



Regenerative Medicine Overview

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Peek'n Peak CME Conference
LECOM Integrative Medicine
March 2, 2018

Objectives:

- Define Regenerative Medicine within musculoskeletal medicine.
- Describe options beyond medications and surgery for chronic pain patterns.
- Review how autologous stem cells are being used within chronic musculoskeletal pain.
- Demonstrate several case examples of the use of regenerative medicine.

LECOM Integrative Medicine



LECOM Integrative Medicine Fellowship

- Immersive Osteopathic Experience (MD/DO)
- Medical Acupuncture
- Functional Medicine Basics
- Yoga for Chronic Pain
- Meditation Training
- Research
- Regenerative Medicine
- MSK Ultrasound
- Physician Self Care Programs
- Dominican Republic Medical Mission/LECOM PRIDE



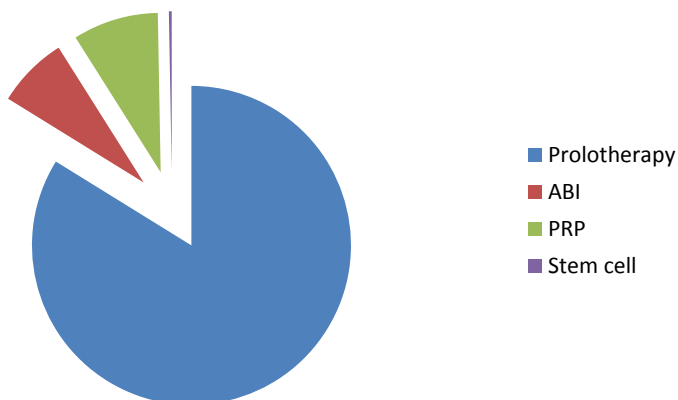
What is Regenerative Medicine?

- A musculoskeletal approach using injections of bioactive substances into degenerative tissue with the intention of improving soft tissue integrity, joint function and pain.
- Prolotherapy
- Autologous Blood
- Platelet Rich Plasma
- Stem Cell Therapies



2017 Regenerative Medicine Procedures

Cases = 692



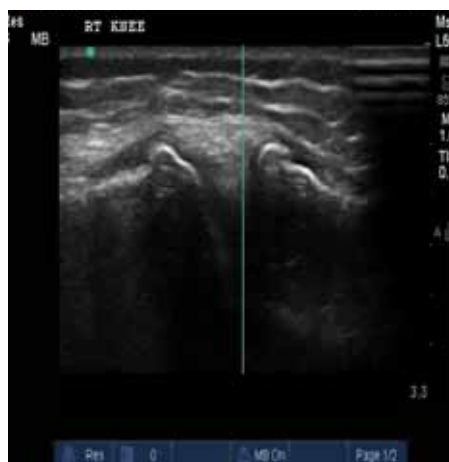
How do we manage chronic pain?

- NSAIDs
- Manual Therapies
- Steroid Injections
(typically last 2-4 weeks and don't modify the disease)
- Viscosupplementation
- Narcotics
- Surgery



Regenerative Medicine Considerations

- History and Physical Exam
- Radiology review (X-rays, MRI and Ultrasound)
- Life circumstances (Stress & ANS)
- Nutrition
- Vitamin D status, CRP
- Biomechanical factors
- Medications
- Supplements
- Cost
- Expectations
- Time frames/Time off/Protecting treatment area
- Pre-injection instructions
- Post-injection instructions



WOMAC Score

The Western Ontario and McMaster Universities Osteoarthritis Index
(WOMAC)

Name _____ Date _____

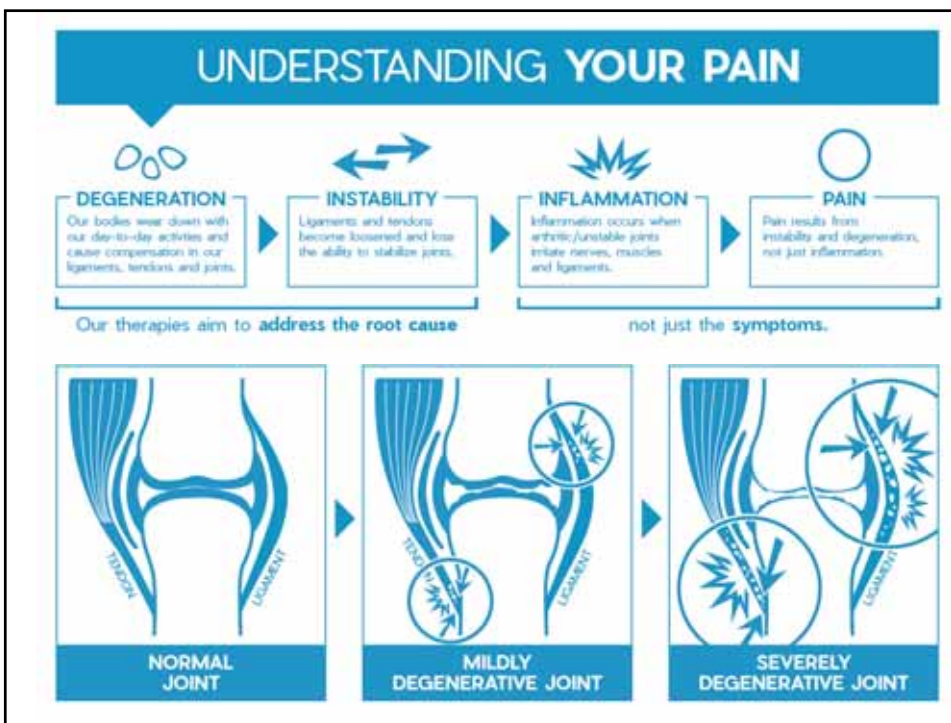
Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle one number for each activity:

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Neutrol	0 1 2 3 4
	4. Rest	0 1 2 3 4
Stiffness	5. Weight bearing	0 1 2 3 4
	6. Morning stiffness	0 1 2 3 4
Physical Function	7. Getting in/out of car	0 1 2 3 4
	8. Getting in/out of bed	0 1 2 3 4
	9. Getting on/off toilet	0 1 2 3 4
	10. Thresh from rest	0 1 2 3 4
	11. Thresh from rest	0 1 2 3 4
	12. Getting in/out of bath	0 1 2 3 4
	13. Sitting	0 1 2 3 4
	14. Getting on/off table	0 1 2 3 4
	15. Thresh domestic duties	0 1 2 3 4
	16. Light domestic duties	0 1 2 3 4
	17. Heavy domestic duties	0 1 2 3 4
	18. Walking on uneven surfaces	0 1 2 3 4
	19. Standing	0 1 2 3 4
	20. Bending to floor	0 1 2 3 4
	21. Bending to pick up	0 1 2 3 4
	22. Getting in/out of car	0 1 2 3 4
	23. Getting on/off toilet	0 1 2 3 4
24. Thresh from rest	0 1 2 3 4	
25. Thresh from rest	0 1 2 3 4	
26. Getting in/out of bath	0 1 2 3 4	
27. Sitting	0 1 2 3 4	
28. Getting on/off table	0 1 2 3 4	
29. Thresh domestic duties	0 1 2 3 4	
30. Light domestic duties	0 1 2 3 4	
31. Heavy domestic duties	0 1 2 3 4	

Total score: _____ / 68 = _____ %

Comments / Interpretation (to be completed by therapist only):



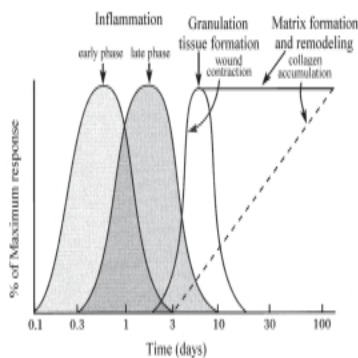
Osteopathic Medicine

- The body is a unit.
- The body possesses self regulatory mechanisms.
- Structure and function are reciprocally interrelated.
- Rational therapy is based upon an understanding of body unity, self regulatory mechanisms, and the inter-relationship of structure and function.



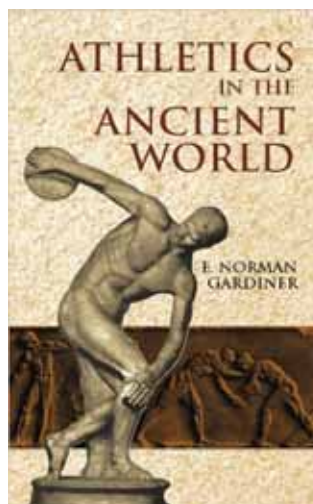
Basics of Regenerative Medicine

- Cellular debris and humoral factors at the injury site attract an initial influx of granulocytes. The granulocytes proceed to secrete a number of factors, among them proteolytic enzymes, which debride the wound area and attract other cells. Ultimately, fibroblasts are recruited and stimulated to produce new intracellular matrix, including new collagen.
- As the collagen is produced, it creates tissue remodeling, strengthens the area, and causes the wound contraction seen in Figure 1. This contraction, resulting from the production of new collagen/ligaments, creates a tightening of the wound, a reduction in joint laxity and therefore a reduction in pain.



History of Regenerative Medicine

- 460 BC Hippocrates treated Olympic javelin throwers with unstable shoulders with a “slender hot iron” to stabilize the shoulder capsule.
- 1939 Earl Gedney, DO
- 1953 George Hackett, MD
- 1958 Gustav Hemwall, MD
- 1988 Jeff Patterson, DO



Orthopaedic Problems. Innovative Solutions. Since 1983

Researchers:



- Brad Fullerton, MD
Austin, Texas



- Brain Shiple, DO
Philadelphia, PA



- Dean Reeves, MD
Kansas City, MO



- Michael Scaropone, DO
Steubenville, OH

Definition of Prolotherapy

Hackett Hemwall Patterson Foundation
University of Wisconsin

- Prolotherapy involves the treatment of ligamentous laxity and pain through the body's natural ability to heal ligaments and muscles without scar tissue.
- Through the injection of solutions directly into the ligament, causing a mild inflammatory reaction, a thickening and strengthening occurs which helps to alleviate chronic pain.
- This therapy is best suited for chronic myofascial pain seen commonly in athletic, repetitive motion, whiplash, and industrial injuries as well as accidental injuries such as those caused by falls.
- 25G 2 inch needle often used
- 15% dextrose (3cc D50, 4cc 1% lidocaine, 3cc normal saline)



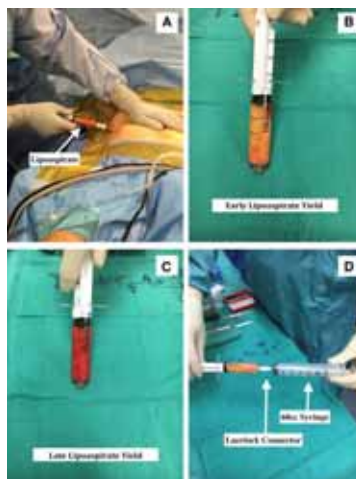
Definition of Platelet Rich Plasma (PRP)

- Blood is composed of 93% RBCs, 6% Platelets, 1% WBCs and Plasma.
- The goal of PRP is to maximize the number or concentration of platelets while minimizing the number of RBCs. Generally speaking, the higher the concentration of platelets, the stronger the growth factor response.
- Platelets are naturally rich in connective tissue growth factors. Injecting these growth factors into damaged ligaments, tendons, and joints stimulates a natural repair process. But in order to benefit from these natural healing proteins, the platelets must first be concentrated.
- High density > 4x's baseline
- Leukocyte poor (joint)/rich (soft tissue)



Stem Cell-Regenerative Medicine Basic Theory

- The ability of adipose and bone marrow stem cells to serve as a cell reservoir for connective tissue and joint repair.
- A stem cell niche (microenvironment which favors healing) is moved from one tissue in which these niches are abundant (adipose>marrow) into one where they are scarce (a non-repairing connective tissue) pain generator.

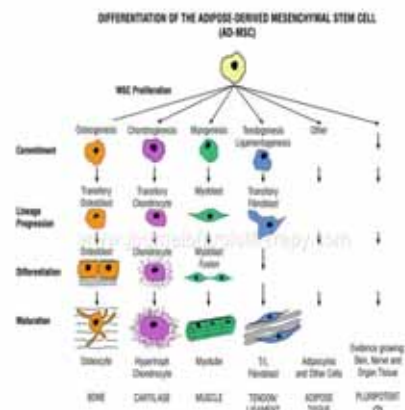


Mesenchymal Stem Cells

- In 2003, Murphy et al. reported significant improvement in medial meniscus and cartilage regeneration with autologous stem cell therapy in an animal model. Evidenced by marked regeneration of meniscal tissue and reduced articular cartilage degeneration, osteophytic formation and subchondral sclerosis compared with controls.
- In 2008, Centeno et al reported significant knee cartilage growth and symptom improvement in a human case using culture expanded MSC's from bone marrow.

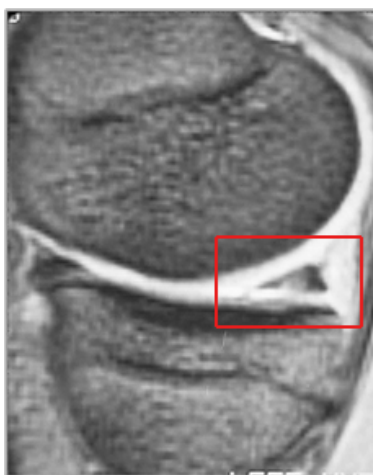
Mesenchymal Stem Cells

- Early 1990's the role of adult mesenchymal stem cells were discovered to have a role in connective tissue repair.
- Caplan (1991) first labeled "MSCs" because of their ability to differentiate to lineages of mesenchymal tissue, and were recognized to be an essential component of the tissue repair process.
- Historically bone marrow used as a source of MSC's, adipose-derived MSC's have been shown to be nearly identical fibroblast morphology and colonization (CFU-F), immune phenotype, successful rate of isolation, and differentiation capabilities.

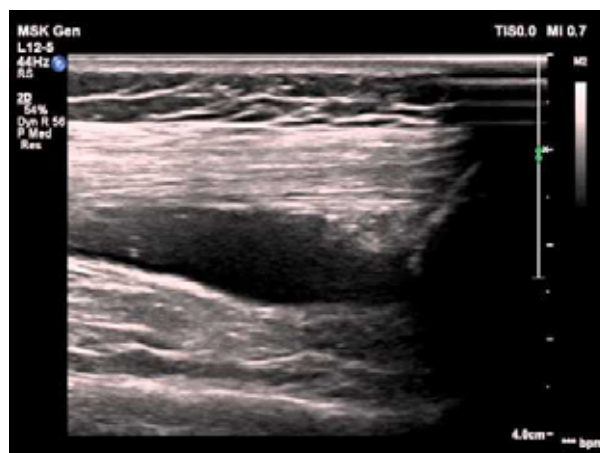


Common Middle Age Realities

- Posterior horn medial meniscal tears.
- Suprapatellar knee effusions
- Reduce range of motion
- Inhibits quadriceps firing normally
- Compensatory patterns
- Inactivity
- Weight gain
- Metabolic concerns



Knee Effusion



Effectiveness of intra-articular injections of sodium bicarbonate and calcium gluconate in the treatment of osteoarthritis of the knee: a randomized double-blind clinical trial

Sandra García-Padilla¹, Miguel Angel Duarte-Vázquez², Karla Elena Gonzalez-Romero¹, María del Carmen Caamaño^{1,3} and Jorge L Rosado^{1,5*}

Abstract

Background: A novel therapeutic management of osteoarthritis (OA) of the knee was assessed. The study aimed to evaluate the effect of monthly sodium bicarbonate with a single (SBCG1) or double dose (SBCG2) of calcium gluconate injections on OA of the knee; as well as the efficacy and safety of both SBCG interventions in the long term.

Methods: A double-blind parallel-group clinical trial with 74 knee OA patients was performed during 12 months, both SBCG interventions were followed-up for another 6mo after intervention. The outcome variables were the Western Ontario-McMaster University Osteoarthritis Index (WOMAC), the Lequesne's functional index and joint-space width changes from serial radiographs.

Results: After 12 months, group SBCG1 decreased -14.8 (95% CI: $-14.2, -17.0$) and group SBCG2 decreased -14.6 ($-16.9, -12.4$) in the global WOMAC score, the mean changes represent 80% and 82% lessened pain, respectively. In the Lequesne Functional Index scale, SBCG1 decreased -11.9 ($-10.4, -14.2$) and SBCG2 decreased -11.9 ($-13.8, -10.0$), representing 66 and 69% of improvement. Both mean scores were maintained after intervention discontinued. SBCG2 improved the knees' joint space width more than SBCG1 at 3 and 18 months. Both SBCG interventions were well tolerated after 12 months of treatment.

Conclusion: A solution of sodium bicarbonate and calcium gluconate is effective on reducing the symptoms associated with OA. Its beneficial effect is maintained for one year of continuous monthly administration and at least for 6 months after the administration is discontinued. When the dose of calcium gluconate is increased, it prevents further narrowing of joint-space.

Trial registration: Clinicaltrials.gov NCT00977444 September 11, 2009.

Keyword: Osteoarthritis therapy; Joint; Knee; Sodium bicarbonate and calcium gluconate.

Clinical Framework:

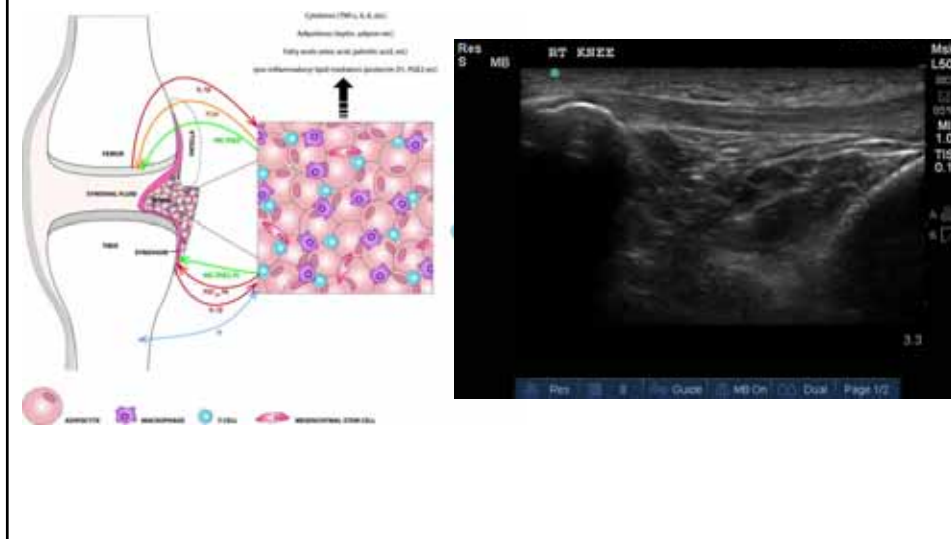
- Musculoskeletal injuries are the most common cause of severe long term pain often affecting psychosocial status, social interactions and employment.
- Worldwide incidence of more than 100 million musculoskeletal injuries annually.
- Osteoarthritis (OA) is the most common joint disorder in the United States.
- Symptomatic knee OA occurs in 10% of men and 13% of women aged 60 years or older.
- The number of people affected with symptomatic OA is likely to increase due to the aging of the population and the obesity epidemic.

Epidemiology of Osteoarthritis

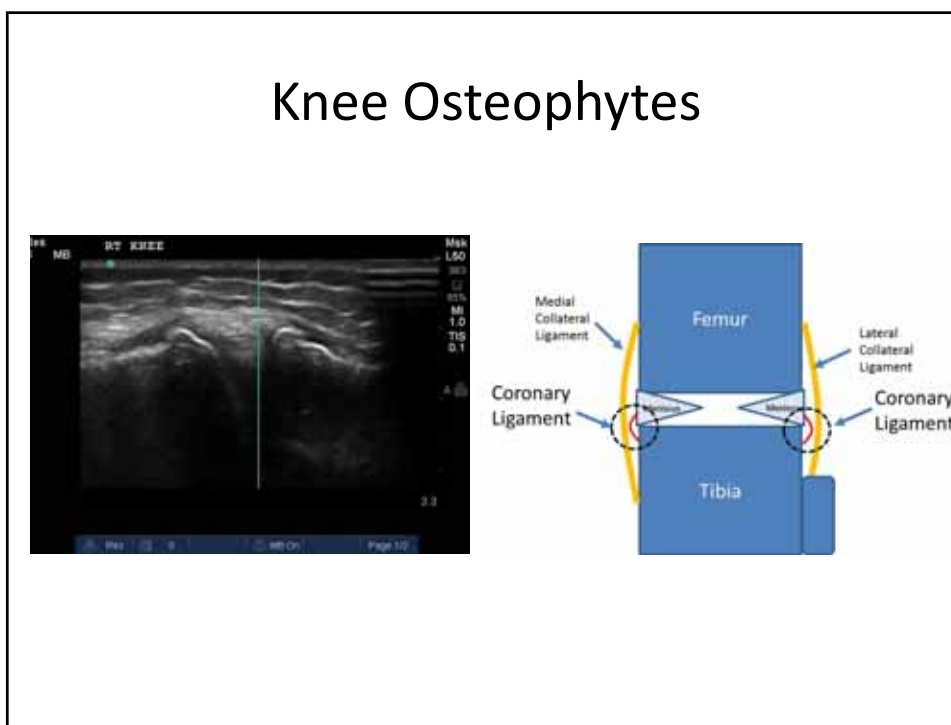
Y. Zhang, J.Jordan
Clin Geriatric Med 2010; Aug: 26 (3) 355-369

- OA has a multi-factorial etiology and can be considered the product of an interplay between systemic and local factors.
- Old age, female gender, overweight and obesity, knee injury, repetitive use of joints, bone density, muscle weakness, and joint laxity all play roles in the development of joint osteoarthritis, particularly in the weight-bearing joints.
- Modifying these factors may reduce the risk of osteoarthritis and prevent subsequent pain and disability.

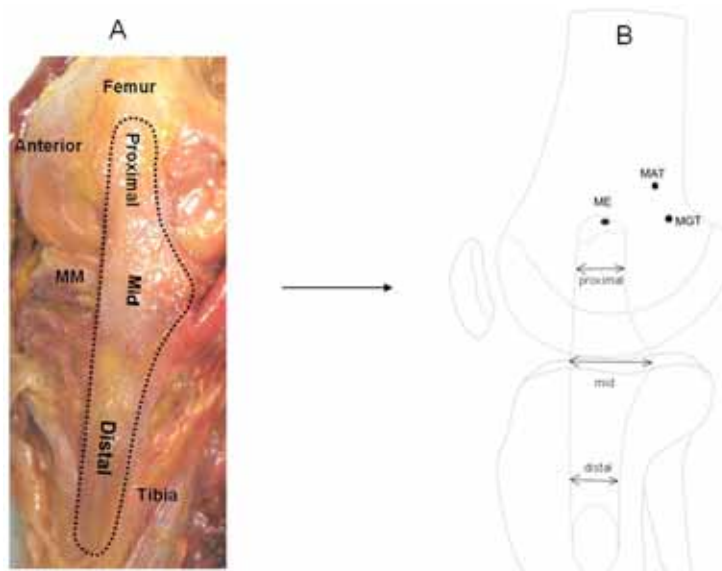
Hoffa's Fat Pad



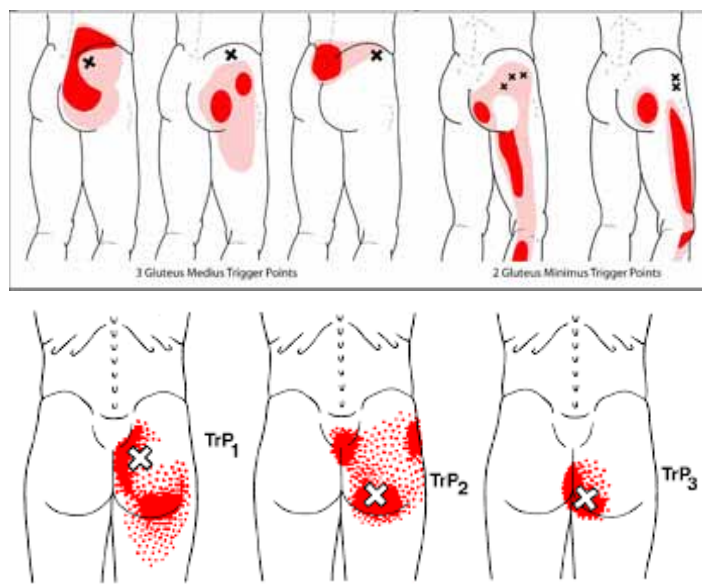
Knee Osteophytes

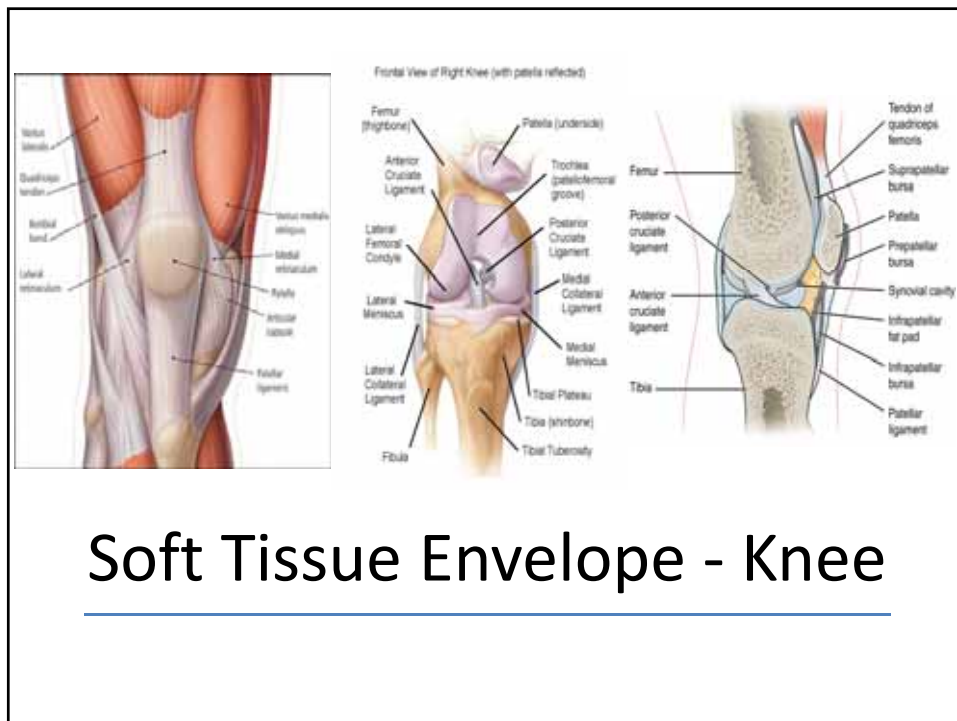
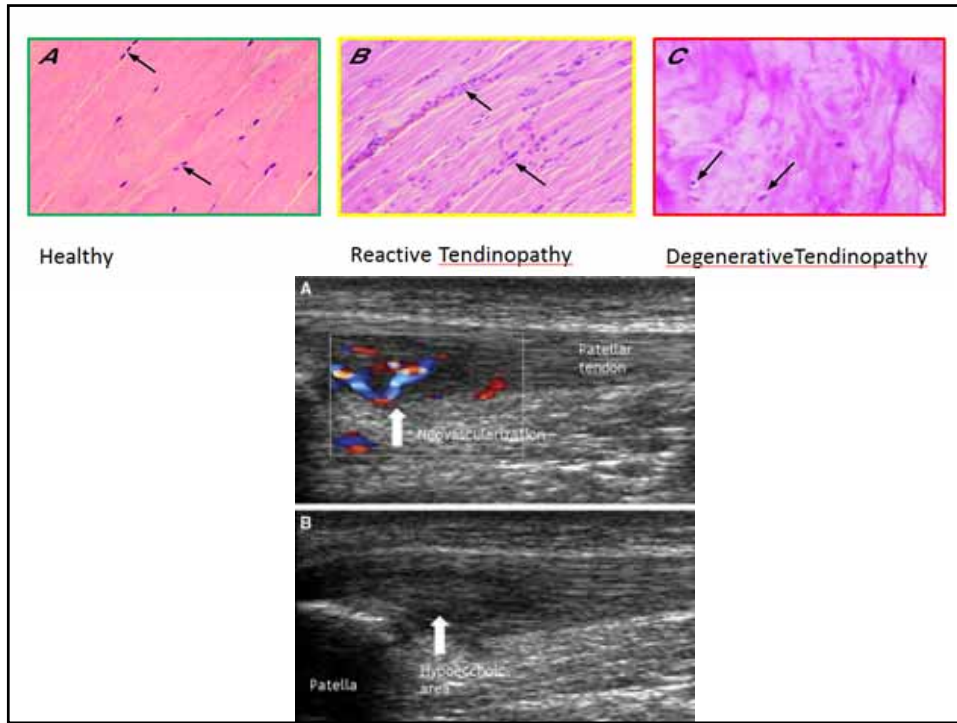


Medial Collateral Ligament



Compensatory Patterns





Regenerative Medicine Treatment Plan

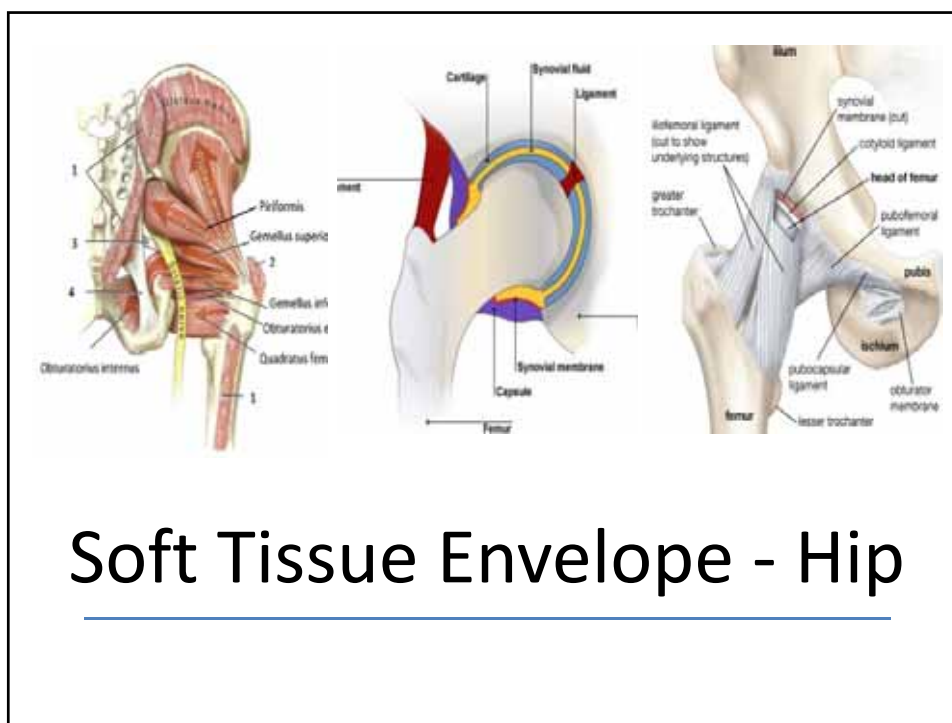
- Maximize patient's biomechanics
- Optimize vitamin D3
- Encourage more plant based foods and healthy spices
- Consistent aerobic exercise & avoid strength training around the treated area for 4 weeks.
- Expect to be stiff, sore and have slower movements for 3-5 days (Prolotherapy) 7-10 days (PRP & Stem Cells).
- Avoid anti-inflammatories 1 week before and 2 weeks after procedure.
- Retreat 4 weeks (Prolotherapy), 6-8 weeks (PRP) and 8-12 weeks (Stem Cells).
- Wear your brace for 2-4 weeks post treatment.



Case 1

- 75 yo WM healthy retired dentist with increasing left anterior hip and groin pain. Patient is s/p right THR 8 years ago. Wants to try an avoid surgery for the left hip.
- AP pelvis and left hip X-rays reveal advanced left hip degenerative changes.
- Several ultrasound guided platelet rich plasma injections have been completed to the left hip.



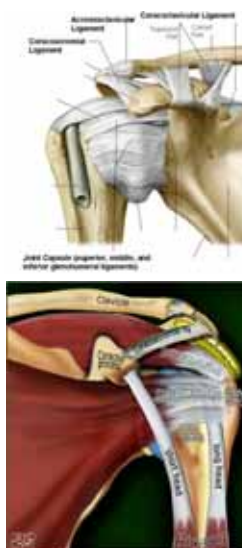


Case Study 1

- 75 yo healthy retired dentist with increasing left anterior hip and groin pain. Patient is s/p right THR 8 years ago. Wants to try an avoid surgery for the left hip. Limited with outdoor activities.
- AP pelvis and left hip X-rays reveal advanced left hip degenerative changes.
- 3 ultrasound guided platelet rich plasma injections (6 weeks apart) have been completed to the left hip with mild to moderate improvement.
- BMAC-PRP (2cc:2cc) injected under US guidance 22G 3 inch needle.
- Tolerated the procedure well.
- WOMAC score reduced 10 points within 3 months of procedure.
- Patient able to cross country ski first time in 5 years.
- No significant change in radiographs or ultrasound to date.

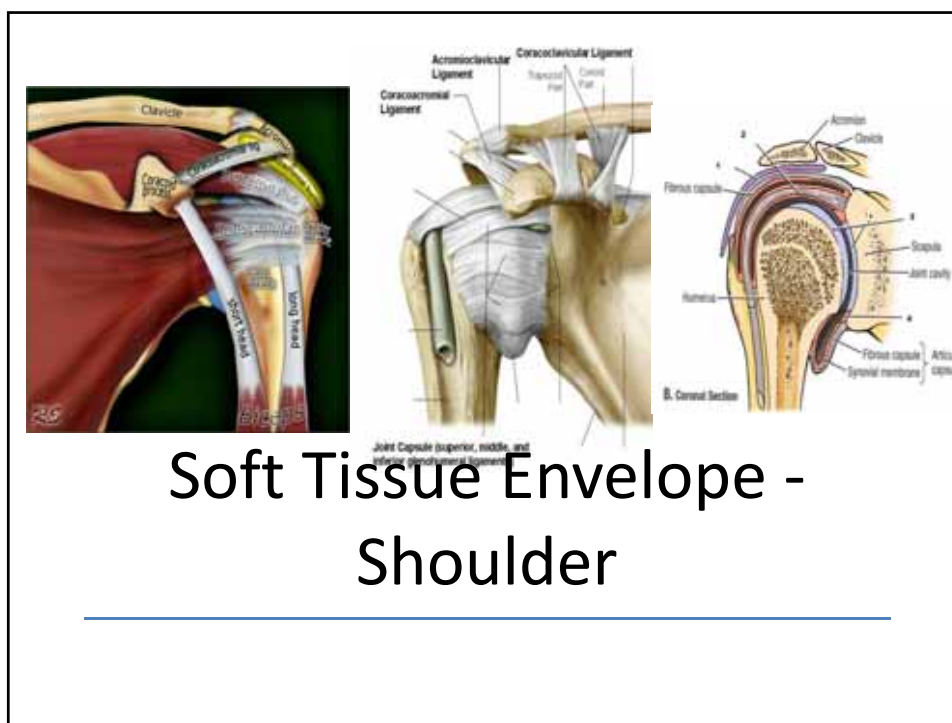
Case 2

- 65 yo WF triathlete presents with worsening left shoulder pain. Patient recently completed physical therapy without significant improvement of symptoms. Steroid injection completed 3 weeks prior to the consultation provided short term relief.
- Left shoulder ultrasound revealed a significant subdeltoid bursitis with tendinosis to the infraspinatus and supraspinatus regions.
- Left shoulder MRI did not reveal any significant rotator cuff tear.



Case Study 2

- 65 yo WF triathlete presents with worsening left shoulder pain. Patient recently completed physical therapy without significant improvement of symptoms. Steroid injection completed 3 weeks prior to the consultation provided short term relief. Unable to swim or run without shoulder pain. Disturbing sleep too.
- Left shoulder ultrasound revealed a significant subdeltoid bursitis with tendinosis to the infraspinatus and supraspinatus regions. X-rays- wnl
- Left shoulder MRI did not reveal any significant rotator cuff tear but confirmed bursitis and supraspinatus tendinopathy.
- US guided aspiration of the subdeltoid bursa completed.
- Orthopedic consultation resulted in confirmation that her shoulder symptoms were non-surgical in nature.
- Prolotherapy X 3 sessions (1 month apart) 25 G 2 inch needle with 15% dextrose used.
- 75% improved with patient able to return to running and swimming. Able to sleep better.



Case 3

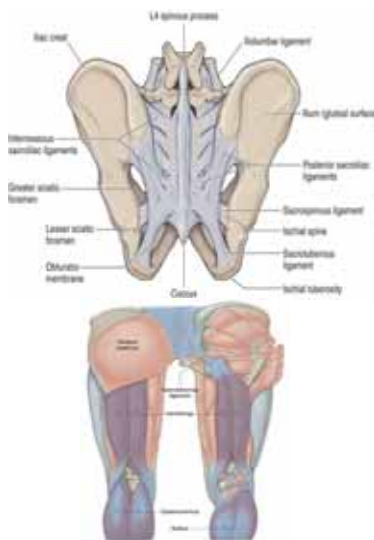
- 46 yo WM lawyer who boxes three times a week presents with worsening right lateral elbow pain X 6 weeks. He has taken 2 weeks off without resolution of symptoms. ADLs are painful to a point he can't shake clients hands without significant pain NSAIDs are not effective with symptoms. He's concerned about what he has heard about steroid injections "weakening tissue". He presents for more information regarding regenerative medicine options.
- Right elbow x-rays are negative.
- MRI

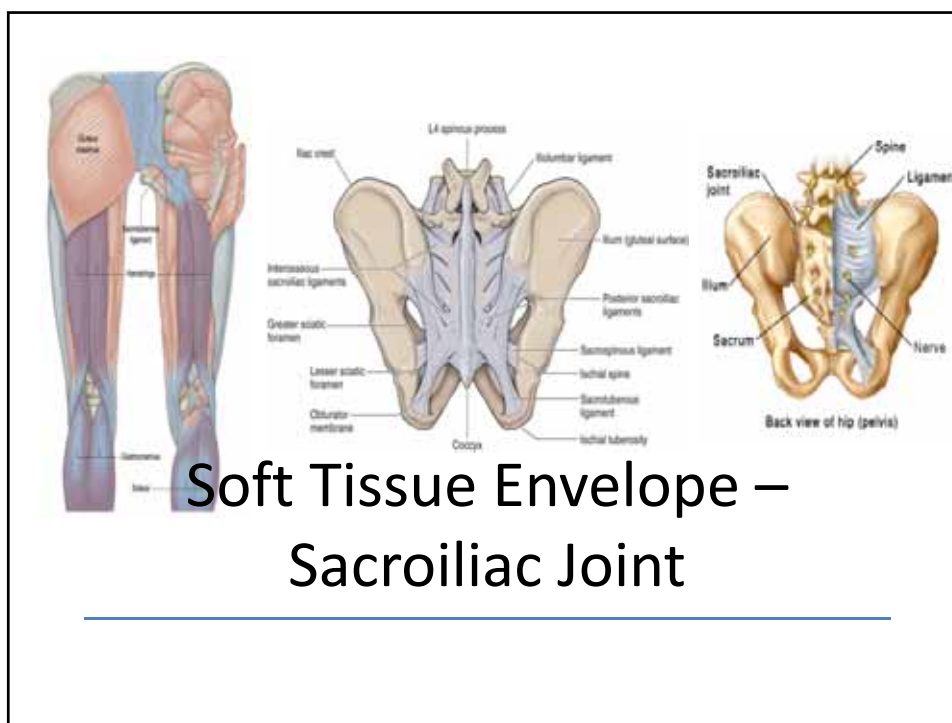
Case Study 3

- 46 yo WM lawyer who boxes three times a week presents with worsening right lateral elbow pain X 6 weeks. He has taken 2 weeks off without resolution of symptoms. ADLs are painful to a point he can't shake clients hands without significant pain NSAIDs are not effective with symptoms. He's concerned about what he has heard about steroid injections "weakening tissue". He presents for more information regarding regenerative medicine options.
- Right elbow x-rays are negative.
- MRI revealed partial tear of common extensor mechanism.
- Initial hand grip strength: 39-43-44 KG-Force
- Prolotherapy and Platelet Rich Plasma (PRP) options discussed.
- We chose to complete 3 Prolotherapy treatments because of less down time given his workout schedule and tennis vacation with his wife. If not improvement after 3 sessions progress to PRP.
- After 2 sessions ADLs are pain-free except for tight gripping.
- Able to play tennis without any significant pain.
- Hand grip strength 46-47-50.
- Ultrasound hasn't revealed much fibroblastic changes yet—still within 90 day remodeling window.

Case 4

- 62 yo WM presents to the clinic for worsening lumbosacral pain. Patient relates a history of a grade 1 spondylolisthesis. Pt describes injuring himself 20 years ago during the running phase of a triathlon. Besides a significant improvement with Roling years ago his pain is now consistent and impacting his ADLs. He presents hoping regenerative medicine may help his symptoms.

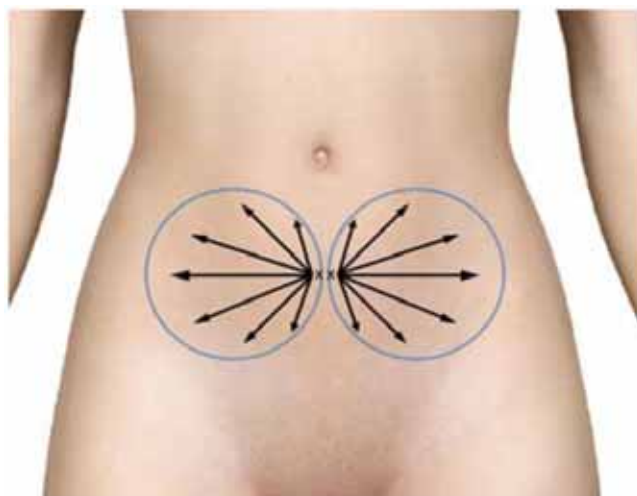




Case Study 4

- 62 yo WM presents to the clinic for worsening lumbosacral pain. Patient relates a history of a grade 1 spondylolisthesis. Pt describes injuring himself 20 years ago during the running phase of a triathlon. Besides a significant improvement with Roling years ago his pain is now consistent and impacting his ADLs.
- He presents hoping a regenerative medicine may help his back symptoms.
- Set up patient to first see personal trainer to maximize core stabilization exercises. HEP QD.
- Recommended based upon physical examination and reproducibility of gluteal pain pattern several sessions of dry needling and acupuncture.
- 5 sessions completed over 8 weeks
- Patients pain pattern resolved significantly. No pain with ADLs and able to resume cycling and cross country skiing.

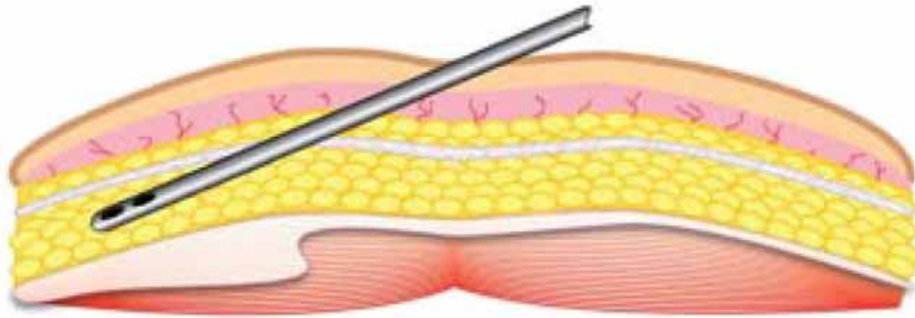
Adipose Harvesting



Disposable microcannula cannulas for closed-syringe lipoaspiration of small-volume autologous adipose grafting



Microcannula below Scarpa's fascia in the adipose tissue plane.



Centrifuge



T-SVF= Tissue Stromal Vascular Fraction



Autologous Adipose-Derived Stem/Stromal Cells (AD-SC)

- Historically mesenchymal stem cells (MSC's) have been studied from bone marrow aspiration.
- Adipose is easier to harvest.
- Offers higher nucleated, undifferentiated stem cell counts versus bone marrow.



Stem Cell Research

Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis

Knee, 19 (2012), pp. 902-907

- Clinical studies performed in human subjects with osteoarthritis have shown promising early results. Patients with knee osteoarthritis undergoing arthroscopic debridement were injected with autologous ADSCs prepared in platelet-rich plasma. Treated patients showed improved mobility and function and reduced pain scores.
- At 2-year follow-up, patients had significantly improved Western Ontario and McMaster Universities Osteoarthritis pain scores, visual analog scale pain scores, and cartilage regeneration on advanced imaging studies.

AD-SC & BM Stem Cells:

Uysai AC et al. Differentiation of adipose derived stem cells for tendon repair. Methods Mol.Bio 2011: 702

- Studies reveal improved wound healing, fibroblast proliferation, migration and collagen secretion, increasing connective tissue strength and healing.
- Differentiation potential to become cartilage, tendon, ligament, bone and skeletal or smooth muscle and are also capable of expressing multiple growth factors that influence, control and manage damaged neighboring cells.

Adipocyte Stem Cell Therapy

Advantages

Largely dispensable tissue and readily accessible.
 Minimal morbidity.
 Uncultured cells with no ex vivo expansion, minimizing risk of infection and immunogenicity.
 Well-vascularized tissue with abundant pericytes.
 Immunosuppressive actions, privileged properties, anti-inflammatory effects.
 Clinical applications for both focal cartilage defects and generalized osteoarthritis.

Disadvantages

Limited proliferation and differentiation potential in comparison with pluripotent stem cells.
 Techniques to optimize cell purity and increase sorting efficiency are needed.
 Randomized control trials are needed to better understand patient outcomes.

FDA Considerations:

- Autologous stem cells are considered “Human Cells, Tissues and Cellular Based Products (HCT/P’s) and thus regulated by the FDA.
- At this time, no chemical manipulation of the adipose-derived tissues for isolation and concentration is permitted in the United States.
- Compliance with the FDA exists if the physician “removes HCT/P’s from an individual and implants such HCT/P’s into the same individual during the same surgical procedure.”

FDA Considerations

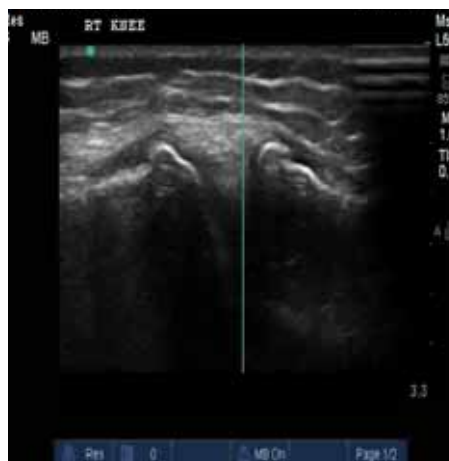
- To be considered as occurring “during the same surgical procedure” the cells must be autologous, minimally manipulated and used within a short period of time.
- Minimally manipulated is defined as “processing that does not alter the relevant biological characteristics of cells or tissues.”
- Short period of time per the FDA Guidance for Industry is considered to be “a matter of hours or less, without the need for shipping.”

FDA Considerations:

- More than minimal manipulation involves “the use of drugs, biologics, and/or additional devices that warrants regulation of the manufacturing process and the resulting cells as biological products.”
- This is where the use of enzymes such as collagenase or culture expansion of cells is problematic.
- At this time harvesting native autologous stem-stromal cells does not pose any problem as far as FDA regulation is concerned.

Regenerative Medicine Considerations

- History and Physical Exam
- Radiology review (X-rays, MRI and Ultrasound)
- Life circumstances (Stress & ANS)
- Nutrition
- Vitamin D status, CRP
- Biomechanical factors
- Medications
- Supplements
- Cost
- Expectations
- Time frames/Time off/Protecting treatment area
- Pre-injection instructions
- Post-injection instructions



Take Home Points

- Are expectations realistic?
- Remodeling tissue takes time~3-4 months.
- Post treatment often requires changing exercise regimens for a significant period of time.



Take Home Points

- Remember the cartilage lining the joint surfaces has no pain fibers.
- The soft tissue envelope is often a significant part of the pain equation.
- Regenerative medicine treatments are capable of building tissue integrity to degenerative areas reducing the need for medications and improving patient's quality of life.



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