Effects of Exercise and Diet in Osteoarthritis

Stephen P. Messier, Ph.D.
**Prevalence of Knee Osteoarthritis Worldwide**

<table>
<thead>
<tr>
<th>Overall</th>
<th>% world population</th>
<th>Men</th>
<th>% world population</th>
<th>Women</th>
<th>% world population</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 million</td>
<td>3.6%</td>
<td>89 million</td>
<td>2.6%</td>
<td>162 million</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

*Vos et al. Lancet, 2012*
How we treat Knee OA

Average time spent living with symptomatic knee OA = 26.1 years

NSAIDS
BRACES
Injections

Average duration (years) of non-surgical regimen or prosthesis survival

Adapted from Losina, ACR Annual Meeting, 2011
162% rise in knee replacement surgery over the past 20 years

Primary and Revision Total Knee Arthroplasty Medicare Volume Between 1991 and 2010

A cost of $5 billion annually

Cram et al., JAMA, 2012
Odds Ratio of Knee OA with Obesity for Women

Klussmann et al., Arthritis Res Therapy, 2010

Odds Ratio

Weight (BMI)
Risk of Premature Death is related to Overweight and Obesity

From: Excess Deaths Associated With Underweight, Overweight, and Obesity

Adapted from: JAMA. 2005;293(15):1861-1867. doi:10.1001/jama.293.15.1861

Ages 25-59
How Can We Reduce Weight and Relieve Pain?
Anti-Obesity Weight Loss Pill

• “Obesity Society President Patrick O’Neil said he’s encouraged by the drug’s approval because it underscores the notion that lifestyle changes alone are not enough to treat obesity”

AP: June 28, 2012
Weight Reduction

Roux-en-Y Gastric Bypass Surgery
Arthroscopic Surgery vs. Sham Surgery.

Pain Relief 2 yrs after surgery

Moseley et al. NEJM, 2002
Treatments of Chronic Non-Cancer Pain

• a general conclusion ..... is that the results are sobering. Turk et al., Lancet. 2011

• the best evidence for pain reduction averages roughly 30% in about half of treated patients
Can A Non-Pharmacologic, Non-Invasive Intervention Be Part of the Solution?

NIAMS: R01-AR052528-01
OVER 25 YEARS OF REDUCING KNEE PAIN IN OLDER ADULTS WITH EXERCISE AND DIET

1991-1996: Fitness Arthritis in Seniors Trial (FAST)

1997-2002: Arthritis Diet and Activity Promotion Trial (ADAPT)

2006-2011: Intensive Diet and Exercise for Arthritis (IDEA)

2011-Present: Strength Training for ARthritis Trial (START)
Intensive Diet and Exercise for Arthritis (IDEA): A Plan for Action


NIAMS: R01-AR052528-01
Obese Adults with Knee OA

Biomechanical pathway

Intensive Weight Loss and Exercise

Decreased Joint Loads

Decreased Subchondral Tissue Damage

Decreased Inflammatory Cytokine Activity

Less Cartilage Loss, Less Synovitis

Decreased PAIN

Improved mobility

Greater strength/power

Disease Progression

Inflammatory pathway
IDEA Intervention Groups

Exercise (control)  Diet  Diet + Exercise

15 MIN. WALKING  Intensive Dietary Restriction  Intensive Dietary Restriction

20 MIN. weight training  ≥10% WEIGHT LOSS OVER 18 MONTHS  Plus Exercise

15 MIN. WALKING
IDEA Exercise Intervention

Exercise

15 MIN. WALKING

20 MIN. weight training

15 MIN. WALKING

Exercise

Diet

Intensive Dietary Restriction ≥10% WEIGHT LOSS OVER 18 MONTHS

IDEA Exercise Intervention

Intensive Dietary Restriction Plus Exercise
IDEA Nutrition Intervention

- Initial energy intake deficit of 800-1000 kcals/day
- Up to 2 meal replacements (300 kcals each) per day
- GNC Lean Shakes
- Third meal between 500-750 kcals (low in fat)
- Weight loss goal: ≥10% body weight over 18 months
- Meetings: weekly/0-6 months
- Biweekly/7-18 months
IDEA Participant Progress

Total Persons Pre-Screened
N = 3035

Prescreen
Eligible = 1953 Not Interested = 1082

SV1
Not Eligible = 1076
Eligible = 877

SV2
Randomized = 454

SV1
Not Eligible = 423

Received
Exercise (control)
N = 150

Follow-up Visits
6 mo (N = 130)
18 mo (N = 134)

Completed
N = 134 (89%)

Received
Diet
N = 152

Follow-up Visits
6 mo (N = 123)
18 mo (N = 129)

Completed
N = 129 (85%)

Received
Diet + Exercise
N = 152

Follow-up Visits
6 mo (N = 138)
18 mo (N = 136)

Completed
N = 136 (89%)
EXERCISE ADHERENCE (intent-to-treat)

0-6 months: 66%
0-18 months: 54%

Exercise-only

0-6 months: 70%
0-18 months: 58%

Diet + Exercise
DIET ADHERENCE
(intent-to-treat)

0-18 months: 61%

Diet-only

0-18 months: 63%

Diet + Exercise
IDEA Adverse Events

454 participants; 18-month Exercise/Diet interventions

3 nonserious adverse events (<1%)
  1- muscle strain
  2- trips/falls

No serious adverse events related to the study

No deaths
### Weight Change

#### Weight (kg) across 18 months

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean (kg)</th>
<th>Change (kg)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>base</td>
<td>93.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FU6</td>
<td>85.5</td>
<td>-7.9</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>FU18</td>
<td>84.5</td>
<td>-8.9</td>
<td>9.5</td>
</tr>
<tr>
<td>Diet+ Exer</td>
<td>base</td>
<td>93.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FU6</td>
<td>84.3</td>
<td>-8.7</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>FU18</td>
<td>82.4</td>
<td>-10.6</td>
<td>11.4</td>
</tr>
<tr>
<td>Exer</td>
<td>base</td>
<td>92.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FU6</td>
<td>92.4</td>
<td>+0.1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>FU18</td>
<td>90.5</td>
<td>-1.8</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Weight loss by month

- Diet + Exercise
- Diet

Weight loss (%)

Time (months)

Weight loss (lbs)
Diet & Exercise:
18 Month Weight Loss

Weight loss (%)

0-4.9%  □  5-9.9%  □  ≥10%  □
N = 34  N = 36  N = 66
### Lean and Fat Mass Change

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Body Wt (kg)</th>
<th>Δ (kg)</th>
<th>Lean, kg</th>
<th>Δ (kg)</th>
<th>Fat, kg</th>
<th>Δ (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet</strong></td>
<td>base</td>
<td>93.4</td>
<td></td>
<td>55.3</td>
<td></td>
<td>36.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FU18</td>
<td>84.5</td>
<td>-8.9</td>
<td>51.1</td>
<td>-4.2</td>
<td>31.5</td>
<td>-4.8</td>
</tr>
<tr>
<td><strong>Diet+Exer</strong></td>
<td>base</td>
<td>93.0</td>
<td></td>
<td>55.6</td>
<td></td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FU18</td>
<td>82.4</td>
<td>-10.6</td>
<td>50.8</td>
<td>-4.7</td>
<td>30.3</td>
<td>-6.5</td>
</tr>
</tbody>
</table>

D+E: 61% of wt loss was fat  
D: 54% of wt loss was fat loss
**Pain vs. Time** [mean (SE)]

WOMAC Pain (range 0-20)

*Adjusted for gender, BMI, baseline values*

Messier et al., JAMA, 2013
Mean (SE) WOMAC Function vs. Time

*Adjusted for gender, BMI, baseline values

Messier et al., JAMA, 2013
Mean (SE) Walk Speed

Distance (m)

Better mobility
- Diet
- Exercise
- Diet + Exercise

Worse mobility

*P = 0.013

Messier et al., JAMA, 2013
Mean (SE) 6 Minute Walk Distance

![Graph showing the mean (SE) 6 Minute Walk Distance with different treatments.

- Better mobility groups:
  - Diet
  - Exercise
  - Diet + Exercise

- Worse mobility:

Messier et al., JAMA, 2013
Musculoskeletal Model

DeVita et al, 2001
Blood Biomarkers

**Blood Collection:** Blood drawn after overnight fast in absence of symptoms of infection/injury

**Blood assays:** All samples measured in duplicate, average used for data analyses

- **Plasma IL-6:** Quantikine® high-sensitivity ELISA (R&D Systems; sensitivity > 0.10 pg/mL, detection range = 0.156-10.0 pg/mL)
- **Serum Leptin:** Quantikine® high-sensitivity ELISA (R&D Systems)
- **Serum MMP-3:** Quantikine DMP300 kit
Compressive Force (N)

Knee Compressive Force (N)

- Diet
- Exercise
- Diet + Exercise

Baseline: 6 months: 18 months

*P = 0.019

*P < 0.0001

E: -5%Δ
D+E: -9%Δ
D: -11%Δ

*Adjusted for gender, baseline BMI, baseline values

Messier et al., JAMA, 2013
**IL-6 (pg/mL)**

* *p*-value from the log-adjusted variable comparisons. Adjusted for gender, BMI, baseline values. Mean + SE

Messier et al., JAMA, 2013
Mean Difference from baseline across all outcomes (Standardized (Z) Scores)

**Greater improvement from baseline**

* D+E > D, p = 0.003

- Exercise
- Diet
- Diet + Exercise

Adjusted for baseline BMI and gender
## Dose response of weight change with pain and function independent of group assignment

<table>
<thead>
<tr>
<th>% Weight Change</th>
<th>N</th>
<th>Pain</th>
<th>P-Value</th>
<th>Function</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High -32.5% to  -10.1%</td>
<td>112</td>
<td>3.72 (0.25)</td>
<td>14.32 (0.77)</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Medium -9.8% to  -5.0%</td>
<td>79</td>
<td>4.55 (0.21)</td>
<td>16.97 (0.68)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Low -4.9% to     9.9%</td>
<td>165</td>
<td>4.61 (0.19)</td>
<td>17.36 (0.60)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for intervention, BMI, gender and baseline values
High < Medium and Low
18-month Knee Compressive Force (N) by Weight Loss Category

Adjusted for baseline values, group, baseline BMI, gender

*p < 0.001
Mean IL-6 (pg/mL) by Weight Loss Category

**p = 0.024 category
*p < 0.001 slope

Adjusted for baseline values, group, baseline BMI, gender
Conclusion

• On average, our D+E intervention was twice as effective at relieving pain as previous long-term OA trials and twice as effective as non-pharmacologic trials of chronic non-cancer pain generally.
Summary

• Intensive weight loss significantly impacts both the biomechanical and inflammatory OA disease pathways
  • by reducing knee joint compressive loads
  • and inflammation
IDEA: Mechanistic Changes and Clinical Improvements

Intensive Weight Loss + Exercise

Reduces Abnormal Stress
Decreased Joint Loads

Reduces Abnormal Physiology
Lowers Inflammation

Less Pain
Less Disability
Summary

• There was a significant dose response to weight loss.
• 10% weight loss resulted in superior results relative to 5-10%, and less than 5% weight loss.
Can physicians help?

• Only 42% older obese adults who visit doctor are advised to lose weight (Galuska et al, JAMA, 1999)

• What’s worse: only 0.7 minutes (42 seconds) are spent discussing diet or exercise. (Flocke, Stange, Prev Med., 2004)
Future of weight loss and exercise interventions

• People need help and regular attention to succeed
My wife said "Watcha doin' today?"
I said "Nothing"
She said, "You did that yesterday"
I said "I wasn't finished."