Multimodal Therapies for OA: Therapy, Exercise, NSAIDs, and So Much More

Ramon Cuevas-Trisan, MD

Disclosure

- Nothing to disclose

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Learning Objectives

- Review individual and multimodal approaches to the management of osteoarthritis
- Discuss proven and unproven, commonly accepted management methods for pain in OA stressing the importance of exercise and non-pharmacological modalities
- Review the medical literature related to various treatment modalities, including common injectables in the management of osteoarthritis

What is OA?

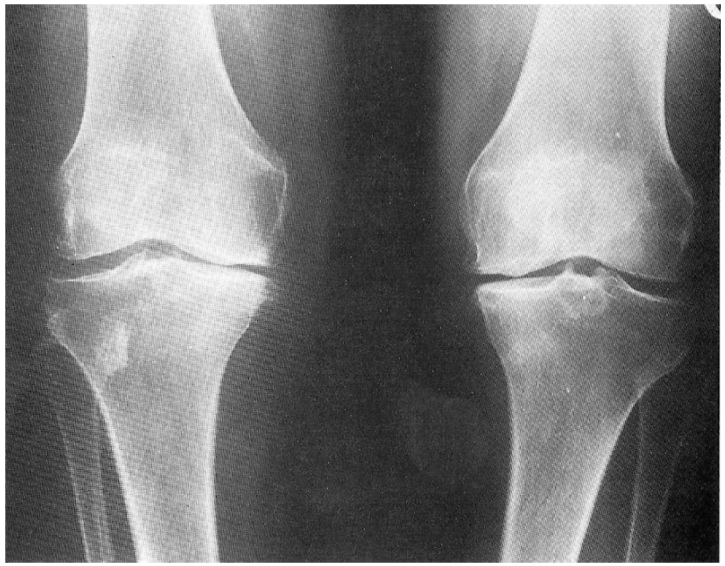
Arthritis due to:

- Wear and Tear → **OA**
- Trauma / Injury → **PTOA**
- Combination of above

Not so fast; now we know that other factors are heavily involved……..

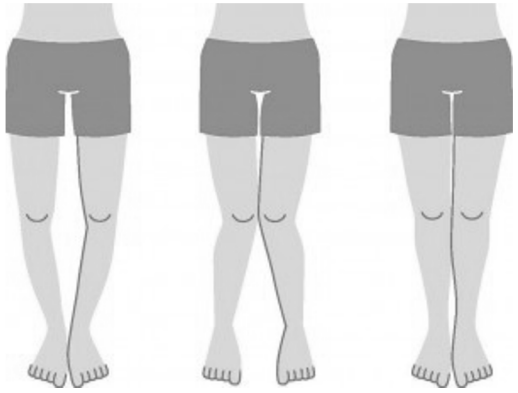
What Happens in OA?

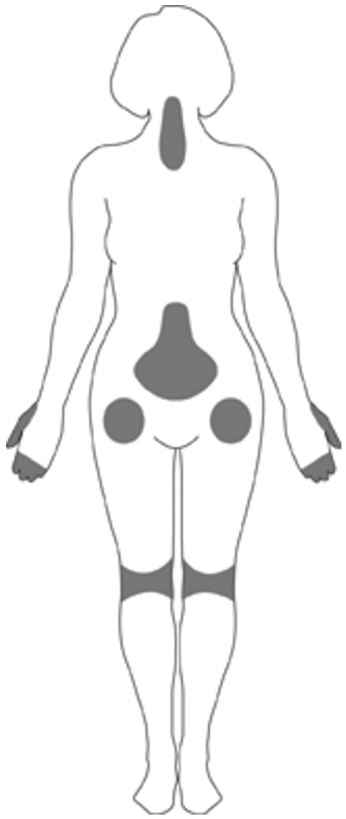
- Articular cartilage loss
- Resulting bone exposure
- Process involves cartilage, bone, and synovium; also soft tissue hardening and ectopic bone formation



Prevalence: Who and When?

- Most common joint disease
- Prevalence increases with age
- Affects nearly 50 million Americans
- Fastest increasing major health condition





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Pathogenesis of OA: Multifactorial

- Genetics / Gender / Age
- Body weight
  - Hip joint forces: 2.5x body weight with normal walking
  - Knee joint forces: 4x body weight with normal walking

Progressive cartilage degeneration

  - Traumatic vs chronic

- Adaptive joint remodeling →osteophytes
- Muscle weakness → abductors (buttocks), quads
- Obesity: other metabolic factors
- Inflammatory changes

Pathogenesis of OA: Obesity

- Link between obesity and knee OA is definitive; ACR OA treatment guidelines recommend weight loss
- No threshold effect has been found but higher BMI leads to higher knee OA

The OA Model

DOGMA

Relation between OA of the knees and obesity:
related to mechanical stress on the joint due to excess weight

THINK AGAIN…..

Compared to single joint PTOA - evidence for the above is weak (lacks direct cause-and-effect relationship)

- Potential influential factors - increased incidence in non-weight bearing joints (i.e., hands and shoulders)
- Widespread and generally symmetric OA, suggesting a systemic etiology
- Compelling evidence suggesting metabolic factors play role in OA

Aspden, et al *Nat Rev Rheumatol* 2001

Inflammatory Mediators

- Inflammatory cytokines have been implicated in the etiology and progression of OA
- Adipose tissue
  - NOT an inert tissue (passive storage of energy)
  - appears to be a real endocrine organ
  - induces chronic low-grade inflammation
  - produces/secretes cytokines (IL-1, TNFα) and inflammatory mediators (adipocytokines or adipokines)

- Pottie et al. Ann Rheum Dis 2006

Management Options in Osteoarthritis

- Oral analgesics (NSAIDs, others)
- Nutritional supplements (G & CS)
- Topicals
- Physical modalities / exercise
- Weight management / activity modification
- Bracing / orthotics
- Assistive devices
- Intraarticular injections (several options) / nerve blocks
- Disease modifying agents?
- Surgical

Management Options in Osteoarthritis

Lifestyle Modification

- 4 distinct trajectories of knee & hip OA patients over 5 years[1]
  - Severe pain and functional limitations
  - Moderate pain and functional limitations
  - Low pain and functional limitations
  - No significant pain and functional limitations
- Some experience OA as chronic rather than progressive disease
- Highly recommend management of weight, fatigue, physical activity, and psychosocial distress
- PT and lifestyle counseling is still highly underutilized[2]

1. Wieczorek, et al. *Rheumatology* 2020; 0:1-11.
2. Khoja SS, et al. *Arthritis Care & Res* 2020; 72(2): 184-192.

Non-Steroidal Anti-Inflammatory Drugs

- NSAIDs – non-specific
  - –ASA, ibuprofen, naproxen, etc.

- COX-2
  - –Celecoxib
  - –Dosing regimen to establish a blood level to maximize anti-inflammatory effect
  - –May take ~ 2-4 weeks of regular use for effect

NSAID Mechanism of Action

- Inhibition of arachidonic acid metabolism
- Two isoforms of cyclo-oxygenase (COX)
  - COX-1
    - Maintains normal physiology of:
      - GI tract
      - Kidney
      - Platelets
  - COX-2
    - Rapidly induced in the context of inflammation

Adverse Reactions Linked to NSAIDs

- Dyspepsia
- GI ulceration / bleeding
- Renal dysfunction
- Platelet disorders
- Also:
  - –Risk in CAD
  - –Exacerbation of CHF / HTN
  - –Hepatic toxicity
  - –Skin and CNS toxicity (very rare)

Non-Steroidal Anti-Inflammatory Drugs

- Management / monitoring of patients on long-term NSAIDs
  - Periodic laboratory monitoring
    - BUN/Cr
    - LFT
    - CBC
- Long-term use
  - Consider intermittent drug holidays

Glucosamine and Chondroitin

- Both are constituents of cartilage matrix
- Taken orally
- Mechanism of action?
  - ??…. “Eating Hair for Baldness”

- Some good clinical results

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Glucosamine and Chondroitin

- Observed clinical response ~ NSAIDs
- Effect appears delayed and persistent
- May take ~ 6-8 weeks for effect
- Minimal side effects
  - –GI upset
  - –Shellfish allergy (?)
  - –Cost

Glucosamine (G) Efficacy in OA

1. N=252, 4 wk, double-blind, G > placebo

2. N=200, 4 wk, double-blind, G = NSAID after 2 wks

3. N=40 pts, 8 wk, double-blind, G = NSAID @ 2 wks, G > NSAID @ 8 wks

1. Noack. *Osteo & Cart*, 1994
2. Muller-Fassenbender, *Osteo & Cart*, 1994
3. Vaz. *Curr Med Res Opin*, 1982

Chondroitin Sulfate (CS)

- EU study; 800 mg/day of pharmaceutical grade CS n= 160 / celecoxib 200 mg/day n = 173 / placebo n = 172
- Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee OA @ 1,3,6 months[1]

- RCT n = 120; effect of CS 1200 mg/day vs celecoxib 200 mg/day on cartilage volume loss (CVL) over time as measured by quantitative MRI @ baseline and at 12 and 24 months[2]
- CS had a beneficial effect vs celecoxib on CVL in the medial compartment in knee OA patients. CS > celecoxib, induced a lesser increase in synovial thickness in the medial suprapatellar bursa (associated with CVL) [2]

1. Reginster et al. *Ann Rheum Dis* 2017
2. Pelletier et al. *Arthritis Res & Ther* 2016

Topicals

- Creams/ointments/patches
  - –Capsaicin – long term application depletes sP
  - –Ibuprofen gel, diclofenac gel
  - –Ben Gay®, Icy-Hot®, etc.
  - –Many others: Blue-Emu®, Australian Dream®, SalonPas®
  - –Biofreeze®

Non-Pharmacological

Physical Modalities

- Cryotherapy
  - Generally after activity or PT
- Heat (superficial / deep)
  - In the AM
  - Before activity
- Electrical stimulation[1]
  - NMES is most effective (knee OA) / best when combined with strengthening
  - Freq 50-75 Hz / pulse dur 200-400 μsec / 20 min

1. Novak, et al. Am J PM&R 2020

Physical Therapy

- Aerobic conditioning
- Muscle strengthening
  - Forces distributed in limb: bone/joint/cartilage → muscle
  - Quadriceps
    - Chronic inhibition may contribute to the progression of OA
    - Isometric exercises: always safe and well tolerated
- Range of motion
  - Exercise bicycle for knee and hip ROM
  - Low / no resistance if necessary

Physical Therapy

- Aquatic therapy
  - Reduces gravitational load
  - Pain relief
  - Relax stiff muscles
  - Improve ROM
  - Improve aerobic fitness
  - Compression

Weight Management / Activity Modification

- Weight reduction reduces stress on lower extremity joints
  - Hip joint loading with normal walking ~ 2.5 x BW
  - Knee joint loading with normal walking ~ 4.0 x BW

That is just mechanical…… but there's much more

Bergmann, et al. *J Biomech*, 2001
Kuster, et al. *JBJS* Br, 1997

Weight Management / Activity Modification

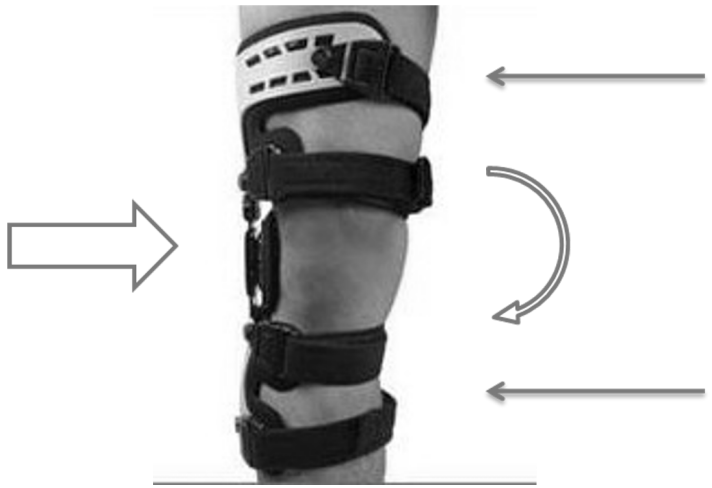
Activity modification

- –Avoid high impact activities
- –Avoid single position for long periods of time

Bracing

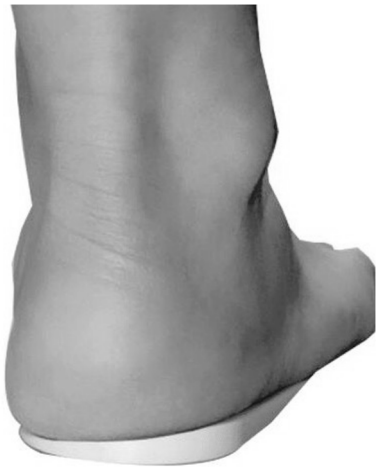
- Braces
  - Neoprene knee sleeve
    - Circumferential compression
  - Unloader braces - for unicompartmental knee OA
    - Valgus
    - Varus

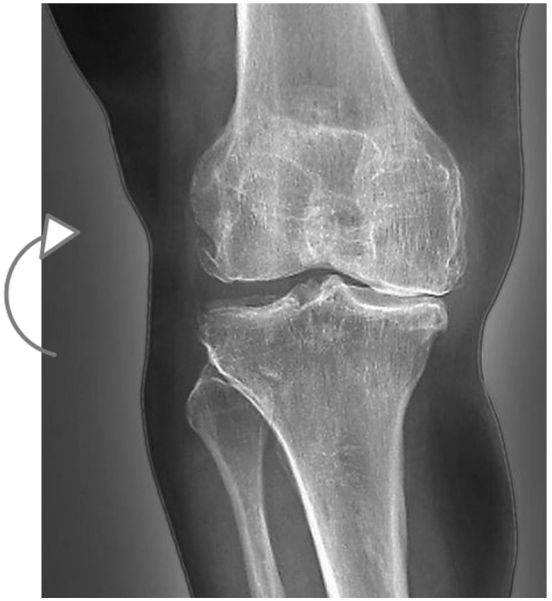
    Patient compliance issues
    - Bulk
    - Discomfort



Orthotics

- Heel wedges
  - Counter effects of knee varus or valgus alignment
  - Lateral for varus
  - Medial for valgus





Reichenbach, et al . *JAMA* 2020; 323(18):1802-1812

Assistive Devices

- Cane
  - Hip unloading →use cane in opposite hand
    - Stabilizes the pelvis during stance on the affected side
    - Supports weak / inhibited Abductor muscles
  - Knee unloading →use cane in either hand
- Walker or crutches
  - Stabilize pelvis as above, and allow for partial or protected weight bearing

A Few Words on Opioids…

- Finally fallen out of favor…
- Systematic review and meta-analysis of 18 RCTs
- N=9,283 with hip and knee OA

- Minimal relief of OA symptoms at each time point; even less for function
- Stronger opioids demonstrated consistently inferior efficacy and overall worse safety compared to weak/intermediate opioids

Osani et al. *Arthritis Care & Res* 2020

Invasive Options

Intraarticular Injections

- Corticosteroids
  - Diagnostic and therapeutic
- Viscosupplementation
  - Therapeutic
- *Regenerative* injection therapies (RIT)
  - Reparative/regenerative?

Steroid Injections

- Helpful in acute flair or to prevent symptoms associated with a specific event (trip, wedding, etc.); *efficacy[1] and even safety[2-4] now questionable*

- Can use repetitively in a degenerated joint
  - Cartilage is already degenerated….
- Maximum frequency →every 3+ months
  - If relief less than this, questionable

1. Saltychev, et al. *Am J Phys Med Rehabil* 2020
2. McAlindon,et. al. *JAMA* 2017 ; 317(19): 1967-1975
3. Wyles CC, et al. *Clin Orthop Relat Res* 2015 ; 473: 1155-1164
4. Kompel, et al. *Radiology* 2019;00: 1-8

Steroid Injections vs PT

- PT vs CSI for Knee OA
- RCT n = 156 @ Brooke AMC; mean age 56 / 48% female
  - 1^{ary} – WOMAC
  - 2^{ary} – other functional tests

- Protocol:
  - Up to 3 injections/year
  - PT – up to 8 sessions in the initial 4-6 wks; 1-3 more at time of 4 and 9 month re-assessments

Results: PT group had less pain and functional disability at 1 year

1. Deyle, et al. NEJM 2020; 382:1420-1429

Viscosupplementation

Hyaluronic acid (HA)

- Major component of synovial fluid
  - Glycosaminoglycan, disaccharide
  - In OA, HA is less viscoelastic and diluted
    - Less lubrication
    - Less mechanical protection

Viscosupplementation

Several formulations

- 4 are derived from rooster combs
  - Supartz: 3-5 inj, 2.5 mL/inj, 1 week apart
  - Hyalgan: 5 inj, 2.0 mL/inj, 1 week apart
  - Synvisc: 3 inj, 2.0 mL/inj, 1 week apart
  - Gel-One: 1 inj, 3.0 mL
- 5 other processes
  - Orthovisc: 4 inj, 2.0 mL/inj, 1 week apart
  - Euflexxa: 3 inj, 2.0 mL/inj, 1 week apart
  - GelSyn-3: 3 inj, 2.0 mL/inj, 1 week apart
  - Durolane: 1 inj, 3 mL
  - Hymovis: 1 inj, 3 mL

- 5 single injections: Synvisc-One, Gel-One, Monovisc, Durolane, Hymovis

Viscosupplementation

- Even in advanced DJD, viscosupplementation may provide some relief
- If effective, may repeat course when symptoms return
  - Space ≥ 6 months apart
- Contraindications
  - Allergy to avian products →don't use animal derived formulations; can use Euflexxa, Orthovisc/Monovisc, Gelsyn-3, Durolane, Hymovis
- Cost:

Cheapest ($250) ----------→ More expensive ($1,200)

Euflexxa – Hyalgan – Gel-One – Supartz – Hymovis – Durolane – Synvisc-1 – GelSyn – Monovisc

Viscosupplementation: Efficacy in Knee OA

Despite FDA approval and longstanding use, efficacy is questioned:

- AAOS: strong recommendation against use[1]
- Ann Int Med: small and clinically irrelevant benefit and an increased risk for serious AEs[2]
- OARSI 2014 – "uncertain"[3]

1. Brown GA. *J Am Acad Orthop Surg* 2013; 21: 577-579
2. Rutjes AWS, et al. *Ann Int Med* 2012; 157(3):180-191
3. McAundon TE, et al. *Cartilage* 2014; 22: 363-368

Viscosupplementation: Efficacy in Knee OA

- Reviewed published clinical trials in US, Europe and Canada
- Conclusions:
  - ✓ viscosupplementation effectively reduces knee pain and improved function caused by OA, particularly 5 to 13 weeks after injection
  - ✓ several viscosupplement products had greater efficacy than CSIs

Bellamy N, et. al. *Cochrane Database Syst Rev*. 2005. Issue 2; No.:CD00532

Emerging Therapies

- Tanezumab – humanized IgG2 monoclonal antibody that binds and inhibits nerve growth factor – effective but concerns about S/Es held release[1]
- Microsphere triamcinolone injectable formulation – true extended release formulation
- Adenosine replacement – animal models[2]

1. Lane NE, et al. *NEJM* 2010
2. Corciulo et al. *Nature Comm* 2016

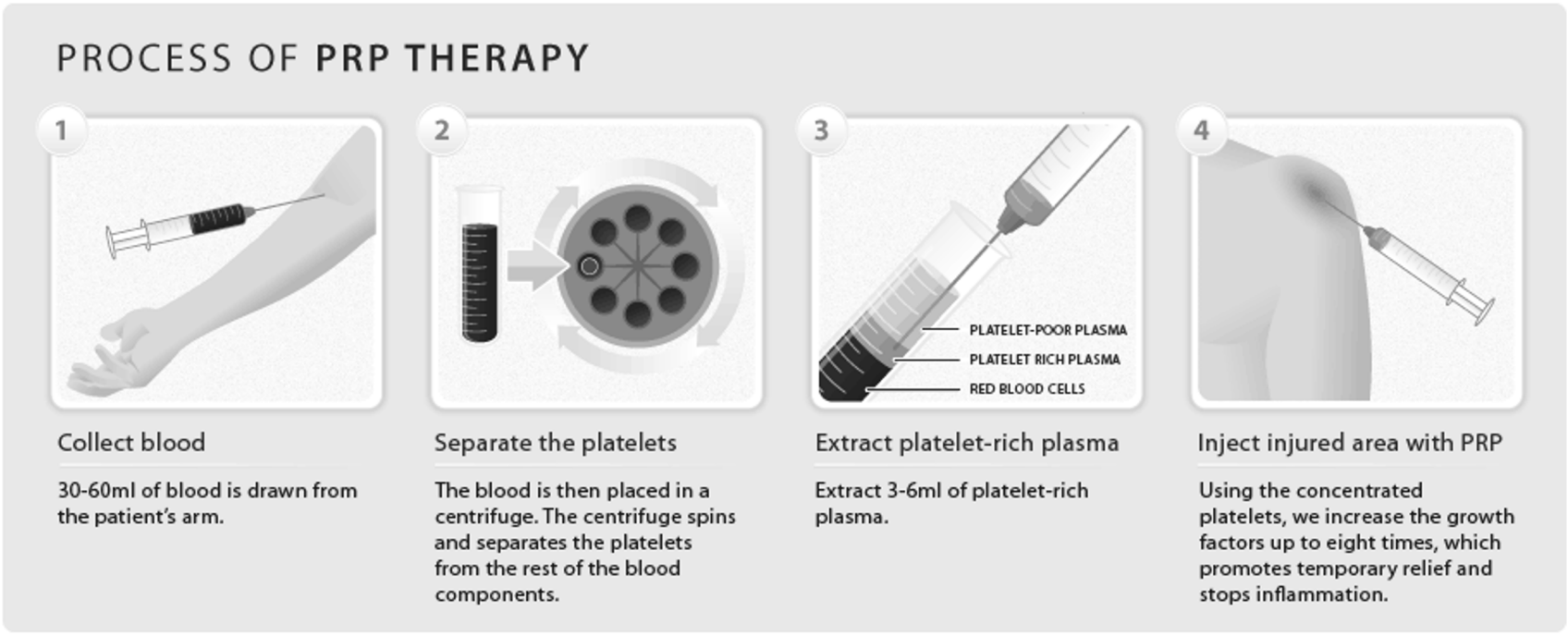
Regenerative Therapies

- Biological alternatives – address underlying inflammation through stimulation of growth factors and suppression of inflammatory cytokines

- PRP
- Amniotic fluid/membrane tissue
- Stem cells

- Prolotherapy

PRP



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PRP – unsolved mysteries…..

Too many variables and unknowns

- –Spin time / method / separation technique
- –Injectate volume
- –Frequency
- –Quality of injectate:
  - Plt concentration
  - WBC rich vs poor
- – Needle gauge (harvest and injection)

….*and lack of evidence for their claims* (tissue regeneration)

Puorcho et al. *Am J Phys Med Rehabil* 2014

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Comparative Therapies

PRP vs viscosupplementation[1,2]

- No significant superiority in 1^{ary} outcomes
- PRP superior in secondary/subjective outcomes
- Tendency towards superiority of PRP in decreasing pro-inflammatory cytokines (IL-1 β and TNF α)
- Improvement in both groups up to 24 wks; then decline to 52 wks F/U
- 10 RCTs were analyzed; PRP showed no superiority HA

1.Cole, et al. *Am J Sports Med* 2016; 45(2) 339-346.
2.Xu, et al. *Am J Phys Med Rehabil* 2017

Amniotic Fluid/Membrane

- Orthoflow® / Amniovisc®
  - Lyophilized amniotic fluid allograft for injection
  - “Baby piss” vs regenerative factors

Stem Cells

- Intra-articular injections of MSCs – pain and functional improvement in a number of pre-clinical and clinical trials
- Recent limited case series evidence – regrowth of cartilage volume and disease modification
- Challenge is still poor engraftment and survival of cells at the site of injury
- Carry some risks

Ethics in Practice

Direct-to-Consumer Advertising of Stem Cell Clinics

Ethical Considerations and Recommendations for the Health-Care Community

Christian A. Pean, MD, MS, Matthew T. Kingery, BA, Eric Strauss, MD, Joseph A. Bosco, MD, and Joanne Halbrecht, MD

Investigation performed at NYU Langone Orthopedic Hospital, New York, NY, and Boulder Regenerative Medicine, Boulder, Colorado

Since the discovery of hematopoietic stem cells in the 1960s and mesenchymal stem cells (MSCs) in 1988[1], there has been an explosion of studies related to potential therapeutic applications of the 2 types of adult stem cells. Hematopoietic stem cell transplantation has been shown to have clear benefits for patients with blood cancers and other blood disorders[2]. However, because of the ability of MSCs to differentiate into various mesodermal tissue types in vitro, MSCs have been studied for a wide range of pathologies involving damaged or otherwise impaired tissue[3,4]. Commonly obtained from bone marrow, adipose tissue, or blood from the umbilical cord, MSCs have shown early but promising results for the treatment of diabetes mellitus, neurological disease, hepatic disease, heart failure, and osteoarthritis[5-10]. As of January 2019, there were 184 studies registered on clinicaltrials.gov related to MSC therapy that were actively recruiting participants.

The proliferation of clinics offering MSC therapy and utilizing direct-to-consumer marketing for the treatment of a myriad of conditions from heart failure to osteoarthritis has prompted several ethical and clinical concerns from the health-care community. At present, the only stem cell products approved by the U.S. Food and Drug Administration (FDA) "consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood" and are "approved for limited use in patients with disorders that affect the body system that is involved in the production of blood."[11]

Many claims for the use of MSC therapy for conditions such as arthritis and tendon disorders lack sound evidence, leading to increasing scrutiny of the efficacy and safety of biologic treatments. There are documented incidents of serious harm to patients after undergoing stem cell treatments in medical tourism destinations and at U.S. clinics using products that violate FDA regulations, including the formation of neoplasms and blindness[12-14]. In the U.S., there are also reports of bacteremia leading to hospitalization in patients receiving injections of umbilical cord blood products[15]. Infections and other consequences are likely underreported by clinics administering stem cells outside of clinical trials[13], and the lack of available longitudinal data means that the potential long-term negative effects of treatment are largely unknown.

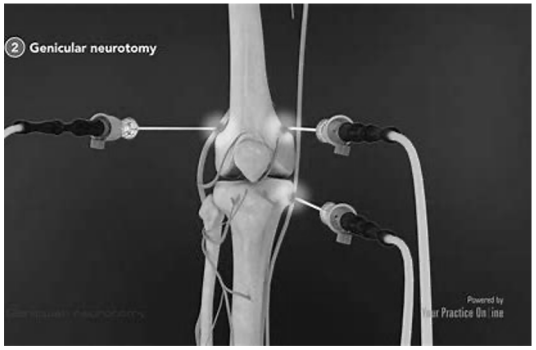
Misleading statements made by MSC therapy clinics abound, and the misconception that clinics operating on false pretenses are predominantly a concern outside the U.S. confounds the reality that hundreds of these clinics exist throughout the country. The potential benefits of MSC therapy for many conditions are not well understood, yet many clinics in the U.S. advertise unsubstantiated benefits of MSC therapy at a cost ranging between $3,000 and $15,000. In response, the Federal Trade Commission has begun investigating these clinics and imposing multimillion-dollar penalties for violating truth in advertising laws[16]. MSC therapy clinics must also comply with FDA regulations pertaining to the use and processing of human cells and tissues intended for use in a human recipient to ensure safety, efficacy, and security[17,18]. The FDA is also investigating MSC therapy clinics and has sought permanent injunctions for the use of products that are not FDA approved and do not comply with good manufacturing practices[19].

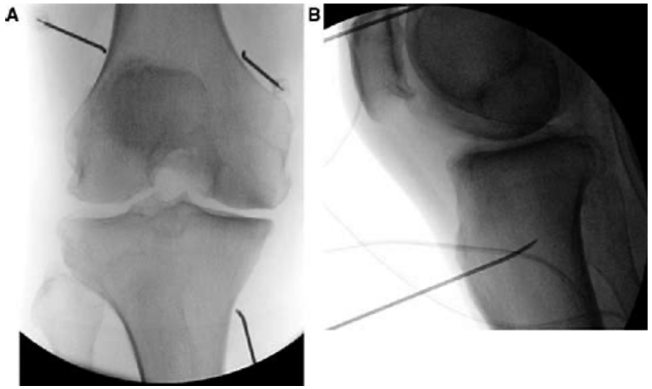
The purpose of this article is to discuss the current state of MSC therapy in the U.S. and address the ethical concerns that direct-to-consumer advertising presents to physicians and other health-care providers.

Disclosure: The authors indicated that no external funding was received for any aspect of this work. The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/F442).

Cool RFA

- CRFA targeting genicular nerves
- CRFA vs Synvisc
- N=177 / crossover @ 6 months in HA group with poor results
- CRFA may provide up to 12 months of relief





Chen et al, *BMC Musculoskeletal Disord* 2020: 21: 363-374

Arthroscopy

- Debridement shown to provide no benefit over conservative management for knees without internal derangements[1,2]
- N = 146; 2-year follow-up of patients without knee OA but with symptoms of a degenerative medial meniscus tear, outcomes after APM were no better than those after placebo surgery

1. Moseley et al. *N Engl J Med* 2002; 347(2): 81-88
2. Kirkley et al. *N Engl J Med* 2008; 359(11): 1097-1107
3. Sihvonen et al. *Ann Rheum Dis* 2017

Total Joint Arthroplasty

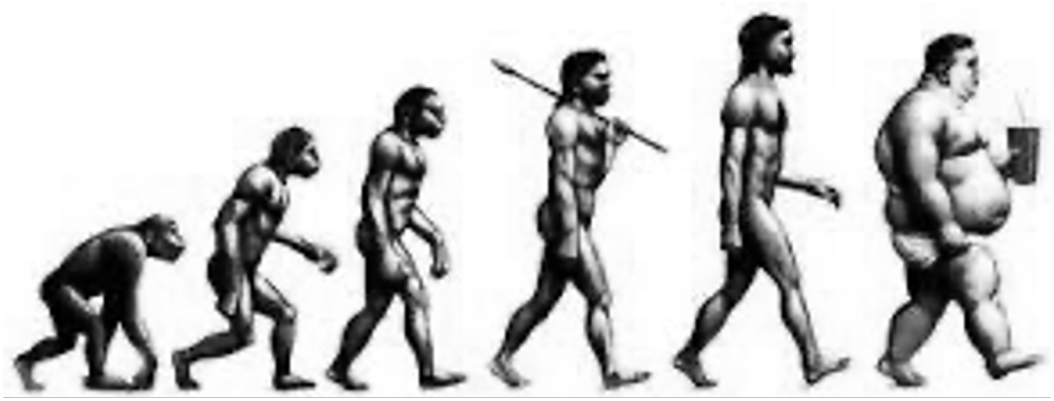
- When conservative management has been maximized and no longer controlling symptoms
- When symptoms are negatively affecting QOL
- Patient is medically/mentally able
- Likely overdone in the US

Total Joint Arthroplasty

- Contraindications: relative & absolute for joint replacement
  - Obesity
  - Substance abuse
  - Open wound/chronic infection
  - Dementia/altered mental status
  - Severe medical issues precluding surgery
  - Chronic opioid use[1]

1. Smith et al. *J Bone Joint Surg* 2017

A few more words on obesity…



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A few more words on obesity…

- Weight loss is essential
- Decreases risks associated with surgery
  - Intraoperative
    - difficulty of the procedure
    - medical and anesthetic complications increase
  - Post-operative
    - Wound complications increase by 20-30% in obese
    - Rehab
      - Utilizing AD more difficult with excess weight
      - Deconditioning due to reduced activity
      - ROM can be limited by subcutaneous tissue

What Works?..... A Comprehensive Approach

- Weight loss positively affect pain outcomes
- Out of all behavioral interventions, research most strongly supports the combination of diet and exercise-based intervention in improving pain outcomes
  - ADAPT (Arthritis, Diet, and Activity Promotion Trial): cohort of overweight adults ≥60 y/o. Diet and exercise group (vs diet only or exercise only) had significant improvement in physical functioning, self-reported pain, mobility and weight

- Messier et al Arthritis Rheum 2004

Wrap-up

Diagnose, reassure & educate

- Target physical factors:
  - Obesity, exercise, braces/ADs
- Oral meds/supplements
- Progress to procedures:
  - CSIs, viscosupplements, RITs
  - Surgical

<<<< Say no to opioids >>>>

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Thanks!

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Ramon.Cuevas-Trisan@va.gov