Arthritis affects all age groups and races; ♀ > ♂ by 1.65 to 1.

Nearly 50% of people > 65 y.o. & 80% > 75 y.o. report arthritic symptoms

What causes osteoarthritis?

- A genetic defect in type II collagen has been found which represents an error in one base in the DNA sequence leading to an amino acid substitution of cysteine for arginine in the collagen matrix.
How do we perceive chronic pain?

Paradoxes

- No pain despite serious tissue damage
- Poor correlation between pain intensity and peripheral pathology (i.e., degenerative changes, inflammation) in OA, RA etc.
- Severe pain despite no obvious tissue damage in myalgia/fibromyalgia

Clinical

OA

OA - why does it hurt?

Pain

Radiological findings

Knee 25%
LBP 25%
Linker et al. 1990

Clinical

OA

DDD or just coincidence

OA knee (> 65 years):
> 50%
McNamee et al. 2010

DDD; (50-55 years):
> 90% (degree correlated with pain)
Cheung et al. 2009

Hypothesis; why does it hurt?

OA pain: "Overactivation" of normal healing mechanisms leading to inflammation

Disc degenerative disease

Hypothesis; why does it hurt?

OA pain: "Overactivation" of normal healing mechanisms (partially NGF – Inflammation

Secondary effects:
Pain modulation (bottom-up and top-down)
CNS inflammation?
Cognitive and emotional factors?
Positive correlations between pressure pain sensitivity and clinical pain in knee OA


Normalization of thalamic volumes in hip OA patients 9 months following total joint replacement

Baseline: Controls had larger thalamic gray matter volumes than patients (green, uncorrected)

A. Increased thalamic gray matter volumes in patients following surgery (red) p < 0.05 corrected.

B. Postop: No difference in thalamic gray matter volumes between patients and controls.

Gwilym et al. Arthr Rheum 2010

Conclusions

• Afferent nociceptive input can induce and maintain increased pain sensitivity and a dysfunction of descending pain modulation

• Pain sensitivity and descending pain modulation can normalize following surgery

CNS inflammation; a crosstalk between peripheral tissues and CNS?

• Link between peripheral inflammation and cytokine production in CNS has been shown in animal models (Watkins and Maier, 2005; Tracey 2009; Inglis et al 2007)

• So, what about humans?

Indirect signs of glia cell activation

• Increased concentrations of pro-inflammatory cytokines and algogenic substances previously reported in CSF
  – Pain of unknown origin (dysfunctional pain); FM (Kadetoff et al. J Neuroimmunumol 2012)
  – Nociceptive pain; OA (Lundborg et al J Neuroimmunology 2010), RA (Lampa et al PNAS 2012)
Increased concentrations of IL-8 and IL-1b in CSF of OA patients (hip/knee) by Lundborg et al. J Neuroimmunology 2010

Hypothetical mechanistic pain model by Langworthy MJ, Saad AM, Langworthy NM

Relevance for pain modulation

Potential effects of glia cell activation:
- "Sickness response":
  - Spontaneous pain
  - Hyperalgesia/allodynia
  - Fatigue
  - Disturbed sleep
  - Depression/anhedonia

Osteoarthritis:
Conservative Treatment Modalities and Outcomes. The Concomitant Pyramid of Treatment

Osteoarthritis:
- Arthritis affects all age groups and races; 
  \[♀ > ♂\] by 1.65 to 1.
- Nearly 50% of people > 65 y.o. & 80% > 75 y.o. report arthritic symptoms

The Physician and Sports Medicine. Spring 2010

Langworthy MJ, Saad AM, Langworthy NM

CDC Wkly Report, 2004
Goodman, Orthopedics, 2000
Simon, Geriatrics, 1999
Stewart, JAMA, 2003
Kraus, Med Clin North Am, 1997
Buckwalter, CORR, 20000
What causes osteoarthritis?

- A genetic defect in type II collagen has been found which represents an error in one base in the DNA sequence leading to an amino acid substitution of cysteine for arginine in the collagen matrix.

Moskowitz, AAOS Symposium, 2001

Other factors causing osteoarthritis?

- Concentration and molecular weight of hyaluronan molecules is ↓ by 33 -50% in OA synovial fluid and thus ability of synovial fluid to lubricate and protect joint cells and tissues is compromised.

DeGroot, Osteo Cart, 2001
Barbero, Osteo Cart, 2004
Manninen, Red Met Dis, 1996
Grossen, Ann Anat, 2001
Watterson, JAAOS, 2000

Projections of hip and knee arthroplasty in the United States: 2005—2030

"By 2030...The demand for primary total knee arthroplasties is projected to grow by 673% to 3.48 million procedures."


Total Joint Replacement

- Immediate
- Corrects deformity
- 95% reproducible
- But in the younger patient......

Parameters

- Total joint replacement is an intercalated amputation.
- What is considered conservative in the aged may be radical in youth.
Total Joint Replacement

CARTILAGE
- Simple in Appearance
- Primarily Extracellular Matrix
- One Cell Type
- No Blood Supply
- No Nerves
- No Lymphatics
- Low Metabolic Activity

ARTICULAR CARTILAGE: LAYERS

SUPERFICIAL
- Flat cells
- High collagen content
- High water content
- High tensile strength

TRANSITIONAL
- Spherical cells
- More proteoglycans
- Low water content
- Fibrils bent to form arcades

RADIAL
- Active groups of cells
- Perpendicular fiber orientation

CALCIFIED CARTILAGE
- Anchor point of collagen

Articular cartilage components
- Water 70-75%
- Collagen 15-20%:
  Mostly Type II
  70% of organic
  half life 114 years
- Aggrecan 5-10%
  50:1 avidity for water

Matrix physiology

AGGREGAN
Structure
- Very Large! 200 X 10^6 D
- Hyaluronic Acid Backbone
- Many Glicosaminoglycans
  - Chondroitin Sulfate
  - Keratan Sulfate
  - Protein Core
  - Negative Charge
- Contains Water
Type II Collagen Degradation

GROSS CARTILAGE APPEARANCE

- Grade 1 - Age 17
- Grade 2 - Age 56
- Grade 4 - Age 87

Normal
Minimal Fibrillation
Overt Fibrillation
Erosion or Ulcer

FEMORAL OA DISTRIBUTION BY AGE

- Age < 40
  - n = 32
- 40 < Age < 60
  - n = 45
- Age > 60
  - n = 72

TIBIAL OA DISTRIBUTION BY AGE

- Age < 40
  - n = 32
- 40 < Age < 60
  - n = 45
- Age > 60
  - n = 72

PATELLAR OA DISTRIBUTION BY AGE

- Age < 40
  - n = 30
- 40 < Age < 60
  - n = 45
- Age > 60
  - n = 72

AGE RELATED CELLULAR CHANGES

- Femoral Condyles
  - < 40 yo: 71,864, 51,502
  - 40-60 yo: 51,709, 47,887
  - > 60 yo: 47,000, 33,068

- Tibial Plateaus
  - < 40 yo: 26,750, 19,868
  - 40-60 yo: 26,523, 25,865
  - > 60 yo: 23,180, 19,175
APOPTOTIC BODIES IN OA CARTILAGE

THE PROBLEM

A Typical Treatment Algorithm for OA

Conservative Treatment Possibilities

Initial tx of osteoarthritis?

- Weight loss
   - 100 people with wt loss
     - 97 will put weight back on

Altman, Council of OA management, 2007
Deyle, Ann Intern Med, 2000
Devos, J Rheumatol, 2006
Roddy, Ann Rheum Dis, 2005
Messier, Ann Rheum Dis, 2001
Hosmane, Cochrane Database, 2006


- Weight Loss/Physical Therapy
- NSAID’s
- COX II/III Inhibitors
- Steroid Injections
- Viscosupplementation Injections
- Nutritional Supplements & Vitamins
- Bracing
- Topical Treatments
- Acupuncture
- Pulsed Electrical Stimulation (PES)
Other factors causing osteoarthritis?

**Weight Gain!!**

Weight loss of 5.1 kg over 10 years will ↓ the risk of OA by > 50%!!

Felson, Ann Intern Med, 1992

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Physical therapy

• Strengthening and conditioning *somehow!!*

• 15-38% Efficacy

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Conservative Treatment Possibilities

Nutritional Supplements

Glucosamine Chondroitin SO₄

• The MOST studied nutraceutical on the market

• **Glucosamine** stimulates the synthesis of matrix & has some anti-inflammatory properties by inhibiting prostaglandin production

• **Chondroitin** stimulates chondrocyte RNA synthesis which results in an *increase in* collagen

Lippiello, CORR, 2000
Piperno, Osteo Cart, 2000

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Glucosamine Chondroitin SO₄ Arthritis Intervention Trial (GAIT)

**Treatment Groups**

- Glucosamine 1500mg /d
- Chondroitin 1200mg/d
- Glucosamine + Chondroitin Sulfate
- Celecoxib 200mg/ d
- Placebo

Clegg, NEJM, 2006

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Glucosamine/Chondroitin SO₄

Glucosamine Chondroitin SO₄ *same as placebo* in reducing pain and were *less effective* than celecoxib at 24 weeks*

*Subset of patients with moderate to severe disease demonstrated some benefit*

Clegg, NEJM, 2006

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Bottom Line

Based upon this study, there is minimal clinical evidence indicating that Glucosamine and/or Chondroitin Sulfate is effective for the treatment of mild-moderate knee OA.

Other nutraceuticals being studied A-Z

- Avocado-Soybean: ↓ inflam.
- (SAMe): Enhances synthesis of PG
- Collagen Hydrolysate: Synthesizes collagen
- Oxaceprol: ↓ leukocyte adhesion

Soeken, J Fam Pract, 2002
NicolaJ, Clin Pharm, 1998
Pantham, Biochem Pharm, 1999
Matheau, Arthritis Rheum, 1998
Herrmann, Clin Rheum Surg, 2000

Vitamins

- High dietary levels of vitamin C may slow OA progression
- Low dietary levels of vitamin D led to a 3X increase in OA progression & ↓ muscle strength
- ↓ in Vitamin D levels in 221 pts. had greater disability scores

Goldberg, AJO, 2002
Baker, ACR Meeting, 2005

Conservative Treatment Possibilities

Unloader Bracing

Lateral heel wedge

- 5˚ lateral wedged insole ↓ peak varus torque by ≈ 6% and a 10˚ lateral wedged insole by ≈ 8% in 15 test subjects with medial gonarthrosis.
**Acupuncture**

- 7 trials consisting of 393 patients
- "Real" acupuncture more effective than sham acupuncture for pain
- Ave. age 65 yrs., ↓ pain in acupuncture group compared to sham and exercise group

Ezzo, Arthritis Rheum, 2001
Hochberg, ACR Mtg., 2005

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**The Role of Pharmacologic Therapy in Pain Relief**

- Analgesic drug therapy is the mainstay of treatment


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**Acetominophen/Cox III Inhib**

- MOST commonly prescribed analgesic to treat symptoms of arthritis
- Similar in efficacy to NSAID's
- Can prescribe up to 4,000mg/day
  - HOWEVER, liver dysfunction & rarely renal toxicity has been reported

Hochberg, Ann. Rheum, 2000
Williams, Arth. Rheum, 1993

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**Number One Cause of Hepatitis**

- Widely prescribed drugs for OA
- 103,000 patients are hospitalized each year as a result of using NSAID’s
- 25% TO 33% of osteoarthritis treatment expenses goes to treat adverse events caused by NSAID’s, including GI bleeding and toxicity

Goldstein, Clin Ther, 2006
Hollenz, Dig Dis, 2006
**NSAID’s**

- The risk of developing significant ulcer disease while taking even a short course of NSAID’s (6 days to 2 weeks) is 16% to 22%.

- As many as 44% of patients can develop **significant dyspepsia** requiring additional medical treatment.

**Topical Treatments**

- Topical Diclofenac (Voltaren) Patch: **Flector**
- 1st approved NSAID patch approved in U.S.
- Peak plasma concentrations of diclofenac were noted between 10-20 hours of application and low amounts remain for 5 days.

**Cox II Inhibitors**

- Celebrex introduced in 1999
- At one time had 44% of NSAID prescribing market!

**Mortality From NSAID-induced GI Complications* vs Other Diseases in the United States**

*NSAIDs. Data from 1997.
† Estimated.

**COX II Inhibitors**

- Cyclooxygenase -2 is the inducible form of the enzyme and it blocks arachidonic acid from reaching the catalytic site, thus **blocking the formation of prostaglandins**.

- COX -1 provides a physiologic maintenance role in most tissues including the GI tract.
**Cox II Inhibitors**

- Significant GI bleeding in a study group of: 1,054 for Celebrex = 0.2%
  1,376 for Mobic = 0.4%

  Layton, Rheumatology, 2003

**Cox II Inhibitors : HBP Effects**

- 385 hypertensive patients, tx’ed with Celebrex, Relafen, and Ibuprofen

  - Systolic BP ↑ more common for:
    - Ibuprofen group -16.7%
    - Relafen - 5.5%
    - Celebrex - 4.6%
    - Control group - 1.1%

  White, J Am Cardio, 2002
  Whelton, Am J Ther., 2001

**Cox II Inhibitors : Effect on platelets**

- No effect on platelet function, hence if A/C is needed, ASA would need to be administered

  Morales, Pharmacology, 2002

**Cox II Inhibitors : ↑ MI risk??**

- Celebrex Long-term Arthritis Safety Study (CLASS) which compared Celebrex with Motrin or Voltaren found no ↑ in the risk of MI associated with Celebrex

- Celebrex vs. placebo : 41,000 patients. No difference in CV events

  Solomon, Circulation, 2004
  White, AJC, 2007

**Steroid Injections**

- Methylprednisolone is most widely used due to its versatility & its ↓ solubility results in ↑ duration of action

  Pyne, Clin Rheumatol, 2004
  Hochberg, Arth Care Res, 1996
Steroid Injections

- Too much steroid will decrease the strength of collagen.
- Steroids do NOT affect articular cartilage integrity unless subjected to large, frequent doses!
- Children’s study showed intra-articular steroids decreased inflammation without toxic effects on cartilage.

Endogenous Hyaluronan

- Endogenous hyaluronan is the major hydrodynamic component of joint synovial fluid
- It's produced by Type B synoviocytes and fibroblasts of the synovial membrane, has a MW of 5 to 7 x10^6 daltons

Viscosupplementation

- Clinical trials indicate viscosupplements are as effective as NSAIDS and last for up to 12 months
- Wobig et al, Adams et al, Raynaud et al, Ramen et al, Waddell et al
- Better than saline, steroids, NSAIDS

Hyaluronic Acid

- Derived from fractionated hyaluronans extracted from chicken combs. 1997 approved for human use

An Important Therapy for OA Knee Pain

Viscosupplementation

- Nonsystemic therapy for OA knee pain relief
- Replaces diseased, osteoarthritic synovial fluid in the knee to reduce pain, which may improve function
- Reduce the use of chronic, systemic pain medications like NSAIDs and COX-2 inhibitors
Viscosupplements: Possible Modes of Action

- Reduce evoked sensory nerve transmission
  - anti-nociceptive
- Reduce levels of excitatory amino acids
  - anti-nociceptive
- Decrease COX-2 gene expression & PGE$_2$ levels
  - anti-hyperalgesic
- Enhance production of HWM HA by synoviocytes
  - improve elastoviscosity of synovial fluid
- Suppress IL-1-stimulated MMP activity
  - MMPs responsible for catabolism of hyaline cartilage matrix
- Preserve hyaline cartilage
- Normalize OA-induced changes in gene expression

Physical Properties of Viscosupplements

<table>
<thead>
<tr>
<th></th>
<th>Molecular Weight (million Daltons)</th>
<th>Elasticity (Pa at 2.5 Hz)</th>
<th>Viscosity (Pa at 2.5 Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy, young synovial fluid</td>
<td>0.5</td>
<td>0.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Osteoarthritic synovial fluid</td>
<td>1.9</td>
<td>1.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Synvisc® (hylan G F 20)</td>
<td>4</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>SYNOVIS® (hylan G F 20)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Hyalgan® (sodium hyaluronate)</td>
<td>0.5 - 0.7</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Supartz® (sodium hyaluronate)</td>
<td>0.6 - 1.2</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Orthovisc® (high molecular weight hylan G F 20)</td>
<td>1 - 2.0</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Synvisc® (0.5% sodium hyaluronate)</td>
<td>2.4 - 3.6</td>
<td>0.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Walking Pain Responder Rate

More than 70% of patients responded to Viscos

Demonstrated Safety Profile in Initial and Repeat Treatments

- Initial course
  - Rate of related local side effects was similar to saline control (5.7% vs. 3.1%)
- Repeat treatment
  - The rate of side effects did not increase with a repeat course of treatment (5.2%)

Pilot study results

Secondary endpoints

- Synvisc-One ranked 1st for
  - Patient Global Assessment (PGQA)
  - Clinical Observer Global Assessment (COGA)

Tolerability

- Safety was similar between the 1 x 6 mL and the 3 x 2 mL groups
  - No serious side effects were reported
Clinical Considerations

Effective Safe

Limitations of OA Treatment Options

- Surgery
- Prescription NSAIDs, including coxibs
- OTC NSAIDs
- Acetaminophen

Patient education, physical and occupational therapy, weight reduction, exercise, assistive devices

Limitations
- GI bleeding or other complications
- CV risks
- Renal complications
- GI bleeding or other complications
- CV risks
- Renal complications
- Poor patient compliance
- Hepatotoxicity
- Costly, invasive procedure
- Primarily indicated for “end-stage” OA patients
- Many OA patients are not candidates for TKR

Limitations of OA Treatment Options

More SYNVIS patients were symptom-free with Concomitant TX

Percent of patients who were “symptom-free” (VAS <20) at week 26

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs</th>
<th>SYNVIS</th>
<th>SYNVIS + Cox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain with motion</td>
<td>6%</td>
<td>30%</td>
<td>80%</td>
</tr>
<tr>
<td>Pain at rest</td>
<td>48%</td>
<td>48%</td>
<td>81%</td>
</tr>
<tr>
<td>Pain at night</td>
<td>48%</td>
<td>63%</td>
<td>81%</td>
</tr>
<tr>
<td>Restriction of activity</td>
<td>10%</td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td>Overall assessment of arthritic pain</td>
<td>10%</td>
<td>19%</td>
<td>62%</td>
</tr>
</tbody>
</table>


Greater improvement when Physical Therapy Combined with SYNVIS

Mean improvement in WOMAC pain score at 6 months

Visco superior to saline control

3. Hyalgan Product Information
4. Supartz Product Information
5. Orthovisc Product Information
6. Euflexxa Product Information
7. Altman et al. FLEXX Trial Poster. 2008
Visco is superior to intra-articular steroid

Wang et al., JBJS 2006

Meta-Analysis of Randomized Controlled Trials

- 1647 knees evaluated for efficacy.
- 2253 knees evaluated for safety.
- Crosslinked HA showed a much greater improvement in all analyzed outcomes than did non-crosslinked.

Future of viscosupplementation: Length of time after delivery?

- The average intrasynovial ½ life of HA is ≈ 20 hrs.
- Cross-liked version has been reported to be present for up to 30 days.
- Perhaps cross-linking, fluid gel ratios and controlled-release carriers may ↑ the duration of action of intra-articular HA treatment

Watterson. JAAOS, 2000
Fraser, Semin Arthritis Rheum, 1993

Future of viscosupplementation

- 120 patients with isolated ACL repair
- comparing injections of saline at 4 wks. and Synvisc at 4, 8 & 12 wks.
- Compared Lysholm, ROM, ambulation speed, muscle peak torque knee flexion
- Best results at 1 yr. in HA group injected at 8 week post-op

Huang, Chin J Sport Med, 2007
Yagishita, Arthroscopy, 2005

RESEARCH