**EM: Bowler and walker with 4 years ankle pain**

- 57 yo city of Framingham health inspector and avid candlepin bowler. Enjoys frequent long walks with his wife.
- 4 year history of non-insertional achilles tendon pain. Refractory to PT, eccentric strengthening, meds
- Gained weight as his activity level decreased

**30 yo female ultramarathon runner with 1 year pubic pain**

- Long distance runner
  - 27 marathons and 6 ultramarathons (50-100 km)
- 1 year of intermittent pain left of the pubic bone
  - Also right hip flexor pain.
- Initially only with running.
- Within 2 months, lateral movements, walking, rolling in bed provoke pain.
  - Single leg stance is difficult, side planks excruciating.

**History of Present Illness**

- No pain with lumbopelvic flexion or extension, coughing/sneezing, urination or bowel movements.
- No neurologic symptoms in the lower extremities.
- No previous injuries.

**History of Present Illness**

- Prior workup including X-ray, MRI
  - Reportedly negative for any osseous abnormality, mild right greater trochanteric bursitis.
- Referred to PT for “hip bursitis.”
- Hip/gluteal strengthening, cross-training, underwater running, yoga.
- Pubic cleft corticosteroid injection (ultrasound-guided), with no improvement.
- Massage, SI belt, chiropractic, meditation, acupuncture.

**Additional History**

- Past Medical History
  - Polycystic ovarian syndrome
  - Fracture of the right foot
    - 4 years prior, no residual pain
- Allergies: Penicillin
- Medications: OCP, vitamins.
- Social History: Single, no children. Works in marketing. Non-smoker, no EtOH.

**Physical Examination**

- Well-developed, athletic
- No skin abnormalities
- Respirations nonlabored
- Abdomen nontender
- Good core control
  - Able to stand from a chair on one foot, single-leg squat
- Normal gait
- Spine
  - No abnormalities on inspection/palpation of the back/posterior pelvis
    - Good, nonpainful lumbopelvic ROM
    - Normal neurologic exam
### Physical Examination

- **Hip/Pelvis examination**
  - Symmetric pelvic alignment
  - Tenderness over pubic symphysis
  - Pain with resisted hip adduction
  - No pain with hip flexor or abdominal activation
  - Thomas test negative
  - SI maneuvers negative
  - Sensation intact over genital region, lower abdomen, medial thigh

### Differential Diagnosis

- **Chronic pelvic pain in a runner**
  - Adductor/hip flexor tendinopathy
  - Osteitis pubis
  - Sports hernia
  - Stress fracture (pubic ramus, femoral neck)
  - FAI
  - Pelvic floor myofascial pain
  - Referred pain (SI, lumbar spine, visceral)
  - Neuropathic pain (Pudendal neuralgia)
  - Inguinal hernia
  - Osteomyelitis of the pubis

### MRI Pelvis

**Coronal**

**Axial**

### 58 yo active tennis player with moderate knee OA

- **Additional history**
  - Aches in the evening after an active day
  - Difficulty with stairs and sports activity
  - No mechanical symptoms or recurrent synovitis
  - Uses aleve most days
  - Wants to wait until 65 as he has been told TKA lasts ~20 years

- **Prior treatments:**
  - Weight loss
  - PT
  - Steroid injection
  - Viscosupplementation no longer helps as much

- **PMH:** hypertension well controlled

### Goals of the Presentation

- **Basic overview of the evolution of the current available techniques**
- **General principles in selecting amongst these treatments**
- **Patient Selection for regenerative treatments**
- **Where is the field headed?**
Baby Boomers and “tweeners”

- “In between” normal joint and arthroplasty

What has been the evolution/convergence?

New treatments: veterinary and surgical
MSK US Science:
Tendon
Joint
Pathogenesis of Osteoarthritis: not just a mechanical disorder

- Synovial joints are richly innervated: type IVa free nerve endings
  - Joint capsule
  - Tendons
  - Retinacula
  - Fat pads
  - Synovium
  - Subchondral bone
  - Ligaments
- Muscle and fascia: substance P and mechanoreceptors
- Periosteum: myelinated and unmyelinated sensory fibers

Neuroanatomic Basis of Pain in OA

Figure 1 Schematic representation of the layered structures on the medial side of the knee joint. (A) Anterior view. (B) Superior view. AC = articular capsule; FC = fascia cruris; Gcm = medial head of gastrocnemius muscle; Gr = tendon of gracilis...

Enthesopathy

- Enthesis=
  - Attachment site to bone
  - Insertion site
  - Osteotendinous junction
  - Osteoligamentous junction
- Conditions
  - Tennis/golfers elbow
  - Jumper’s knee
  - Achilles insertional tendinopathies
- Rarely, if ever, inflammatory
The “cult” of corticosteroid

Anatomic targets for regenerative sports medicine
- Bone
- Enthesis
- Tendon
- Ligament
- Muscle
- Joint/cartilage
- Nerve

COMMON REGENERATIVE METHODS

Prolotherapy
Autologous Blood Products
- Bone Marrow
- Adipose

Definition of Prolotherapy

- Prolotherapy = “Proliferative therapy”
  - “Method of injection treatment using irritant solutions designed to stimulate healing and pain relief.”
  - Targets: Joint space, ligament, tendon insertion

History of Prolotherapy

- “Prolotherapy”
  - Term first used in the 1950s by Dr George Hackett
  - Dr Hackett was a trauma surgeon and began using solutions to heal “soft tissues” causing chronic pain after trauma.
  - Trained Dr Hemwall
  - 1956: published textbook
  - Dr C Everett Koop was treated with prolotherapy for his chronic back pain
  - Major research: Kansas, U of Wisconsin, U of Pittsburgh, Virginia Tech

Nomenclature: Dr Reeves

- Biologic Repair therapy
  - Injection of biologics to repair connective tissue
- Prolotherapy (Prolo)
  - Injection to repair connective tissue (tendon, ligament, cartilage) not including biologics
- PSI: perineural subcutaneous injection (introduced as neural prolotherapy)
  - Subcutaneous injection to restore function in pain producing sensory nerves
- Perineural deep injection (also called hydrodissection)
  - Deep nerve treatment with ultrasound guidance
Solutions Used in Prolotherapy and their proposed mechanisms of action

<table>
<thead>
<tr>
<th>Injected Solution</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperosmolar dextrose</td>
<td>Creates hypertonic atmosphere, which leads to cell rupture, Upregulates expression of platelet derived growth factors</td>
</tr>
<tr>
<td>Morrhuate Sodium</td>
<td>Attracts inflammatory mediators</td>
</tr>
<tr>
<td>Vascular sclerosant</td>
<td></td>
</tr>
<tr>
<td>Phenol – glycerine - glucose</td>
<td>Cellular irritant * no longer used</td>
</tr>
</tbody>
</table>

Proposed Mechanisms of Dextrose Prolotherapy

- Natural GF elevation
- Stimulation of the healing cascade
- Needling effect
- Reduction of neurogenic inflammation (PSI, neural)

Growth factors the Dextrose Elevates (non inflammatory effect)

- Ligament/tendon healing:
  - PDGF, TGFβ3, EGF, bFGF, CTGF
- Cartilage Healing
  - PDGF, TGFβ3, IGF,

Dextrose Levels > 10% Stimulate the Inflammatory Cascade

- Osmotic effect – cell shrink – stress – leakage of lipids – temporary inflammation

The Needle Itself Stimulates Repair

- Cell membrane disruption
- Small blood vessel disruption
- Bleeding with platelet and blood effects
- Challenge to do injection control studies.

PSI (neural prolotherapy)

- Dr. John Lyftogt: sports medicine, New Zealand
- 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 Capsaicin receptor on the nerve.
Perineural Deep Injection

- Ultrasound guidance
- Injection about a nerve in a deeper region where the nerve travels through facial layers
- Stretch by fluid = hydrodissection
- 5% dextrose

The “prolotherapy approach” to treatment

- Treat the region; not a point
- Postural models of assessment
- Combine with manual therapy**
- Meticulous knowledge of ligament and tendon anatomy

Treatment Paradigm for Prolotherapy

- Technique: important concepts — “ABC’s”:
  - Anatomy: entheses, vasculature, nerves
  - Bony endpoint: always touch bone with needle tip before injecting
  - Compression of superficial tissues while injecting to maximize accuracy

Best practice recommendations for dextrose prolotherapy: 2016

- CMC/finger OA: (B)*
  - DPT preferable to steroid in chronic CMC OA
  - May reduce pain and stiffness in PIP and DIP OA
- Knee OA: (A)*
  - DPT effects are both positive and significantly beneficial in symptomatic knee OA.
- Low Back Pain
  - No definite recommendation at this time
- Sacroiliac Pain*
  - DPT lasted longer than steroid and provided significant relief of SI joint pain
- Osgood-Schlatter*
  - Consider for adolescents with persistent pain or limitation of sport

Adapted with permission from Dr. Dean Reeves
Takashi Saito, a star pitcher for the LA Dodgers suffered a tear of his ulnar collateral ligament. Just prior to the kickoff of superbowl XLIII, on field reporters from NBC credited Hines Ward’s rapid recovery with a knee sprain (MCL) to Platelet Rich Plasma therapy.

IOC consensus paper on the use of platelet rich plasma in sports medicine


- **WADA:**
  - Intramuscular injections prohibited until 2011, then approved
  - All other routes of administration, such as intra-articular, intra-or peritendinous are permitted and require a declaration of use.
  - Isolated growth factors are prohibited: IGF-1, VEGF, PDGF

Platelets: Not just for clotting

- Platelets are the first cells to arrive at the site of injury
- Responsible for initiation of healing cascade
- α-granules and dense granules

Alpha Granules

- Platelet derived growth factor (PDGF)
- Transforming growth factor (TGF)
- Epidermal growth factor (EGF)
- Vascular endothelial growth factor (VEGF)
- Fibroblast growth factor (FGF)
- Connective tissue growth factor (CTGF)

Dense Granules

- Serotonin
- ADP
- Histamine
- Calcium

Does PRP work?

- Published article: 6,047
- No difference
- Significant difference

50% 50%
Best practice recommendations for PRP: 2016

- **BEST STUDIES**
  - Chronic tendinopathy
  - Positive for chronic lateral epicondylosis
  - Possible for Achilles and patella
  - No additional benefit for RTC repair

- **GOOD EVIDENCE and BEING ACTIVELY STUDIED**
  - Osteoarthritis
    - Knee is best studied and supported with L-PRP
    - Possibles: hip, ankle

- **UNCERTAIN / CONFLICTING DATA**
  - Acute muscle injury

- **GOOD CASE SERIES**
  - Partial tear of the UCL: (Podesta)

Mesenchymal stem cells

- **Bone marrow derived**
- **Adipose derived**
- **Synovium derived**
- **Muscle derived**
- **Umbilical cord**

Mesenchymal stem cells

- MSC: cells that have the ability to proliferate and differentiate into progenitors of different mesenchymal tissue
- They have unique cell surface markers, adhesion molecules, cytokines, growth factors and receptors
- Anti-inflammatory and immunomodulatory

**Mechanism of Action: Bone Marrow Mesenchymal Cells**

- Not completely understood
- Replace degenerated tissue
- Through paracrine activity, exhibit a secretory or "trophic" function; with anti-inflammatory, immunomodulatory, pro-angiogenic, anti-apoptotic, anti-fibrotic, and wound healing properties with proliferative effects

- Slides from Dr. Steve Sampson
Bone marrow derived mesenchymal stem cells

- Preclinical Efficacy of MSCs in Cartilage Regeneration
  - Goat study demonstrates cartilage regeneration with IA injection of BMSCs suspended in hyaluronan (Murphy 2003)
  - Donkey study demonstrates reparative effect of injected MSCs clinically and radiologically (Mokbel 2011)
  - Undifferentiated BMSCs on biodegradable scaffolds yield encouraging results in rabbit and sheep models of OA

Adipose

- Adipose is a connective tissue, thus a structural tissue – FDA
- Does not undergo processing steps beyond rinsing, cleansing, or sizing - minimal manipulation
- Used for the repair, reconstruction, replacement, or supplementation of a recipient's tissues performs the same basic function - homologous

Lipoaspirate: Mechanical Breakdown

Amniotic Tissue

- Appropriate Uses
  - Maintain entire structure of tissue
  - Use in soft tissues

- Inappropriate Uses
  - Isolating MSC's (SVF)
  - Use in bones and joints
**Potential Uses**

- Source of Stem Cells and rich in cytokines
- Living cells???

---

**Advantages and Concerns**

- Source of cells
- Screening methods
- Industry standards

---

**Bioscaffolds**

- A number of studies demonstrate that seeded constructs have better histological and biomechanical properties than scaffold alone
- Studies
  - Synthetic biodegradable polymers
  - PLGA (poly-lactide-co-glycolide)
  - Acellularized tendon grafts
  - Collagen sponge

---

**Silk Polymers**

*Cocoon Biotech to Explore New Treatments for Joint Disease using Silk Biomaterial Platform Developed at Tufts University*

BOSTON (November 4th, 2014) — Cocoon Biotech today announced that it has entered into exclusive option and sponsored research agreements with Tufts University to explore the commercialization of new treatments for joint disease and arthritis using silk protein polymers....

---

**Patient Selection**

- Age and medical factors
- Alignment
- Prior treatments
- Peri vs intra-articular component
- Severity of arthritis
- Candidacy for joint replacement
- Patient preference
- Particular joint
  - Knee
  - Hip
  - Shoulder
Patient education and counseling

- Literature
- Active rehabilitation
- Expense
- Benefits vs risks
- Set expectations
  - Pain
  - Function
  - Range of motion
  - Durability

Selection of Treatment

- Accurate diagnosis
- Target tissue(s) and volume needs
- Severity and size of injury/defect
- Time frame (in season? geography)
- Cost
- Other medical co-morbidities
- Pain tolerance of patient
- Patient preference

I was heading toward total knee replacement…. Walking was minimal and difficult necessitating a cane or crutches. … (fall 2008)

……… I just returned from a trip to Bhutan where I made several day long hikes including one hike up and down a very steep incline to visit the famous "Tiger’s Nest" Monastery. (Fall 2010)

I think the PRP therapy was able to turn things around so that I could increase my physical activity and strengthen my knee to the point where my activities include regular hiking. …..

Medical Assistant Review

Physical Therapy
Preparation

- Physical therapy ** evaluation
  - Education
  - Activity expectations
  - Return to play expectations
  - Exercise review
  - Brace/crutches/sling
  - Protocol review
  - Double check: meds

Treatment selection: soft tissue

<table>
<thead>
<tr>
<th>Injectate</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMAC</td>
<td>Theoretical tissue repair; Few human studies (tendon)</td>
<td>Invasive; Expensive; FDA non compliant</td>
</tr>
<tr>
<td>Prolotherapy</td>
<td>Less expensive Treat region, not point Increased volume Tendon / synxthesis Reduce hypermobility</td>
<td>More research needed Needing effect may be primary</td>
</tr>
<tr>
<td>Platelet Rich Plasma</td>
<td>More data for intra and peri-tendinous application UCL</td>
<td>Small volume; Expensive; Synxthesis may be primary</td>
</tr>
<tr>
<td>Adipose graft</td>
<td>Filling of tissue defect</td>
<td>Invasive; Expensive</td>
</tr>
</tbody>
</table>
### Treatment selection: osteoarthritis

<table>
<thead>
<tr>
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<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMAC</td>
<td>Paracrine effect</td>
<td>invasive, expensive</td>
</tr>
<tr>
<td>Fat graft</td>
<td>Less expensive</td>
<td>No good research</td>
</tr>
<tr>
<td>Prolotherapy</td>
<td>Insufficient data, points, no point.</td>
<td>Research support: knee, CMC, SI joint</td>
</tr>
<tr>
<td>Platelet Rich Plasma</td>
<td>Knee best Hip</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less data on small joints</td>
</tr>
</tbody>
</table>

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### Summary: Cell Delivery for Musculoskeletal Regeneration

- Processed: (cells from tissue, blood or bone marrow)
- Unprocessed: blood or bone marrow

- **Cell and/or tissue harvest**:
  - Blood
  - Bone marrow
  - Tissue

- **Regenerative ingredients**:
  - Cells
  - Biologic carrier
  - Signals

---

### The tissue engineering paradigm

- Biophysical stimuli
- Biochemical signals
- Cells
- Scaffolds