 OR DEXTROSE (PROLOTHERAPY)
- US GUIDANCE SHOULD BE USED FOR ALL TENDON RELATED PROCEDURES AS IT IMPROVES
 ACCURACY AND SHOULD IMPROVE EFFICACY

PRP EVIDENCE: JOINTS

JOINTS:

- CERZA ET AL, AJSM, OCTOBER 2012 +
 RCT OF 120 PTS. TREATED WITH ACP OR HA. 4 WEEKLY INJECTIONS. FOLLOWED FOR 6 MONTHS.
 MORE EFFECTIVE THAN HA IN TREATMENT OF GRADES I, II AND III OA OF THE KNEE. WOMAC
 BETTER FOR ACP IN ALL GRADES
- DOLD ET AL, CLIN J SPORTS MED, JANUARY 2014: 31-43 +/REVIEW OF 10 STUDIES (2 RCTs) MAINLY OF OA KNEE AND ALSO CHONDRAL DEFECTS. POSITIVE
 RESULTS DECLINE AFTER 6 MONTHS
- Halpern et al, Clin J Sports Med, May 2013: 238-239 +
 PROSPECTIVE COHORT, 22 PTS. TREATED WITH PRP. 15 FOLLOWED FOR 1 YR. DECREASED PAIN,
 IMPROVED FUNCTIONAL SCORES, 73% NO CHANGE IN MRI

PRP: HIP OA

- SANCHEZ ET AL, RHEUMATOLOGY, 2011
 - 45 PTS WITH MODERATELY SEVERE HIP OA GIVEN US GUIDED HIP INJECTION WEEKLY X 3 WKS
 - 57.5% HAD CLINICALLY RELEVANT REDUCTION IN PAIN
 - 40% WERE EXCELLENT RESPONDERS
 - Pain reduction by 6-7 wks
 - RESULTS SUSTAINED AT 6 MONTHS
- Dallari D, Stagni C, Rani N, et al. Ultrasound guided Injection of Platelet Rich Plasma and Hyaluronic Acid, Separately and in Combination, for Hip Osteoarthritis: A Randomized controlled Study
 - PRP >> HA
 - PRP +HA NOT ANY ADDED BENEFIT

SUMMARY: PRP FOR OA

- REASONABLY GOOD STUDIES AND POSITIVE RESULTS FOR OA
 - KNEE JOINT AND HIP JOINT STUDIED
 - L- PRP PREFERRED OVER L+ PRP
 - MIGHT SERVE AS PREVENTATIVE FOR FURTHER DAMAGE
 - PRP MECHANISM IS LIKELY AN INCREASE ANABOLIC EFFECT ON CHONDROCYTES AND A
 DECREASE CATABOLIC EFFECT IN THE INFLAMMATORY ENVIRONMENT
 - MAY PREVENT APOPTOSIS OF CHONDROCYTES.

EVIDENCE: PRP

- NGUYEN R, BORG-STEIN J ET AL. APPLICATIONS OF PLATELET-RICH PLASMA IN MUSCULOSKELETAL AND SPORTS
 MEDICINE: AN EVIDENCE-BASED APPROACH. PM R 2011; 3:226-250
- Sampson S, Gerhardt M, Mandelbaum, B. Platelet Rich Plasma Injection Grafts for Musculoskeletal Injuries: A Review. Cur Rev Musculoskelet Med 2008; 1:165-174
- CASTILLO T, POULIOT M, ET AL. COMPARISON OF GROWTH FACTOR AND PLATELET CONCENTRATION FROM COMMERCIAL PLATELET RICH PLASMA SEPARATION SYSTEMS. AJSM 2011; 39:266-271
- FINNOFF J, FOWLER S, ET AL. TREATMENT OF CHRONIC TENDINOPATHY WITH ULTRASOUND-GUIDED NEEDLE TENOTOMY AND PLATELET-RICH PLASMA INJECTION. PM R 2011; 3:900-911

DEHYDRATED HUMAN AMNION/CHORION MEMBRANE (DHACM)

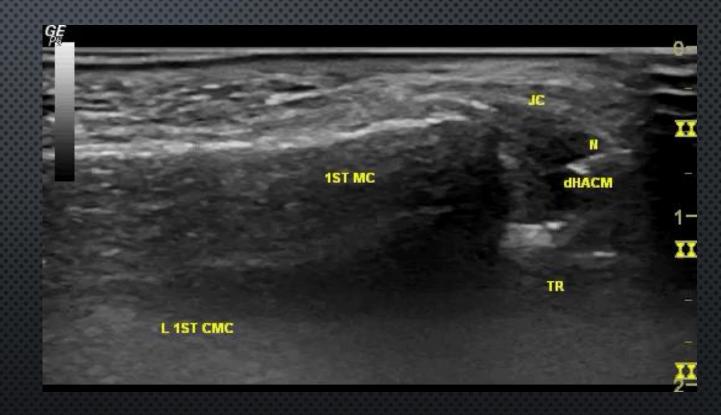
- MICRONIZED DEHYDRATED HUMAN AMNION/CHORIONIC MEMBRANE ALLOGRAFT DHACM
- KOOB TJ, RENNERT R, ZABEK N, ET AL BIOLOGICAL PROPERTIES OF DEHYDRATED HUMAN AMNION/CHORION COMPOSITE GRAFT: IMPLICATIONS FOR CHRONIC WOUND HEALING. INT WOUND J 2013; 10:493-500
 - Anti-inflammatory cytokines, tissue inhibitors of metalloproteinases and growth factors
 - Capable of inducing fibroblast proliferation and recruitment of mesenchymal stem cells
 - DHACM IS VIABLE IN VIVO

DHACM

- GELLHORN, AC, HAN, A. THE USE OF DEHYDRATED HUMAN AMNION/CHORION
 MEMBRANE ALLOGRAFT INJECTION FOR THE TREATMENT OF TENDINOPATHY OR ARTHRITIS: A
 CASE SERIES INVOLVING 40 PATIENTS. PM R 2017; 9:1236-1243
 - Case Series: 40 patients treated with DHACM injection for <u>tendinopathy or OA</u>
 - OUTCOMES: PAIN LEVEL, ACTIVITY LEVEL
 - 30% IMPROVEMENT CONSIDERED SUCCESSFUL
 - Data collected at 1, 2 and 3 months post
 - 30% THRESHOLD REACHED
 - 68% at 1 month / 82% at 2 months / 91% at 3 months

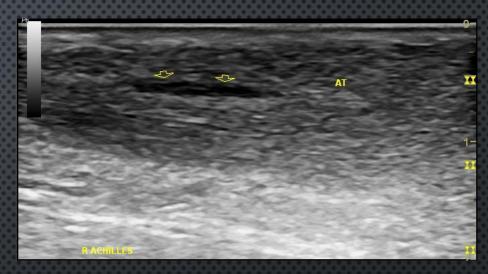
DHACM FOR CMC ARTHRITIS

- SMALL JOINT WHICH DOES NOT ACCEPT MUCH VOLUME
- DHACM 40MG IN 1CC 0.9NS SPLIT BETWEEN THE LEFT AND RIGHT 1ST CMC JOINTS
- 1-2 DAYS OF POST INJECTION PAIN
- GOOD PAIN RELIEF AND IMPROVED FUNCTION WITHIN DAYS



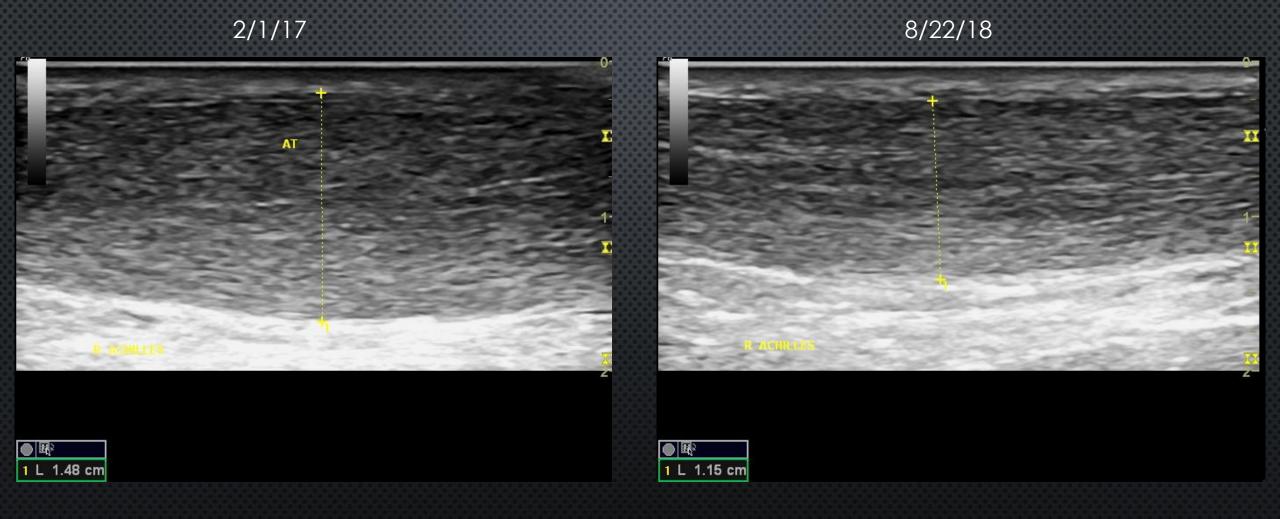
DHACM FOR ACHILLES TENDINOPATHY

- TREATED WITH FAIR RESULTS FOR SEVERAL CYCLES OF PROLOTHERAPY
- TRIAL OF DHACM 40 MG IN 1 CC 0.9NL SALINE
- MODERATE PAIN POST
- COMPLETE RESOLUTION OF PAIN IN 2-3 WEEKS
- Post injections changes on exam and US





DHACM FOR ACHILLES TENDINOPATHY



SUMMARY: DHACM

- DHACM IS RELATIVELY NEW
- STUDIES ARE FEW; BUT RESULTS ARE PROMISING
- More likely to be painful post injection for 1-2 days
- IMPROVEMENT MAY BE FASTER THAN PRP OR PROLOTHERAPY

SUMMARY: BIOLOGICS

- As a whole there is still limited understanding of mechanisms of action
- PROLOTHERAPY HAS THE BEST STUDY DATA
- PRP FORMULATIONS ARE STILL BE WORKED OUT
- DHACM MAY HAVE A FASTER ONSET OF ACTION BUT IT IS MORE PAINFUL INITIALLY
- Delivery should be done under visualization
- CLINICAL IMPROVEMENT TAKES MONTHS

THANK YOU