Osteoarthritis-induced joint pain: Impact of Sex, Site and Exercise

Tamara King
University of New England
Disclosures

• No financial conflicts of interest to disclose.
Learning Objectives

1. Understand the relationship between joint pathology and clinical characteristics of osteoarthritis pain

2. Gain an understanding of how exercise modulates osteoarthritis pain
Talk Overview

- Key features of osteoarthritis.
- What is known regarding mechanisms driving OA pain.
- What is the impact of exercise on OA pain.
  - Clinical studies and reports
  - Preclinical studies and proposed mechanisms
  - Differences between different joints?
Arthritis is the most common joint pain

- pain (arthralgia)
- stiffness
- swelling
- limited function of joints
In the US, arthritis is a leading cause of disability;

- ~52.5 million (22.7%) adults in 2010–2012
- In 2014, approximately one fourth of adults with arthritis report severe joint pain (27.2%)
- Number of adults with severe joint pain was significantly higher in 2014 (14.6 million) than in 2002 (10.5 million)

Osteoarthritis is the most common form of arthritis

Source: Wang et al., Lancet 2011

Projected Increase

Obesity

Population Growth

SOURCE: CDC/NCHS, Health, United States, 2009, Figure 1A. Data from the U.S. Census Bureau.

Arthritis

Data from CDC

Hand 8%
2.9 million

Knee 16%
4.3 million
60+ yrs

Feet 2%

Hip 4%

Osteoarthritis is the most common form of arthritis
Osteoarthritis

Data from CDC

- Hand 8% 2.9 million
- Hip 4%
- Knee 16% 4.3 million
- Feet 2%

- Women are more likely to have OA
- Woman report more severe OA
Other risk factors include:

- Joint injury
  - trans-articular fracture
  - meniscal tear requiring meniscectomy
  - anterior cruciate ligament injury

- Repetitive use of joints at work
Osteoarthritis

Radiographic OA

- Focal and progressive loss of the hyaline cartilage
- Radiographic changes include joint space narrowing, osteophytes, and bony sclerosis

Symptomatic OA

- Pain that worsens during activity and gets better during rest.
- Muscle spasms and contractions in the tendons.
- A grating sensation with joint use

Degree of pathology observed on radiograph does not correspond to symptomatic OA
Osteoarthritis is marked by changes in cartilage and bone:

- Cartilage loss
- Subchondral bone shows sclerosis
- Development of bone marrow lesions and cysts
- In subsets of patients there are indices of bone resorption indicating loss of trabecular bone

There are currently no treatments available to patients for modifying the underlying disease.

Current treatments focus on pain relief.
Early OA (stage 1): Predictable sharp or other pain
- Usually brought on by a trigger (usually an activity)
- Eventually limits high impact activities
- Has relatively little other impact.

Mid OA (stage 2): Predictable pain that becomes more constant
- Unpredictable locking (knees) or other joint symptoms
- Begins to affect daily activities

Advanced OA (stage 3): Constant dull/aching pain
- Punctuated by short episodes of intense, often unpredictable pain
- Significant avoidance of activities
  - Including social and recreational activities.
OA Pain: Potential mechanisms

Potential Contributors to Pain:
- Inflammatory mediators
- Mechanical factors
- Nerve damage

Not all patients receive adequate pain relief.
All have side effects.

NSAIDs, steroids
Joint splints or braces,
Duloxetine

NSAIDs,
steroids
Joint splints or braces,
Duloxetine

Peripheral Sensitization
- Hyperalgesia—enhanced pain response to noxious stimuli
- Allodynia—pain response to non-noxious stimuli

Central Sensitization
- Amplified Signal
- Descending Facilitation
  Enhances pain
- Descending Inhibition
  Diminishes pain

Dorsal Root Ganglia
CPP to intra-articular lidocaine was observed in 4.8 mg, but not 3.0 mg MIA treated rats.
Advanced OA Joint Pain
Male vs Female Rats

- A 5-fold lower concentration of MIA is sufficient to induce CPP in females.
- Consistent with clinical reports that females are more likely to develop OA and report more severe pain.
Hypothesis: An important component underlying chronic pain is a change in descending pain modulation resulting in net pain facilitation.
Clinical studies demonstrated signs of increased pain sensitization in OA patients reporting moderate to severe pain.

OA Pain: Central Sensitization


Increased Temporal Summation
Clinical studies demonstrated signs of *increased pain sensitization* in OA patients reporting moderate to severe pain.

Consistent with observations that patients with more severe pain ratings develop central sensitization.
Clinical studies indicate that there is **impaired pain inhibition** in chronic pain patients including OA patients.
Clinical studies indicate that there is impaired pain inhibition in chronic pain patients including OA patients.

From Arendt-Nielsen et al, PAIN, 2010
Diminished CPM as a predictive tool?

Prediction of future pain

Prediction of analgesic efficacy

Table 1
Correlation of DNIC, acute and chronic post-operative pain scores

<table>
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<th>Variable</th>
<th>By variable</th>
<th>Correlation</th>
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<tr>
<td>Acute pain</td>
<td>DNIC</td>
<td>0.1469</td>
<td>0.2546</td>
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<tr>
<td>Chronic pain</td>
<td>DNIC</td>
<td>0.3684</td>
<td>0.0032</td>
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<tr>
<td>Chronic pain</td>
<td>Acute pain</td>
<td>0.5947</td>
<td>&lt;0.0001</td>
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</table>

Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy

Fig. 1. Drug efficacy and pretreatment CPM. Patients with less efficient CPM (positive scores) reported higher drug efficacy and vice versa.
Treating OA Pain: Exercise

Exercise is the #1 recommended non-pharmacological treatment for patients with OA pain.

A meta-analysis of clinical studies examining exercise induced pain reduction of knee joint OA reported:

• Similar pain reduction for aerobic, resistance, and performance exercise.
• Single-type exercise programs were more effective than programs with multiple exercise types.
• The effect of aerobic exercise on pain relief was better with supervised sessions (3 times a week).
• For resistance exercise more pain reduction occurred with quadriceps specific exercise than with lower limb exercise.

- (Juhl et al, 2014, Arthritis & Rheumatology)
Treating OA Pain: Exercise

Exercise is the #1 recommended non-pharmacological treatment for patients with OA pain.

A meta-analysis of clinical studies examining exercise induced pain reduction of knee joint OA concluded:

- For best results, the exercise program should be supervised and carried out 3 times a week.
- Such programs have a similar effect regardless of patient characteristics, including radiographic severity and baseline pain.

- (Juhl et al, 2014, Arthritis & Rheumatology)
OA Pain: Potential mechanisms

Potential Contributors to Pain:
- Inflammatory mediators
- Mechanical factors
- Nerve damage

Descending Inhibition Diminishes pain

Central Sensitization

So how does exercise reduce OA pain?

Descending Facilitation Enhances pain
Descending Inhibition Diminishes pain

Amplified Signal

Peripheral Sensitization

Hyperalgesia—enhanced pain response to noxious stimuli

Allodynia—pain response to non-noxious stimuli

Dorsal Root Ganglia

Central Sensitization
The same exercise treatment produced reversal of MIA-induced tactile hypersensitivity and weight asymmetry.

Rats are placed onto treadmills starting **10 days** post-MIA.

- Exercise consisted of 30 min sessions 4 days/wk.
- Behavioral analysis of weight was performed weekly in the absence of exercise.

**Weight Asymmetry**

Exercise begins D10 post-injection

% Weight (ipsi/contra*100)

Time Post-MIA (Days)

Exercise begins D10 post-injection

<table>
<thead>
<tr>
<th>Time Post-MIA (Days)</th>
<th>BL</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
<th>35</th>
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* The same exercise treatment produced reversal of MIA-induced tactile hypersensitivity and weight asymmetry.*
Exercise diminishes pain in animals with MIA-induced knee OA

Radiographs indicate that exercise treatment reverses MIA-induced pain without altering cartilage loss or joint pathology

Allen et al, 2017
Exercise diminishes pain in animals with MIA-induced knee OA.

μCT indicates that exercise treatment protects from MIA-induced joint pathology.
Descending Facilitation

Descending Inhibition

Endogenous opioids

Perhaps exercise is a way to alter the balance away from pain facilitation towards increased pain inhibition.
Treating OA Pain: Targeting Pain Modulation

Exercise induces increased endogenous opioidergic signaling

Naloxone, an opioid antagonist, blocks the pain alleviating effects of exercise.
Exercise diminishes pain in animals with MIA-induced OA

Male rats show pain relief after 4 weeks of treadmill exercise in the knee joint OA model.

Female rats with TMJOA did not show full blockade of ongoing pain until after 9 weeks of exercise.
Free will-Voluntary Exercise

Exercise is top RECOMMENDED non-pharmacological therapy for OA patients.

• Most patients are not forced to exercise.
• What about voluntary exercise?
• Will pain diminish exercise?

"You have to actually exercise. Jumping to conclusions, stretching the truth, skipping breakfast, and juggling two jobs won't do it."
MIA diminishes voluntary wheel running

- The rate of 16 m/min was the rate used in the treadmill studies.
- MIA treated rats were capable and willing to achieve this rate.
- MIA treated rats maintained peak rates of 16-20 m/min for remaining 4 weeks of the study.
Voluntary Exercise

Exercise begins D10 post-injection

MIA-induced Weight Asymmetry

BL 1 2 3 4 5

Time Course (weeks)

Weight Asymmetry (%L/R)

MIA-Low
MIA-High

** ** **
**
***
*** ***
*
* *

Exercise begins D10 post-injection

Ongoing Pain

Difference Scores (Test - Baseline)

**

Low
High

Running Group

Intra-articular Lidocaine Induced CPP

**

Pairing Chamber
Unpaired (Neutral)
Pairing Chamber

Pairing Chamber
Unpaired (Neutral)
Pairing Chamber
Voluntary Exercise

Contralateral | MIA-Sedentary | MIA "Low" Runner | MIA "High" Runner

Metaphysis Bone Volume Fraction
Bone Volume (BV/TV) Contralateral
Sedentary
Low Runners
High Runners

4.8 mg/60 ml MIA

Metaphysis Connection Density

4.8 mg/60 ml MIA

Metaphysis Trabecular Number

4.8 mg/60 ml MIA

Metaphysis Trabecular Spacing

4.8 mg/60 ml MIA
Conclusions

LO 1. Understand the relationship between joint pathology and clinical characteristics of OA pain

• There is evidence that joint pathology does not predict pain.
• We need to gain a better understanding of what does generate pain, including understanding of pathology that we have missed using radiographs.
• Understanding sex differences in pain perception and modulation.
• Psychosocial factors and how these may impact descending modulation.
Conclusions

LO 2. Gain an understanding of how exercise modulates OA pain

1. Exercise has been found to be successful in alleviating OA pain in patients (mostly knee joint studies) and in animal studies.
2. Exercise can alleviate pain in load bearing and non-load bearing joints.
3. Exercise can diminish joint pathology – evidence in knee joint
4. Exercise induced pain relief is through recruitment of pain inhibitory circuits in the brain and separate from effects on joint pathology.
UNE Histology and Imaging Core
  • Peter Carodonna, Core Manager

Glenn Stevenson

Microcomputed Tomography Services
  • Lucy Laiw, PhD Core Director
  • Terry Henderson, Core Manager

Laboratory Manager
  • Victoria Eaton
  • Sebastien Sannajust

Peter Morgane Research Fellows
  • Joseph Heath
  • Elizabeth Kim
  • Alex Chasse

Undergraduate Students
  • Jeremy Gervais  Andrew Elkinson
  • Owen Peterson  Colby Williams
  • Meredith Walker  Caitlyn Daly
  • Chelsea Nation
  • Ian Imbert

GSBSE Graduate Student
  • Joshua Havelin
Fin