



## **Osteoarthritis Pain: Past, Present, and Future**

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### **Disclosures**

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- Speakers Bureau/Honoraria: Allergan, Ipsen



## Learning Objectives

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- Review the pathogenesis of OA
- Review the medical literature related to various therapies (conservative and interventional) for the management of pain in OA
- Discuss proven and unproven, commonly accepted management methods for pain in OA focusing on the knee OA model
- Review the evidence and indications for current and emerging therapies for pain management in OA including newer regenerative injection therapy approaches

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## What is OA?

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- 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.....

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## What Happens in OA

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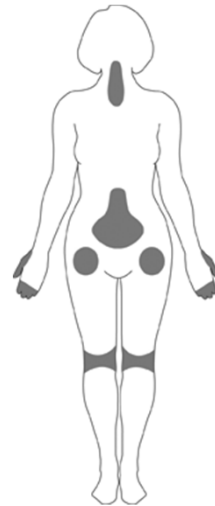
- Articular cartilage loss
- Resulting bone exposure
- Process involves cartilage, bone, and synovium; also soft tissue hardening and ectopic bone formation

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## Prevalence: Who and When?

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- Most common joint disease
- Prevalence increases with age
- Affects nearly 50 million Americans
- Fastest increasing major health condition
- Present in 18%+ of 65-year-old women



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## Pathogenesis of OA: Why?

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<< Multifactorial >>

- Genetics/age
- Inflammatory changes
- Progressive cartilage degeneration
  - Traumatic vs chronic
- Adaptive joint remodeling → osteophytes
- Mechanical compromise of the joint
- Further cartilage degeneration
- Joint loading > joint compensation/healing

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## Pathogenesis of OA: Key Factors

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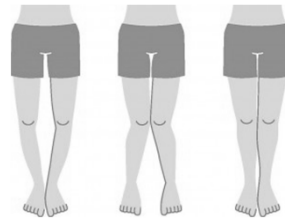
- Genetic influences (perhaps 40-60% of etiology)
  - Gender: Women > Men
  - Family history
- Body weight
  - Hip joint forces: 2.5x body weight with normal walking
  - Knee joint forces: 4x body weight with normal walking
- Trauma/repetitive loading
- Muscle weakness → abductors (buttocks), quads
- Obesity: other metabolic factors

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## Diagnosis of OA: Symptoms/Signs

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- Joint pain
- Stiffness
  - Decreased ROM
- Crepitus
- Bony tenderness/enlargement
- Deformity
  - Affected leg shorter
  - “Bow-legged” or “knock-kneed”



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## Diagnosis of OA: Plain Films

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- Joint space narrowing
- Subchondral sclerosis
- Osteophytes
- Subchondral cyst formation
- Helpful to image both sides for comparison



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## Management Options in Osteoarthritis

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

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## Glucosamine and Chondroitin

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- 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 (cont'd)

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

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## Chondroitin Sulfate (CS)

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- 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 osteoarthritis @ 1,3,6 months<sup>1</sup>
- 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. performed at baseline and at 12 and 24 months<sup>2</sup>
- 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) <sup>2</sup>

<sup>1</sup>Reginster et al. Ann Rheum Dis 2017

<sup>2</sup>Pelletier et al. Arthritis Res & Ther 2016

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## Physical Modalities

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- Cryotherapy
  - Generally after activity or PT
- Heat (superficial / deep)
  - In the AM
  - Before activity
- Electrical stimulation

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## Topical Modalities

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- Creams/ointments/patches
  - Capsaicin: long term application depletes sP
  - Ibuprofen Gel, Diclofenac Gel & Flector Patch®
  - Ben Gay®, Icy-Hot®, etc
  - Many others: Blue-Emu®, Australian Dream®, SalonPas®
  - Biofreeze®

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## Physical Therapy

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- Aerobic conditioning
- Muscle strengthening
  - Forces distributed in the limb → bone, joint/cartilage, muscle
  - Quadriceps
    - Chronic inhibition of quad function 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

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## Physical Therapy (cont'd)

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

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## Weight Management/Activity Modification

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

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## Inflammatory Mediators

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- 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/secretates cytokines (IL-1, TNF $\alpha$ ) and inflammatory mediators (adipocytokines or adipokines)

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## Weight Management/Activity Modification

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

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## Bracing

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- Braces
  - Neoprene knee sleeve
    - Circumferential compression
  
  - Unloader brace for unicompartmental knee OA
    - Valgus
    - Varus
    - Patient compliance issues
      - Bulk
      - Discomfort



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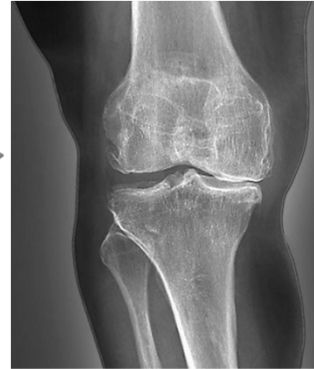
## Orthotics

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### ▪ Orthotics

#### – Heel wedges

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



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## Assistive Devices

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### ▪ Cane

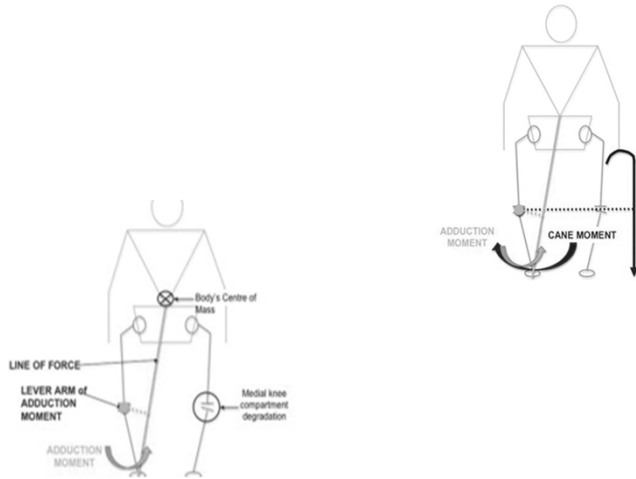
- Hip unloading → use cane in opposite hand
  - Stabilizes the pelvis during stance on the affected side
  - Supports weak/inhibited Abductor muscles
- Knee unloading → use cane in either hand

### ▪ Walker or crutches

- Stabilize pelvis as above, and allow for partial or protected weight bearing

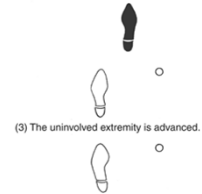
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## The Physics of a Cane



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(4) Cycle is repeated.



(3) The uninvolved extremity is advanced.

(2) The cane and involved extremity are moved forward simultaneously.

(1) Starting position. In this example, the left lower extremity is the involved limb.

Source: Perry, J.D. Gait Analysis: Theory and Practice, 2nd Edition. Copyright © Humana Press 2002. All rights reserved.

## Intraarticular Injections

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

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## Steroid Injections

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- Helpful in acute flare or to prevent symptoms associated with a specific event (trip, etc); efficacy and even safety now questionable
- Can use repetitively in a degenerated joint
  - Cartilage is already degenerated....
- Maximum frequency → every 3+ months
  - If relief less than this, questionable

McAlindon, et. al. JAMA 2017 ; 317(19): 1967-1975  
Wyles CC, et al. Clin Orthop Relat Res 2015 ; 473: 1155-1164

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## Viscosupplementation

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

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## Viscosupplementation (cont'd)

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- 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
- 3 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
- 3 single injections: Synvisc-One, Gel-One, Monovisc

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## Viscosupplementation: Indications

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- 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
- Cost: cheapest (\$250) -----→ more expensive (\$1,200):

Euflexxa – Hyalgan – Gel-One – Supartz - Synvisc-One – GelSyn – Monovisc

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## Viscosupplementation Efficacy in Knee OA

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- Despite approval by the FDA and longstanding use, the efficacy has been questioned:
  - AAOS: strong recommendation against use<sup>1</sup>
  - Ann Int Med: small and clinically irrelevant benefit and an increased risk for serious AEs<sup>2</sup>
  - OARSI 2014 – “uncertain”<sup>3</sup>

<sup>1</sup>Brown GA. J Am Acad Orthop Surg 2013; 21: 577-579

<sup>2</sup>Rutjes AWS, et al. Ann Int Med 2012; 157(3):180-191

<sup>3</sup>McAundon TE, et al. Cartilage 2014; 22: 363-368



## Viscosupplementation Efficacy in Knee OA (cont'd)

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- Reviewed published clinical trials conducted in the 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, including Synvisc, had greater efficacy than CSIs

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





## Future Therapies?

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- Tanezumab: humanized IgG2 monoclonal antibody that binds and inhibits nerve growth factor (now in Phase III): very effective but concerns about S/E<sup>1</sup>
- Microsphere triamcinolone injectable formulation: true extended release formulation under phase III [Zilretta (FXoo6)]
- Adenosine replacement: animal models <sup>2</sup>

<sup>1</sup>Lane NE, et al. NEJM 2010

<sup>2</sup>Corciulo et al. Nature Comm 2016



## The State of Affairs

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*“The need to find new drugs to treat OA is critical. We really don’t have anything that slows its course and most people with severe disease end up dependent on narcotic analgesics while waiting to have a joint replaced.”*

Nancy E. Lane, MD  
PI, Tanezumab study



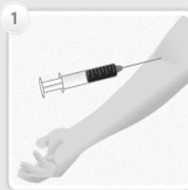
## Regenerative Therapies

- PRP
- Amniotic fluid/membrane tissue
- Stem cells
- Biological alternatives address underlying inflammation through stimulation of growth factors and suppression of inflammatory cytokines
- Prolotherapy

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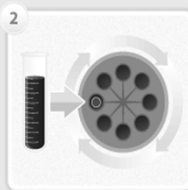
## PRP

### PROCESS OF PRP THERAPY



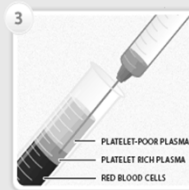
**1** Collect blood

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



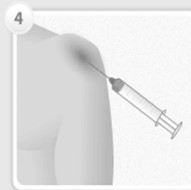
**2** Separate the platelets

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



**3** Extract platelet-rich plasma

Extract 3-6ml of platelet-rich plasma.



**4** 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.

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## PRP—Unsolved Mysteries

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- 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

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- PRP vs viscosupplementation<sup>1,2</sup>
- No significant superiority in 1ary outcomes
- PRP superior in secondary/subjective outcomes
- Tendency towards superiority of PRP in decreasing pro-inflammatory cytokines (IL-1  $\beta$  and TNF  $\alpha$ )
- Improvement in both groups up to 24 wks; then decline to 52 wks F/U
- 10 RCT's were analyzed; PRP showed no superiority HA

<sup>1</sup>Cole, et al. Am J Sports Med 2016; 45(2) 339-346.

<sup>2</sup>Xu, et al. Am J Phys Med Rehabil 2017

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## Amniotic Fluid

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- OrthoFlo/AmnioVisc
- Lyophilized amniotic fluid allograft for injection
- “Baby piss” vs regenerative factors

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## Stem Cells

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- 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

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## Arthroscopy

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

<sup>1</sup>Moseley et al. N Engl J Med 2002; 347(2): 81-88

<sup>2</sup>Kirkley et al. N Engl J Med 2008; 359(11): 1097-1107

<sup>3</sup>Sihvonen et al. Ann Rheum Dis 2017

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## Total Joint Arthroplasty: When

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- 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

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## Total Joint Arthroplasty

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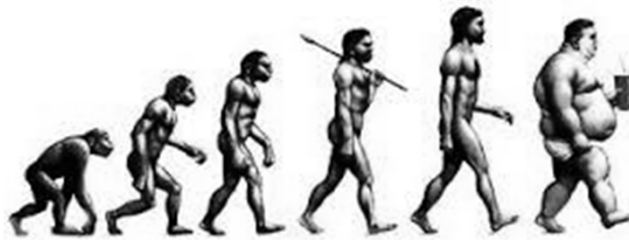
- Contraindications: relative & absolute for joint replacement
  - Obesity
  - Substance abuse
  - Open wound/chronic infection
  - Dementia/altered mental status
  - Severe medical issues precluding surgery
  - Chronic opioid use<sup>1</sup>

<sup>1</sup>Smith et al. J Bone Joint Surg 2017

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## A few more words on obesity...

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## Obesity

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- Weight loss is essential
- Decreases risks associated with surgery
  - Intraoperative
    - Difficulty of the procedure
    - Medical and anesthetic complications increase
  - Postoperative
    - 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

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## Obesity (cont'd)

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- Long term risk and failure of components
  - Joint replacements are mechanical entities
  - Wear and failure due to stress
  - Excess body weight causes increased joint stress

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## Wrap-up

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- Diagnose, reassure, & educate
- Target physical factors:
  - Obesity, exercise, braces/ADs
- Oral meds/supplements
- Progress to procedures:
  - CSIs, viscosupplements, RITs
  - Surgical
  - <<<< Try to avoid opioids >>>>

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# Thanks!

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