Planning knee OA prevention studies in obese populations
Lessons from the Multicenter Osteoarthritis Study (MOST) and Osteoarthritic Initiative (OAI)

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Disclosures

- NONE
Why prevention in Knee OA?

- Like some other common degenerative diseases of aging, such as Alzheimer’s, we are not able to successfully treat Knee OA.
  - Unlike Alzheimer’s, at least one very potent and modifiable risk factor is known for knee OA: OBESITY.
  - Like Alzheimer’s, focusing on detection of early abnormalities that lead to disease may afford additional opportunities and new approaches to prevention and treatment.
1° and 2° prevention of Knee OA in obese populations

Goal: reduce disease incidence

1°: Focus on people at high risk with modifiable risk factor(s)
   - modify ≥1 risk factor

Hybrid: Focus on people at high risk with risk factors and early abnormalities
   - modify risk factors and/or
   - treat early abnormalities

2°: Focus on people at high risk with (treatable!) early (preradiographic) abnormalities causal in disease development
   - treat ≥1 abnormality

Interventions in obese

- weight loss
- ± ? (e.g. strengthening?)
- weight loss, ± ?
- Tx malalignment? meniscal degeneration? inflammation?

Detect and treat
- malalignment?
- meniscal degeneration?
- inflammation?
- ?
Why focus on people at high risk for disease?

- Increased number of endpoints, ability to detect effect of intervention, ↓ sample size
- Those most likely to be the focus of, and interested in, prevention and Tx
- Interventions more cost effective in high risk; ↓ NNT

Total sample size needed for an intervention trial to detect a reduction in knee OA incidence

- 25% reduction in incidence
- alpha=0.08, Power=80%
- equal group size
Using cohort study data to model a prevention trial in obese individuals

Useful data

- Natural history:
  - rates of disease development, incidence
  - initiating events → sequence of development → outcomes

- Modifiable risk factors that predict disease onset

- Biomarkers that predict disease onset

- Model subject selection for prevention trial using risk factors, biomarkers and outcomes
  - Example: Prevention trial in obese women with incident radiographic knee OA as the outcome
Two Knee OA cohort studies: OAI, MOST

Similarities

- NIH-funded community-based cohorts ages 45/50-79
- Apply MRI to population epidemiology of knee OA
- 7-8 yr follow-up for X-ray, MRI, clinical outcomes
- Many common exposure and outcome measures
- Spectrum of disease in the population
  - People with knee OA to study disease progression
  - People at high risk for knee OA to study disease onset
- Recruitment method would work in prevention trial: mass mailing and phone screen for risk factors
- Publicly available data sets
OAI, MOST: subjects

With Knee OA at baseline

- X-ray knee OA: K-L grade ≥ 2**
  - Subset with symptomatic knee OA (Sx KOA):
    - K-L ≥2 and frequent knee pain (pain most days of past month)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>OAI (4,796)</th>
<th>MOST (3,026)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee OA (K-L ≥2)</td>
<td>57%</td>
<td>53%</td>
</tr>
<tr>
<td>Sx Knee OA (frequent pain and K-L ≥2)</td>
<td>29%</td>
<td>33%</td>
</tr>
<tr>
<td>X-ray knee OA only (No Sx OA)</td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td>Unilateral knee OA (K-L ≥2 in one knee)</td>
<td>25%</td>
<td>24%</td>
</tr>
</tbody>
</table>

**Standard definition of X-ray knee OA
- Marginal osteophytes and possible JSN
- Insensitive to pathology on MRI
OAI, MOST: subjects

- At risk for radiographic knee OA at baseline

<table>
<thead>
<tr>
<th>Eligibility risk factors in those without knee OA</th>
<th>OAI</th>
<th>MOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 45/50</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Knee pain on most days of month</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hx Knee injury (difficulty walking)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Family Hx knee replacement</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Hand OA (exam)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Frequent knee bending</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Infrequent knee pain</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
Baseline characteristics of “at risk” cohorts

<table>
<thead>
<tr>
<th>Pts with NO K-L ≥2 knee OA at BL</th>
<th>OAI - 43% (2,051)</th>
<th>MOST - 48% (1,419)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 65-79</td>
<td>30%</td>
<td>33%</td>
</tr>
<tr>
<td>Female</td>
<td>58%</td>
<td>58%</td>
</tr>
<tr>
<td>African-American</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>**BMI ≥30 * (90&lt;sup&gt;th&lt;/sup&gt; %tile BMI in obese) ***</td>
<td>27%</td>
<td>39%</td>
</tr>
<tr>
<td>Frequent knee pain</td>
<td>33%</td>
<td>39%</td>
</tr>
<tr>
<td>Hx knee injury (difficulty walk ≥2 days)</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td><em>Family Hx of TKR</em></td>
<td>14%</td>
<td>--</td>
</tr>
<tr>
<td><em>Hand OA (exam)</em></td>
<td>40%</td>
<td>33%</td>
</tr>
<tr>
<td>Frequent knee bending</td>
<td>72%</td>
<td>--</td>
</tr>
<tr>
<td>Infrequent knee pain (not most days)</td>
<td>43%</td>
<td>29%</td>
</tr>
</tbody>
</table>

*OAI had upper weight/ BMI limits for MRI
Cumulative incidence of radiographic knee OA in the “at risk” cohorts

- **Subjects**: Bilateral KL 0-1, with one or more eligibility risk factors, ages 50-79
- **Incident radiographic knee OA**
  - K-L \( \geq 2 \) during follow-up, either knee
    - OAI: 4 years
    - MOST: 5 years

<table>
<thead>
<tr>
<th></th>
<th>Cumulative incidence % [annual %]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OAI (1,930)</td>
</tr>
<tr>
<td><strong>Men, 50-79</strong></td>
<td>8.9 [2.3]</td>
</tr>
<tr>
<td>50-64</td>
<td>8.6 [2.2]</td>
</tr>
<tr>
<td>65-79</td>
<td>9.3 [2.3]</td>
</tr>
<tr>
<td><strong>Women, 50-79</strong></td>
<td>12.1 [3.0]</td>
</tr>
<tr>
<td>50-64</td>
<td>12.6 [3.2]</td>
</tr>
</tbody>
</table>
Studies with data for incident K-L ≥ 2

- **Framingham** (Felson, 1997): 598, M(217), W(381); mean age 70; F-Up 8 yrs; 43% LFU
  - Men: 1.3%/yr
  - Women: 2.2%/yr

<table>
<thead>
<tr>
<th></th>
<th>OAI</th>
<th>MOST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, 50-79</td>
<td>2.3%/yr</td>
<td>4.4%/yr</td>
</tr>
<tr>
<td>Women, 50-79</td>
<td>3.0%/yr</td>
<td>5.7%/yr</td>
</tr>
</tbody>
</table>

- **Bristol** (Cooper, 2000): 354 M+W; mean age 70; enriched for frequent knee pain; F-Up 5 yrs; 40% LFU
  - M+W: 2.5%/yr

- **Chingford** (Leyland, 2013): 715 W; 45-64; F-Up 5 yrs; 39% LFU
  - M+W: 2.3%/yr
Prevention trial in obese women: Identifying subgroups with highest risk

- **OAI, MOST**: annual incidence % in women by presence/absence of individual RFs

*Eligibility threshold different from present definition, e.g. “overweight” but BMI <30.*
Prevention trial in obese women: Risk factor combinations with highest risk

- OAI and MOST: annual incidence % in women by combinations of RFs

![Bar graph showing risk factors with highest risk](image)

Osteoarthritis Initiative
Multicenter Osteoarthritis Study
Sample size for weight loss prevention trial

- Include obese women with multiple risk factors
  - High BMI + knee pain + Hx of injury
  - 4-year incidence of K-L ≥ 2: 30-35% (vs 20-25% in all obese women)

- Will weight loss prevent knee OA in obese women with knee pain and a Hx of knee injury?

Total sample size needed for an intervention trial to detect a reduction in knee OA incidence
- 25% reduction
- alpha=0.08, Power=80%
- equal group size
Will weight loss prevent OA in obese women with knee pain and a Hx of injury?

- Observational data show obesity an independent risk factor after adjustment for knee pain and Hx of injury.

  - But this is about possible interactions: What is the relationship of obesity and incident knee OA in those with the other risk factors?

![Graph showing 5-yr cumulative incidence % in MOST women with knee pain/ Hx injury]
Getting a larger Tx effect in a weight loss prevention trial: multiple interventions?

- Increase intervention effect to 35% risk reduction
  - Modify additional risk factors (strengthening?)
  - Treat early pathology

Total sample size needed for an intervention trial to detect a reduction in knee OA incidence
- 25% and 35% reduction
- alpha=0.08, Power=80%
- equal group size

- Include obese women with other modifiable risk factors and/or treatable early abnormalities
  - High BMI + knee pain/Hx injury + ? + ?
Additional modifiable risk factors/early abnormalities: malalignment?

- In knees with existing OA, varus and valgus mechanical alignment (HKA) strongly predict structural progression in the more loaded compartment.

- Varus malalignment also a risk factor for incident knee OA, in a high risk cohort.

MOST KL 0-1 knees
varus 41%
valgus 19%

Is varus malalignment a pre-existing risk factor or an early disease abnormality (or both)?

- In nonOA knees **without T-F cartilage damage**
- Varus malalignment before OA initiates cartilage morphological damage in more loaded compartment

**MOST** knees with normal T-F cartilage
- Varus ($\leq 178^\circ$) 38%
- Valgus ($\geq 182^\circ$) 19%

- **OR**: 2.4 (1.1, 5.4)
- **OR**: 0.6 (0.1, 2.8)

*Adj age, gender, body mass index, knee injury, laxity, meniscal tears/extrusion

Sharma L, et al. The role of varus and valgus alignment in the initial development of knee cartilage damage by MRI: MOST. ARD 2013; 72:235
Would weight loss prevent OA onset in malaligned knees of obese subjects?

- **MOST:** Effect of obesity on incidence is greater in varus than neutral knees
- **Role of varus malalignment in weight loss trial**
  - Inclusion criterion to ↑ risk
  - Intervention target?
- **Severe malalignment may negate effect of obesity on risk**

### Table 2. BMI and the risk of incident tibiofemoral osteoarthritis*

<table>
<thead>
<tr>
<th>Alignment group/ BMI category</th>
<th>No. of at risk, knees</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varus (≤178°)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>248</td>
<td>3.2</td>
<td>1.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Overweight</td>
<td>519</td>
<td>6.0</td>
<td>1.9 (0.8–4.7)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>387</td>
<td>8.0</td>
<td>2.4 (1.0–5.8)</td>
<td></td>
</tr>
<tr>
<td>Very obese</td>
<td>175</td>
<td>15.4</td>
<td>4.0 (1.6–9.7)</td>
<td></td>
</tr>
<tr>
<td>Neutral (179–181°)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>259</td>
<td>2.3</td>
<td>1.0</td>
<td>0.0126</td>
</tr>
<tr>
<td>Overweight</td>
<td>560</td>
<td>5.2</td>
<td>2.2 (0.9–5.4)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>364</td>
<td>6.9</td>
<td>2.9 (1.2–7.3)</td>
<td></td>
</tr>
<tr>
<td>Very obese</td>
<td>164</td>
<td>8.5</td>
<td>3.2 (1.2–8.7)</td>
<td></td>
</tr>
</tbody>
</table>

* The relative risk (RR) was adjusted for age, sex, race, bone mineral density, and history of knee injury. BMI = body mass index; 95% CI = 95% confidence interval.

Additional modifiable risk factors/early abnormalities: meniscal damage?

- In older adults, incidental meniscal damage is present in 1/4 of asymptomatic knees without OA (Englund, NEJM 2008;359:1108)

- In knees with OA, meniscal pathology is strongly associated with same compartment cartilage loss and BMLs (Lo G, et al. OsteoCart 2009; 17:743)

- Is meniscal damage in knees without OA and no Hx of surgery a risk factor for knee OA onset?

Functions of meniscus
- transmit load to cartilage
- shock absorption
- joint stabilization
Meniscal damage is a risk factor for knee OA onset

- MOST: nested case-control study of incident OA
  - Cases (n=121) BL KL 0-1 → KL 2+ at 30m
  - Controls (n=294) KL 0-1 at BL and 30m
- Meniscal damage before OA increases risk of OA onset, in a high risk cohort

![Graph showing incidence of KL 2+ and Meniscal damage]

*Adj age, sex, BMI, physical activity, HKA


**Osteoarthritis Initiative**

**Multicenter Osteoarthritis Study**
Prevention trial in obese with early meniscal damage

- Meniscal damage an early structural abnormality of the knee that increases risk of incident knee OA and can initiate cartilage damage
  - Early meniscal pathology can be detected on MRI

- Potential role in a weight loss trial
  - Inclusion criterion to boost risk
    - Would weight loss be effective in this group?
    - Does obesity increase risk in those with meniscal damage?
  - A Tx target to increase intervention effect?
Additional steps to boost risk of incident knee OA: early radiographic OA

- Include obese women with K-L grade 1 knees?
- KL 1 knees in obese women: cumulative incidence 65-75%
- Obesity remains a risk factor for OA onset
Prevention trial in obese women with K-L grade 1 knees

- Include obese women with early radiographic knee OA and other risk factors and treatable abnormalities
  - High BMI + knee pain/hx injury + KL 1 knee + ?
  - Increase incidence in controls to 50-55%?

- K-L 1 knees have a mix of early abnormalities
  - Too far along or an opportunity for Tx?

Total sample size needed for an intervention trial to detect a reduction in knee OA incidence
- 25% and 35% reduction
- alpha=0.08, Power=80%
- equal group size
Discussion: Knee OA prevention in obese women

- Trials with other (more clinically relevant?) endpoints
  - Prevention of knee pain and pain worsening
  - Onset of clinical OA (?? radiographic OA)
  - Biomarkers/surrogates for incident radiographic OA
- Higher risk of endpoint in prevention trials is advantageous
  - Evidence that interventions may work in high risk?
  - Trade-off of recruitment effort for higher risk
  - Cost/ppt of intervention and follow-up >> than screening
- Besides weight loss, other modifiable risk factors and treatable early pre-radiographic abnormalities?
  - strength, malalignment, meniscus damage, inflammation, ??
- Explore use of MRI cartilage composition (e.g. T2 relaxation) to select for early/reversible cartilage degradation
  - MRI requirement reduces BMI and risk
Acknowledgements

- OAI and MOST participants
- Investigators and staff at MOST and OAI centers
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- OAI industry partners: Pfizer, Merck, Novartis, Glaxo-Smith-Kline

Publicly available data sets

www.oai.ucsf.edu
www.most.ucsf.edu
Thank you!