Osteoarthritis: Quo Vadis
Where are we now - Where are we going?

Roland W. Moskowitz, MD
Clinical Professor of Medicine
Division of Rheumatology
University Hospitals Case Medical Center

DISCLOSURES
- Pfizer Inc - Speaker’s Bureau
- Novartis Pharmaceutical - Speaker’s Bureau
- Iroko Pharmaceuticals - Consulting fees
- Johnson and Johnson - Consulting fees
- Lilly Company - Consulting fees
- Wyeth Pharmaceuticals - Consulting fees
- Cypress Biosciences Inc - Consulting fees
- Smith and Nephew - Consulting fees

Klemperer Lecturership
Collagen Disease-Historical Insights

Klemperer P, Pollack AD, Baehr G
Pathology of Disseminated Lupus
Arch Path 32:569, 1941

“Collagen Disease” - coined by Dr Paul Klemperer
Mt Sinai Hospital, NYC, 1941

Nomenclature
Klemperer P, Pollack AD, Baehr G
Diffuse Collagen Disease, acute disseminated LE and diffuse scleroderma
JAMA 119:331, 1942

OSTEOARTHRITIS-HISTORICAL BEGINNINGS
History of OA
N. Abrams-Hollander’s Arthritis

• As old as history itself
• In Prehistoric Dinosaurs-200,000,000 years ago
• Exostoses in JAVA MAN-Pleistocene Age-500,000 years ago
• Oldest known human case-Neanderthal Man-40,000 years ago
• Prehistoric American Indian Remains

OA Epidemiology - U.S.

• Year 2000 - 20 million with OA
• Year 2020 - 40 million with OA
• Prevalence Radiographic Knee OA-
  - Women age 80+: 53-55%
  - Men age 80+: 22-33%

OA Epidemiology

• Western countries
  - 10-50% seniors affected
  - 25% severely symptomatic
• Japan
  - 10 million of 120 million people affected
  - Increase by 900,000 per year

Epidemiology of OA

• Pain and Functional Limitation Related to Knee OA
  - Ages 55-64: 13% of Americans
  - Ages 65-74: 17% of Americans

PART 1

• ETIOLOGY
• PATHOPHYSIOLOGY
• CLINICAL FEATURES
OA-Etiopathogenesis

• “Disease of failed cartilage repair caused by increased mechanical stress”

• (Brandt, K, Dieppe, P, Radin, E, Rheumatic Diseases Clinics of North America, 34.531:12008)

ABNORMAL STRESS-NORMAL JOINT ANATOMY PHYSIOLOGY

• NORMAL STRESS-ABNORMAL JOINT ANATOMY PHYSIOLOGY

• Poole, AR, Guilak, F, Abramson, SB in Moskowitz, RW, Osteoarthritis, 4th ed.

OA of the Knee

Osteoarthritis: More than a Disease of Cartilage

WORMS (Whole Organ MRI Scoring Method)

• Articular cartilage integrity
• Subarticular bone abnormality
• Subarticular bone attrition
• Marginal osteophytes
• Cruciate ligament integrity
• Synovitis/effusion
• Loose bodies

Early Osteoarthritis: Histopathology
Advanced Osteoarthritis: Histopathology

Osteoarthritis: Synovitis

Schema: Cartilage Component Architecture
- “Lamina splendens”
- Artificial split line
- Collagen
- Chondrocyte
- Proteoglycans (and) water
- “Tide mark”

Partial Meniscectomy Model (Rabbit)

Etiology

Ageing

OA vs. AGING

PREVALENCE OF SEVERE OA (Grades 3 & 4) IN PERCENT

AGE IN YEARS

Females

Males
IV Disc: Ageing Pigmentation

Non-enzymatic Cross-links
Advanced Glycation End Products

Collagen Cross-linking with Ageing

Desert Sand Rat: Intervertebral Disc
Cross-linking Changes with Age

Pyridinoline

Pentosidine

Pentosidine

Pyridinoline

nmols/mg collagen

Age (months)

nmols/mg collagen

Age (months)

0 3 6 12 18 24

Lid Tendon Skin

Lid Skin
Genetics

Gene Contributions

• Occurrence
• Age at Development
• Sites of Involvement
• Disease Severity
• Rate of Progression
MSCs In-Vitro Culture

Heritable Cartilage Debonding Syndrome: a New Disease Entity - Clinical Features


Heritable Cartilage Debonding Syndrome: Clinical Features

- Joint symptoms late first decade
- Shoulder, hip, and knee pathology
- Femoral head deformity: coxa valga
- Dx: Perthes, Osgood-Schlatter, SED, MED, metaphyseal dysplasia
Arthroscopic Findings

Results: Sequence Analysis

- Two unique, tightly linked SNP’s identified in hereditary chondrolysis family:
  - Exon 6 C->G Arg-Gly
  - 3’ UTR G->A

Advances in Diagnosis

Biomarkers
**GOGO Biomarkers**

- **Matrix Turnover**
  - COMP (Cartilage Oligomeric Matrix Protein)
- **Synthesis**
  - NEOEPITOP 846 (proteoglycan synthesis)
  - PIANP (type II collagen synthesis)
  - CII Propeptide (type II collagen synthesis)
  - PINP (type I collagen synthesis)
- **Collagen degradation**
  - CTX-II (Urine) (type II collagen)
  - NTX-I (Urine) (type I collagen)
- **Inflammation**
  - CRP (C-Reactive Protein)
  - HA (Hyaluronic Acid)
- **Bone Turnover**
  - BSP (Bone sialoprotein)
  - ALP (Bone alkaline phosphatase)

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**BIOMARKERS**

- **B**—Burden
- **I**—Investigational
- **P**—Prognostic
- **E**—Efficacy of therapy
- **D**—Diagnostic

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**Biomarker Responses Over Time**

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Biomarkers</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degradation</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Synthesis</td>
<td>↑↑↑</td>
<td>↑↓</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>

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**Table - Pearson Correlation Coefficients**

<table>
<thead>
<tr>
<th></th>
<th>CTX-II (N = 55)</th>
<th>HA (N = 93)</th>
<th>COMP (N = 91)</th>
<th>Epitope 846 (N = 89)</th>
<th>CII Propeptide (N = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TJQOL variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K.L 0 - IV</td>
<td>.298*</td>
<td>.302**</td>
<td>.226*</td>
<td>-.072</td>
<td>.066</td>
</tr>
<tr>
<td>JSN 0 - 3</td>
<td>.229</td>
<td>.430***</td>
<td>.297***</td>
<td>-.131</td>
<td>.032</td>
</tr>
<tr>
<td>Osteophyte 0 - 3</td>
<td>.327*</td>
<td>.277**</td>
<td>.246*</td>
<td>.002</td>
<td>.069</td>
</tr>
<tr>
<td>Sclerosis 0 - 1</td>
<td>.374*</td>
<td>.226*</td>
<td>.195</td>
<td>.063</td>
<td>-.034</td>
</tr>
</tbody>
</table>

* p < 0.05 (2-tailed test). ** p < 0.01 level (2-tailed test). *** p < 0.001 level (2-tailed test).
Radiological Assessment - Caveats

Radiographic Evaluation of DMOADs

- What parameter(s) to study
  - Joint space narrowing
  - Osteophyte
  - Bone sclerosis

Standing AP view extension

Lyon schuss view PA in 30° flexion

OA-PART-2

Advances in Treatment

Intra-articular-Historical

- Liquid petrolatum
- Procaine HCl
- IA Lactic Acid-"stimulate repair"
- Hollander- Cortisone acetate-Compound E-helped in less than 30%
- Compound F-Hydrocortisone-effective


- Rest
- Weight reduction
- Physical therapy
- Aspirin, phenacetin
- IA hydrocortisone
- Warm, dry climate
- X-ray therapy(?)
Treatment – OA – 1972
(RW Moskowitz)

- Rest
- Correct strain
- Lose weight
- Physical therapy
- Aspirin, indomethacin, butazolidin, ibuprofen
- Roentgen therapy
- IA silicone oil

Baseline Non-pharmacologic Management
(Exercise - Weight Loss – Avoidance of Overuse)

**Mild-to-moderate Pain**
- Simple analgesics (e.g., paracetamol)
- Topical creams

**Moderate-to-severe Pain**
- COX-2 selective inhibitors
- NSAIDs + gastroprotection

**Additional Therapies**
- IA hyaluronan
- IA steroids

**Surgery**
- Chondroplasty
- Biologic resurfacing
- Osteotomy
- Joint replacement

**IA** = intra-articular

American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000

**Assessment of Small-Bowel Lesions by Video Capsule Endoscopy**

**NSAID-Induced Small-Bowel Lesions (cont.)**

Therefore, Protein Pump Inhibitors may not be gastroprotective with NSAIDs

American College of Gastroenterology
Safety Cardiovascular

Medi-Cal: NSAIDs and Risk for AMI

Medi-Cal Population (>18 years) with Physician-diagnosed Arthritis (1999-2004)*

<table>
<thead>
<tr>
<th>NSAID</th>
<th>OR for AMI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>1.09 (0.99-1.21)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.11 (1.01-1.22)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1.28 (1.10-1.50)</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>1.27 (1.05-1.53)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.25 (1.08-1.44)</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>1.18 (0.92-1.52)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1.29 (0.93-1.79)</td>
</tr>
<tr>
<td>Celecoxib ≤25 mg</td>
<td>1.49 (1.16-1.92)</td>
</tr>
<tr>
<td>Other NSAIDs</td>
<td>1.44 (1.16-1.78)</td>
</tr>
</tbody>
</table>

*2,356,885 person-years of follow-up; 15,343 cases of AMI

P = 0.0001 vs celecoxib
P = 0.02 vs celecoxib
P = 0.04 vs celecoxib
P = 0.005 vs celecoxib
P < 0.0001 vs celecoxib

AMI=acute myocardial infarction; SCD=sudden cardiac death.
Adj = adjusted for age, gender, health plan region, medical history, smoking, and medication use.

Ibuprofen Interaction with Aspirin

Nutraceuticals

- Glucosamine
- Chondroitin sulfate
GAIT Study

Primary Outcome Measure:
• 20% improvement in WOMAC Pain Scale from baseline to week 24.

Results: (Approx 315 patients/group)
  • Celecoxib vs. Placebo = Sig. (p=0.008)
  • G + CS vs. Placebo = Not Sig. (p=0.09)
  • CS vs. Placebo = Not Sig. (p=0.17)
  • G vs. Placebo = Not Sig. (0.3)

GAIT Study

• Moderate-to-Severe Pain Stratum (WOMAC Pain Score= 301-400 mm)

• Results: (Approx 70 patients/group)
  - G + CS vs. Placebo = Sig. (p=0.002)
  - Celecoxib vs. Placebo = Not Sig. (p=0.06)
  - G vs. Placebo = Not Sig. (p=0.17)
  - CS vs. Placebo = Not Sig. (0.39)

Intra-articular Therapy

• Corticosteroids
• Hyaluronans

HAs: Proposed Biologic MOA

Viscosupplementation
• Physical and biomechanical
• Analgesia-coating nociceptors

Biologic Activity
• Biosynthesis and degradation
• Antiinflammatory

Intra-articular Interleukin-1ra in Osteoarthritis

• 150 mg IL-1ra intra-articular
• Symptomatic knee osteoarthritis
• Improvement through day 30
• No toxicity observed
Structure Modification - The Holy Grail of Therapy

Therapeutic Agents

Disease Modification?
- MMP-Inhibitors
- Cathepsin Inhibitors
- IL-1 RA; TNF-alpha inhibitors
- Growth Factors (IGF-1, TGF-β)
- RAGE-(Receptor-Advanced Glycation Endproducts)
- Inhibition iNOS(inducible NO synthase)
- Oral salmon calcitonin

Reduction in Experimental Osteoarthritis by Nitric Oxide Synthase Inhibition
- Experimental ACL Dog Model
- Selective inhibitor iNOS(0.3,1,10 mg/Kg/day-12 weeks
- Decreased size gross and histologic lesions
- Dose-dependent

**Structure-Modification Results: Mean Joint Space Narrowing (JSN) at Three Years**

<table>
<thead>
<tr>
<th></th>
<th>Mean JSN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucosamine 1500 mg/d</td>
<td></td>
</tr>
<tr>
<td>Placebo (n=71/106)</td>
<td>0.31 mm</td>
</tr>
<tr>
<td>Glucosamine (n=68/106)</td>
<td>0.06 mm</td>
</tr>
</tbody>
</table>


**Structure Modification Results**

<table>
<thead>
<tr>
<th></th>
<th>Mean JSN</th>
</tr>
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<tbody>
<tr>
<td>Placebo (n=71/106)</td>
<td>0.18 mm</td>
</tr>
<tr>
<td>Doxycycline (100 mg b.i.d)</td>
<td>0.12 mm</td>
</tr>
</tbody>
</table>

Brandt et al.

**Chondrocyte Repair**

**The Mesengenic Process**

- **Progenitor**
  - Bone marrow / periosteum
  - Myogenesis
  - Osteogenesis
  - Chondrogenesis
  - Marrow stroma
- **Lineage progression**
  - Transitory osteoblast
  - Transitory chondrocyte
  - Transitory stromal cell
  - Transitory fibroblast
- **Commitment**
  - Myoblast fusion
- **Maturation**
  - Osteocyte
  - Hypertrophic chondrocyte
  - Myotube
  - Stromal cells
- **T/L fibroblast**
  - Adipocytes, dermal and other cells
- **Unique micro-niche**
  - BONE
  - CARTILAGE
  - MUSCLE
  - MARROW
  - TENDON / LIGAMENT
  - CONNECTIVE TISSUE

**Cell Therapy**

- Harvest bone marrow
- Mitotic expansion medium
- Cryo-preserve for future use
- Repopulate marrow
- Effects on homoeosis
- Normal bone homeostasis (anti-aging)
- Massive bone repair
- Repair cartilage defect
- Harvest expanded MSC
- Culture dish bonded MSC - McAb
- Push to osteoblast
- Push to chondrocyte
- Masses on hemopoiesis

**Cartilage Repair**

- Caplan, A, et al.
OARSI Cardiovascular Guidelines

- Therapeutic approaches to the management of acute myocardial ischemia
  - Drug coated-stent VS
  - Non-drug coated-stent VS
  - Immediate bypass surgery

“Doctors pour drugs of which they know little to cure diseases of which they know less into human beings of whom they know nothing”

Voltaire

OARSI Guidelines

- General modalities: 1
- Non-pharmacologic modalities: 2–12
- Pharmacologic modalities: 13–20
- Surgical modalities: 21–25
- Selected from 60+ submitted propositions

All patients with hip and knee OA should be given information access and education about the objectives of treatment and the importance of changes in lifestyle, exercise, pacing of activities, weight reduction, and other measures to unload the damaged joint(s). The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals. Subsequently, emphasis should be placed on encouraging adherence to the regimen of non-pharmacologic therapy.
Pharmacologic Therapy: Representative Propositions

In patients with symptomatic hip or knee OA, non-steroidal anti-inflammatory analgesic drugs (NSAIDs) should be used at the lowest effective dose but their long-term use should be avoided if possible. In patients with increased GI risk, either a COX-2 selective agent or a non-selective NSAID with co-prescription of a proton pump inhibitor or misoprostol for gastroprotection may be considered, but NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with cardiovascular risk factors.

The use of weak opioids and narcotic analgesics can be considered for the treatment of refractory pain in patients with hip or knee OA where other pharmacological agents have not been effective or contraindicated. Stronger opioids should only be used for the management of severe pain in exceptional circumstances. Non-pharmacological therapies should be continued in such patients and surgical treatments should be considered.

Treatment with glucosamine and/or chondroitin sulfate may provide symptomatic benefit in patients with knee OA. If no response is apparent within 6 months, treatment should be discontinued.

“Doctors pour drugs of which they know much to cure diseases of which they know a great deal into human beings of whom they know a lot”

Voltaire
(Moskowitz editorial revision)


“I’m concerned and many people are concerned that the pendulum is swinging too far back” -

Dr. Russell Portenoy