Prevention and Treatment of Knee Osteoarthritis

Bob Kinnamon, MD
Associate Professor
Dept of Family Medicine
University of Michigan Medical School
Neither I, Robert Kiningham, nor any family member(s), have any relevant financial relationship to be discussed, directly or indirectly, referred to, or illustrated with or without recognition, within the presentation.
Diagnosis of Knee Osteoarthritis

- Clinical diagnosis, but x-rays usually the “gold standard” for research
  - Standing AP and lateral views, notch, and patella (Merchant) view
- EULAR: Confident diagnosis of knee OA can be made without radiographic confirmation (even with normal x-rays) in adults > 40 and all of the following:
  - Usage-related knee pain
  - Short-lived morning stiffness
  - Functional limitation
  - ≥ 1 typical sign on exam (crepitus, restricted movement, bony enlargement)
Knee OA Diagnostic Imaging
Sensitivity and Specificity

- Up to 50% of patients with radiographic knee OA defined as presence of bony enlargements (osteophytes) and loss of cartilage (joint space narrowing) do not experience significant knee pain.
- Up to 50% of patients with knee pain suggestive of knee OA do not have radiographic features of knee OA.
- 89% of asymptomatic knees without radiographic signs of OA had abnormalities on MRI thought to be associated with knee OA.

Osteoarthritis is characterized by the progressive focal loss of breakdown of hyaline cartilage and underlying bone within a joint, as well as bony overgrowth.

Cartilage loss is not uniform.
Hyaline articular cartilage loss is the signature pathologic feature of OA, but all structures are affected.

Bone remodeling and attrition occur relatively early in the disease process.

Fibrocartilage degeneration, including the menisci in the knee and labrum in the hip, is characteristic, and causes changes in the load-distributing function, inducing more injury to adjacent hyaline cartilage.

Chondro-osteophytes form both at the joint margin and centrally at areas where cartilage has eroded.

Pathology of Osteoarthritis

A Disease of the Entire Joint

- The synovium develops lining cell hyperplasia and can become infiltrated with sub-synovial inflammatory cells.
- Activated synovium secretes excessive synovial fluid, leading to capsular swelling.
- Capsular swelling (through a spinal reflex) inhibits complete activation of muscles bridging the joint, contributing to muscle weakness and atrophy.
- The synovial inflammation affects the afferent processing of nociceptive signals from the joint and surrounding tissues.
Knee Pathology in OA

Marked Peripatellar Synovitis (white arrows)

Extensive bone marrow lesion (small black arrows)/bone cysts (bright white structures at end of long black arrow)

Felson DT. Arthritis Research & Therapy 2009;11:203-214
Osteoarthritis is caused by increased forces across a local area of a joint by:

- Abnormal anatomy (congenital or acquired) leads to increased focal stress with the overall load across the joint being normal, or
- Excess overall load either acutely (sports injury) or chronically (obesity), or
- Combination of anatomy and excess load

A Conceptual Model of Knee OA

Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2015.135
Knee Osteoarthritis Prevalence

- Estimated to affect over 19% of American adults 45 years of age and older
- Affects over 2 million Americans under age 45
- Symptomatic RKOA present in 20% of individuals > 65 years of age.
- Annual incidence rate of 1% in woman aged 70-89.

Knee Osteoarthritis Prevalence
Historical Perspective

Wallace IJ, et al. PNAS 2017;114: 9332-9936
Knee Osteoarthritis
“Mismatch Disease”

“Mismatch disease”: A disease that is more prevalent or severe because our bodies are inadequately adapted to modern environments

Other examples
- Hypertension
- Atherosclerotic heart disease
- Type 2 diabetes mellitus and metabolic syndrome
- Upper (and lower) back pain
Knee Osteoarthritis
Not a Benign Disease

- Most common cause of activity limitations in USA
- Knee and hip OA associated with reduced life expectancy, with walking disability the main risk factor
- Knee OA also associated with premature death from CVD
- Radiographic hip and knee OA associated with 16-25% increase in risk of developing type 2 DM, even when controlling for other risk factors
  - About 40% of this relationship attributable to limitations in walking

The Osteoarthritis Continuum

Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2015.135
Prevention of Knee Osteoarthritis

- Knee OA is due to loading-induced damage to the joint tissues
  - Due to abnormal loads
  - Structural weakness/abnormalities
- Primary risk factors
  - Obesity
  - H/o trauma
  - Impaired muscle function
Knee Osteoarthritis and Obesity

- Obesity precedes the onset of RKOA and symptomatic knee OA.
- Lifetime risk of symptomatic RKOA 30.3% greater in obese individuals compared to individuals with normal (less than 25) BMI

Weight Gain and Risk of Knee OA

Knee Osteoarthritis and Obesity
Mechanism

- Increased mechanical load, often asymmetric
- Decreased physical activity
- Systemic inflammatory elevation due to cytokines produced by adipose tissue
  - Fat mass, not lean mass or total body mass, associated with development of knee OA
Weight loss as Primary Prevention of Knee Osteoarthritis

- Framingham study of 796 women
- A weight loss of 5.1 kg reduced the risk of developing symptomatic RKOA over 10 years by 46% compared to women without weight loss.

Knee Injury and Development of Knee Osteoarthritis

- 50% of individuals who sustain an ACL injury develop RKOA in 10-15 years regardless of whether or not they have surgery or the type of surgery.
- Adolescents who sustain a traumatic knee injury in sports have an increased risk of symptomatic knee pain and impaired physical function, and are 3.75 times more likely to be obese/overweight 3-10 years later compared to controls matched for age, sex, and sport.

Whittaker et al. Osteoarthritis Cartilage 2015;23:1122-1129
Meniscal Injury and Osteoarthritis

- Meniscal tears markedly increase the risk of OA by increasing focal loading or stress across adjacent areas of cartilage, leading to cartilage breakdown.
- Surgery certainly does not decrease the risk of OA, and may increase it.
- Felson: “Meniscal tears may account for as much as 40-50% of human knee OA”.
- Englund: “A meniscal tear can lead to knee OA, but knee OA can also lead to a meniscal tear”.

Meniscal Surgery and Osteoarthritis

- 123 patients s/p meniscal surgery for torn meniscus compared to 68 sex-and age-matched controls followed for 21 years.
- 48% of meniscal surgery patients and 7% of controls had radiographically significant OA. RR of 14.0.
- Independent of gender, type of meniscal tear, localization to compartment, activity level, BMI.
- Four times as many subjects in the surgery group reported knee pain during the previous week as in the control group (68% v. 17%) at 21 year follow-up.

Meniscal Surgery and Osteoarthritis

- 155 patients (age 54±12 yrs) with intact ACL who had undergone subtotal or partial meniscectomy an avg of 16±1 yrs earlier compared to 68 controls matched for age, sex, and BMI.

- Patients who had meniscus surgery were 3.4 times more likely to have symptomatic ROA compared to matched controls regardless of the type of resection (subtotal or partial).

- Patients who underwent surgery for a degenerative meniscal tear (as opposed to a traumatic tear) were 7 times more likely to have symptomatic ROA.

- Patients with a traumatic meniscal tear were 2.7 times as likely to have symptomatic ROA.

Meniscal Surgery and Osteoarthritis

Meniscal Surgery and Osteoarthritis

Primary and Secondary Prevention of Knee Injury Associated Osteoarthritis

A meta-analysis combining data from 27,000 individuals found that neuromuscular and proprioceptive training programs were successful in preventing approximately 50% of expected ACL injuries.

Neuromuscular training has been shown to be more effective than strength training alone on patient reported pain and function, but not objective measures, at 6 months after ACL reconstructive surgery.

Knee Osteoarthritis Neuromuscular Functioning

- Measurements of isolated strength do not totally represent lower extremity functioning that may be critical in the development and progression of knee OA.

- Core strength, including pelvic and hip stabilizers, appear to play an important role in knee health.
Knee Osteoarthritis and Muscle Function

- In subjects with mild/mod knee OA, knee extensor strength associated with decreased cartilage loss at the lateral compartment of the patello-femoral joint but not at the tibio-femoral joint.
  
  Arthritis & Rheumatism 2009;60:189-198

- In 2078 subjects (mean age 62) without baseline symptomatic knee OA, highest tertile of knee extensor strength developed less incident symptomatic whole knee OA (odds ratio 0.5-0.6).
  
  Arthritis & Rheumatism 2009;61:1210-17
Knee Osteoarthritis
Strength and Instability

Amsterdam cohort: 283 patients with knee OA by ACR criteria referred to rehab center.

- 64% women, avg BMI 29, age 61± 7 yrs
- 67% reported knee instability
- Only lower extremity muscle strength and knee pain differed between instability and “non-instability” groups

Knee Osteoarthritis
Goals of Treatment

- Reduce pain
- Stop, or at least reduce, progression of the cartilage and bone break-down
- Increase function, including balance and endurance by improving neuromuscular control
Where is the Pain Coming From?

Articular cartilage is both aneural and avascular
Subchondral bone
  ► Bone marrow lesions on MRI are strongly correlated with pain
Synovitis and joint effusion
  ► Synovium has sensory nerve endings which can be irritated by osteophytes and release of prostaglandins, leukotrienes, proteinases, neuropeptides, cytokines
  ► Synovitis and effusion correlate with pain and other clinical signs/symptoms
Where is the Pain Coming From?

- **Meniscus**
  - An intact and functioning meniscus is important to the preservation of joint integrity and prevention of further joint damage
  - Minimal role in symptom genesis
  - Degenerative meniscal tears with horizontal cleavages, flap, complex tears, meniscal maceration or destruction are associated with older age and are almost universal in persons with OA
  - Subjects mean age 65 (Bhattacharyya, et al 2003)
    - Symptomatic: 91% MT
    - Asymptomatic: 67% MT


Where is the Pain Coming From?

- Peri-articular muscles
  - Contribute to the stability of OA
  - Can spasm and be sore from supporting the unstable OA joint
  - Subject to effects of inflammatory agents
# Knee OA Structure Pain Correlation Studies

Table I. OA structure pain correlation studies

<table>
<thead>
<tr>
<th>Structural feature</th>
<th>Number of supportive studies (references)</th>
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<tr>
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<td>Supportive of association</td>
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<td>Bone marrow lesions</td>
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<tr>
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<td>Effusion</td>
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<tr>
<td>Osteophytes</td>
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<tr>
<td>Peri-articular lesions</td>
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Compartment Patterns of Knee OA

- Study of 745 people with knee pain
  - Mean age 65.2 years, 55% women, mean BMI 29.6

- X-ray findings
  - No radiographic OA: 32%
  - Isolated patellofemoral OA: 24%
  - Isolated tibiofemoral OA: 4%
  - Combined PF and TF OA: 40%

Compartment Patterns of Knee OA

Compartment Patterns of Knee OA

- Moderate to severe patellofemoral OA
  - h/o dramatic swelling
  - Valgus malalignment
  - Markedly reduced quadriceps strength
  - Pain on PF joint compression
- Tibio-femoral joint involvement
  - Previous injury
  - Varus malalignment
  - Bony enlargement
  - Reduced knee flexion range of motion
  - Fixed flexion deformity
- Age and BMI are strong indicators of knee OA, but equally important to PF and TF joint disease subsets

Knee Osteoarthritis

- Knees with OA are stiff but unstable, with poor ligamentous support and neuromuscular control
  - 63% report knee instability with ADLs, 44% report that instability effects their ability to function
Current Treatments of Knee OA

- Exercise
- Weight loss
- Braces
- Medications
- Supplements
- Injections
- Acupuncture
- Surgery
Knee Osteoarthritis
ACSM Effects of Physical Activity in Knee and Hip OA

- Physical activity reduces pain and improves physical function and HRQoL for persons with lower limb OA
  - Regardless of mode of exercise (aquatic or land)
  - Muscle strengthening exercise, aerobic exercise, and Tai Chi all effective
- Following cessation of intervention, the beneficial effects of PA lasted for up to 6 months for pain and beyond 6 months for physical function.

Weight Loss
Grade A Recommendation

- One pound of weight loss above the knee equals a decrease in 4-5 times less force on the knee when weight-bearing
- Reduces pain and improves function
- Appears to have additive effect with exercise
Weight Loss for Treatment of Knee OA

- Meta-analysis of RCT that dealt with the effectiveness of weight loss to decrease symptoms of knee OA
- Only 4 RCTs met criteria for inclusion
- Weight loss had a significant but relatively small impact in decreasing pain and more of an impact on decreasing physical disability
- Authors concluded that weight loss of at least 5% within a 20-week period (or approximately 0.25% per week) was necessary to significantly decrease pain and physical disability

Knee Braces

- Cochrane review found 2 studies with “limited evidence” that braces provided additional benefit to medical treatment alone
Summary of Medications Treatment of Knee Osteoarthritis

- NSAIDs improve pain better than acetaminophen but more side effects (SOR A)
- Tramadol has some benefit with less risk than stronger opiates (SOR A)
- Modest benefit at best with glucosamine sulfate, no benefit with chondroitin (SOR A)
Summary of Medications Treatment of Knee Osteoarthritis

- Intra-articular injections
  - Corticosteroids may provide pain relief for up to 4 weeks
  - HA provides greater benefit from 5-13 wks
  - PRP shows greater pain reduction and improved function at 6 months but high risk of bias in trials
  - None have shown long-term functional improvement
  - Most trials show high risk of bias
Acupuncture

- Cochrane: acupuncture may improve pain and function in knee OA
- No significant difference when compared to supervised or home exercise
- No additional benefit when combined with exercise
Arthroscopy with saline lavage, debridement of cartilage, resection of proliferative synovium, excision and removal of loose articular fragments have been advocated and performed for several years for knee OA.

Small uncontrolled case series reported small improvements in pain and function.

Large controlled trials have found no benefit of arthroscopy in the treatment of knee OA.

AAOS assigns level 1 evidence and Grade A recommendation to the statement: “We recommend against performing arthroscopy with debridement or lavage in patients with the primary diagnosis of symptomatic OA of the knee”

http://www.aaos.org/research/guidelines/GuidelineOAKnee.asp
A Randomized Trial of Arthroscopic Surgery for Osteoarthritis of the Knee

- Subjects: over 18 (avg 59 yrs), knee pain with grade 2 or higher K-L OA on x-ray
  - Excluded: previous arthroscopic surgery, “bucket handle” meniscal tear on exam or MRI, OA in 2 compartments on x-ray and over 60 yrs
- Randomized to “optimal PT and medical therapy” alone or “optimal PT and medical therapy” plus arthroscopic knee surgery
- Surgery: knee irrigation, debridement, excision of degenerative meniscal tear, fragments of articular cartilage, chondral flaps and osteophytes

A Randomized Trial of Arthroscopic Surgery for Osteoarthritis of the Knee

- Primary outcome: WOMAC at 2 years
  - Subscales for pain, stiffness, and physical function
  - Patients with moderate to severe knee OA typically have scores of about 1000 (scores range 0 to 2400)
- 92 subjects randomized to surgery, 86 no surgery
- Average duration of symptoms: 47 months in surgery group, 40 months in control group
- WOMAC at baseline: Surgery 1187, control 1043
- Surgery: 97% debridement of articular cartilage, 81% debridement or partial resection of meniscus

A Randomized Trial of Arthroscopic Surgery for Osteoarthritis of the Knee

- WOMAC at 24 months
  - Surgery 874±585; Control 897±583, not significant when adjusted for baseline score and radiographic grade of disease severity.

- No significant difference in Physical Component Summary score (quality of life) between groups at 24 months

Incidental Meniscal Findings on Knee MRI in Middle-Aged and Elderly Persons

- 991 random subjects over age 50 (avg 62 ± 8.6 yrs) with no h/o knee replacement, RA, dementia or terminal cancer
- 29% had knee pain or stiffness in the previous month
- 18% had x-ray evidence of tibiofemoral OA (K-L grade 2 or higher)
- 10% had symptomatic tibiofemoral OA
- MRI of right knee performed on all subjects

Incidental Meniscal Findings on Knee MRI in Middle-Aged and Elderly Persons

- 35% had meniscal pathology - tear or destruction
  - 31% had a meniscal tear in isolation or in combination with meniscal destruction

- Prevalence of meniscal damage increased with increasing age in both sexes
  - Ages 50-59: men 32%, women 19%
  - Ages 70-90: men 56%, women 51%

- Women with meniscal pathology had higher BMIs than women without. No difference in men

Incidental Meniscal Findings on Knee MRI in Middle-Aged and Elderly Persons

- Among subjects with knee OA on x-ray
  - 63% of subjects with knee pain had meniscal pathology
  - 60% of subjects without knee pain had meniscal pathology

- Among subjects without knee OA on x-ray
  - 32% of subjects with knee pain had meniscal pathology
  - 23% of subjects without knee pain had meniscal pathology

- Majority of meniscal tears on MRI were in subjects without knee pain (180 of 297 = 61%)


Total knee replacement associated with reduced pain and improved function, including elderly and patients < 55 years old.
Total Knee Arthroplasty

- Complication rate: 17%
  - Clinically significant venous thrombus: 8%
  - Fatal pulmonary embolism: 0.05-0.2%
  - Infection: 1.0-1.8%

- Patients who are more physically fit and lower BMI have fewer surgery complications and improved functional outcomes
High-intensity post surgical rehab programs that emphasize early weight-bearing that progresses to machine-based exercise and eccentric muscle contractions as soon as tolerated have proven to be effective in regaining function and reducing pain.
Summary of Treatment of Knee Osteoarthritis

- Treatment of knee OA is based on stabilizing an unstable joint and preventing further cartilage degeneration
- Pain is probably coming from bone and supporting structures: synovium, muscle/tendons
- Exercise and weight reduction are the mainstays of treatment (SOR A)
  - Only exercise has been shown to improve cartilage structure
Summary

- No benefit from arthroscopy (SOR A)
- Do not look for or treat a degenerative meniscus!
Medications
Acetaminophen

- Most major organizations recommend acetaminophen (≤4 g/day) as first line therapy for symptomatic knee OA.

- Cochrane review
  - Acetaminophen more effective than placebo but effect may be small
  - Inferior to NSAIDs in pain reduction, global assessment, and improvement in functional status
Medications

NSAIDs

- NSAIDs slightly improve pain in the short term (SOR A) but no evidence of long-term efficacy (SOR B)
  - BMJ 2004;329(7478):1317
- Should be used for acute relief of pain and improvement of function for as short amount of time as possible. SOR A
- Benefits of use should be weighed against potential adverse effects. SOR A
Medications

NSAIDs

- All oral NSAIDs and COX-2 inhibitors have similar efficacy. SOR A
- All NSAIDs and CoX-2 inhibitors can cause or aggravate hypertension, heart failure, edema, and impaired renal function. SOR A
- Naprosyn has been less associated with increased risk of MI and CHF than other NSAIDs and COX-2 inhibitors. SOR A
Topical NSAIDs

- Meta analysis of 13 RCT
- Improved pain, function, and ROM vs. placebo for 3-4 weeks
- Less effective than oral NSAIDs for pain relief, but no difference in overall clinical response
Tramadol

- Cochrane review of 11 RCT
- Conclusion: decreases pain intensity and produces symptom relief and improves function, but these benefits are small. SOR A
- Best used for refractory pain
Chondroitin

Meta-analysis and Cochrane review indicate no benefit in treatment of knee OA

Combination of chondroitin and glucosamine sulfate not more effective than placebo in improving pain in knee OA
Intra-articular Corticosteroid Injections

- Associated with short-term pain relief (up to 3-4 weeks) greater than placebo
- No evidence for functional improvement, and no clinically important difference in pain or function beyond 4 weeks
- Few side effects
  - Can raise blood glucose levels in diabetics
  - Local reactions: postinjection inflammatory reaction, skin atrophy, joint infection
Viscosupplementation

- Synvisc, Supartz, Orthovisc, Hyalgan, Euflexa
- Cochrane
  - Hyaluronic acid more effective in improving pain and ROM than corticosteroids @ 5-13 wks (no difference at 1-4 wks)
  - Comparable efficacy to NSAIDs with fewer side effects
- Other meta-analyses and systematic reviews of the literature report mixed results
- Few side effects
Platelet-Rich Plasma (PRP)

- Intra-articular injection of PRP: 4 recent systematic reviews/meta-analysis and a meta-analysis of the meta-analyses
- Lots of studies, but “all trials revealed a high risk of bias”
- Comparisons difficult: different platelet and leukocyte concentrations, different injection protocols, different follow-up periods