The New Science of Osteoarthritis

What it means in managing our patients

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Osteoarthritis: Key Points

Perspective: OA is a disease of the whole joint, not just cartilage.

Diagnosis: Dx of OA is based on clinical features and supported by radiography.

Course: of OA is variable.

Treatment: is based on structural changes, pain, and function and can benefit OA.

Surgical intervention should be considered when medical treatment has failed.
The public health impact of Osteoarthritis

- Medical Costs: $2,017 average per person per year attributed to OA
- Lost Work: $80 billion in earnings/yr attributed to OA
- OA affects 30+ million US Adults
- 23.7 million have difficulty with usual activities due to arthritis
- 40% of adults with arthritis are Inactive
- Inactivity makes it harder to manage Obesity, Diabetes, & Heart Disease
- 1 in 3 Veterans affected, compared with 1 in 5 Civilians
Osteoarthritis
A group of distinct overlapping diseases characterized by the biomechanical failure of a diarthrodial joint with:
1. Cartilage loss and
Some people have risk factors for osteoarthritis, but no disease; some have radiographic changes but no symptoms; and some have symptoms and signs associated with osteoarthritis. Our understanding of drivers of conversion from one of these states to another is incomplete.
Epidemiology of OA

- Estimates of the prevalence are imprecise because of difficulties in definition.
- 80% over 55 have x-ray evidence. 10-30% have significant pain and functional impairment.
- Hands (DIP, PIP, 1st CMC), knees, hips, and 1st MTP joints are the most commonly affected.
Distribution of Peripheral Joints in Osteoarthritis

- First carpometacarpal joint
- Hip
- Distal and proximal interphalangeal joints
- Knee
- First metatarsophalangeal joint
Pathologic changes in osteoarthritis
A NORMAL VERSUS AN OSTEOARTHRITIC SYNOVIAL JOINT

Normal

OA

irregular thickening and remodeling of subchondral bone, with sclerosis and cysts

thickening, distortion and fibrosis of the capsule

fibrillation, loss of volume and degradation of articular cartilage

modest, patchy, chronic synovitis

osteoophytosis and soft tissue growth at joint margin

Fig. 1.2 The characteristics of OA. Normal versus osteoarthritic synovial joint.
Articular Cartilage

- Avascular, aneural, alymphatic
- Water - 66-79% depending on age
- Chondrocytes - synthesize all components
- Collagen - (mostly type II) gives strength and form
- Ground substance - give flexibility, glycosaminoglycans and proteins
Healthy Cartilage

- Chondrocyte
- GAG
- Collagen
- Water & Mobile Ions
- Hyaluronic Acid

Damaged Cartilage

Progressive loss of Glycosaminoglycans

© Going
Cartilage structure

Surface layer

Collagen fibres

Calcified cartilage

Subchondral bone
Aging        Osteoarthritis

Water content

GAG        nl or sl

C4S/C6S

Keratan sulfate

Deg. enzyme

GAG- glycosaminoglycan,
Common clinical features of osteoarthritis that allow a bedside diagnosis to be made

**Increased age**

It is unusual to develop the disease before age 40 years.

**Pain**

Use-related joint pain, relieved by rest, is one of the cardinal features of the disease; in more advanced cases rest pain and night pain can also develop.

**Stiffness**

Most people with symptomatic osteoarthritis of large joints experience short-lasting inactivity stiffness or gelling of joints, which wears off in a few minutes with use.

**Reduced movement**

The range of movement of the joint is often restricted, and there is generally pain on movement, particularly at the end of the range.

**Swelling**

Many osteoarthritic joints develop palpable firm swellings at the joint margin due to the formation of osteophytes; some have minor soft tissue swelling due to secondary synovitis.

**Crepitus**

Osteoarthritis joints often crack or creak on movement.
Tissue | Mechanism of OA Pain
---|---
Subchondral bone | Medullary hypertension
Osteophytes | Periosteal nerve stretching
Ligaments | Stretch
Capsule | Distension, inflammation
Muscle | Spasm
Synovium | Inflammation

Cartilage has **no** nerves and is **not** a direct pain generator.
FACTORS AFFECTING PAIN RESPONSE

- Demographic features (e.g. ethnicity, gender)
- Genetics
- Personality
- Catastrophizing and coping skills
- Expectations of treatment
- Previous pain experiences
- Presence of comorbidities (e.g. depression)
Age
Genetics
Systemic factors (e.g., obesity)

Predisposition to osteoarthritis

Joint biomechanics

Biochemical pathways (cytokines, proteases, and so on)

Site and severity of osteoarthritis

Psychosocial and socioeconomic characteristics

Comorbidities

Pain

Disability
Distress

Injury
Overload
Instability
OA: An Amplified Pain Response

Subjective Pain Intensity vs. Stimulus Intensity

- **Hyperalgesia**
  - (e.g., when a pinprick causes an intense stabbing sensation)

- **Allodynia**
  - (e.g., hugs that feel painful)

Pain in OA

Pain amplification response

Normal Pain Response

## Risk factors for osteoarthritis

<table>
<thead>
<tr>
<th>Systemic factors</th>
<th>Biomechanical factors</th>
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<td>• Age</td>
<td>• Obesity</td>
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<td>• Ethnicity</td>
<td>• Joint biomechanics</td>
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<td>• Gender</td>
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<td>• Joint Injury</td>
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<td>• Hormonal status</td>
<td>• Occupation</td>
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<td>• Physical Activity</td>
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# Factors in the Pathogenesis of Osteoarthritis

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<td><strong>Factors</strong></td>
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Dolly
First cloned sheep
Named for Dolly Parton
**Osteoarthritis**

**Pathomechanisms**

- **Differentiation**
- **Anabolism**
  - Proliferation
- **Catabolism**
  - Calcification
  - Cell death/apoptosis

**Developmental model:** endochondral ossification

**Developmental steps**

- Chondrogenesis
- Matrix synthesis
- Proliferation
- Matrix degradation
- Hypertrophy
- Calcification
- Cell death/apoptosis

**Marker genes**

- COL2A
- COL2/9/11
- aggrecan
- Sox-9
- Ki-67
- ssDNA
- COL10
- MMP-13

**Ossification**
Local OA Factors
- Obesity
- Joint injury
- Joint alignment
- Joint anatomy

Systemic OA Factors
- Gender/hormonal
- Genetics
- Race
- Obesity
- Nutrition
- Occupation

Aging changes affecting joint function
- Sarcopenia
- Increased fat mass
- Reduced activity
- Loss of proprioception and balance
- Joint laxity

Aging changes affecting joint tissues
- Cell senescence – secretory phenotype, reduced growth factor response, oxidative stress/damage
- Brittle cartilage from AGEs
- Loss of normal bone structure
- Increased stiffness of ligaments and tendons
- Meniscal degeneration

Osteoarthritis Site and Severity
<table>
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<th>Table 1. Common Risk Factors for Knee Osteoarthritis</th>
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<tr>
<td>Female sex</td>
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<tr>
<td>Inflammatory joint disease (e.g., infection, gout, rheumatoid arthritis)</td>
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<tr>
<td>No history of osteoporosis</td>
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<tr>
<td>Obesity (strongest modifiable risk factor)</td>
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<tr>
<td>Occupation requiring repetitive knee bending</td>
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<tr>
<td>Older age</td>
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<tr>
<td>Previous knee injury (e.g., torn meniscus, intra-articular mechanical damage)</td>
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Symptoms Of Knee Osteoarthritis

- Pain
- Stiffness
- Hard swellings (caused by osteophytes)

- Soft swellings (caused by extra fluid in the joint).
- Crepitus, a creaking, crunching, grinding sensation when you move the joint.
Factors associated with hip osteoarthritis:

- Increasing age
- Family history of osteoarthritis
- Previous injury to the hip joint
- Obesity
- Improper formation of the hip joint at birth, a condition known as developmental dysplasia of the hip
Osteoarthritis of the hands

- Distal interphalangeal (DIP) joints are most often affected
- Proximal interphalangeal (PIP) joints and the carpometacarpal (CMC) joints at the base of the thumb are also typically involved
- Heberden’s nodes (palpable osteophytes in the DIP joints) are more characteristic in women than in men
- Frequently have few or no symptoms
- Inflammatory changes are typically absent, less pronounced, or go unnoticed
Inflammatory osteoarthritis

Narrowing and osteophytes affecting multiple interphalangeal joints. Note the "gull-wing" configuration of the distal interphalangeal joint of the middle finger due to central erosion. There is also ankylosis of the distal interphalangeal joint of the index finger.
Cytokines in OA
Does osteoarthritis always progress in flares?

- The natural history of osteoarthritis has not yet been fully elucidated.
- It varies widely depending on the joint affected and the patient.
- Once diagnosed, it seems to progress in a non-linear fashion.
- Two other patterns of progression have also been described:
  - Rapidly destructive osteoarthritis, which causes complete destruction of the cartilage within 24 months.
  - Slowly progressing osteoarthritis, without obvious flares.

Natural history of OA

• Progression in the knee may take many years. Cohort studies have found that radiographic deterioration occurs in one-third.

• Progression of hip disease is variable. A Danish study found that 66% of hips worsened radiologically over 10 years, although symptomatic improvement was common.

• Hand disease is relapsing and remitting with episodic inflammatory phases associated with redness and swelling. Flares then reduce in frequency, and pain also improves.
OA is a condition that progresses slowly over years and cannot be cured. Treatment is directed at decreasing symptoms and slowing the progression.

- Control *pain* and other symptoms.
- Correct *functional limitations* and disability.
The gap in treatment modalities between rheumatology and orthopaedics.

Floris P J G Lafeber, and Jacob M van Laar Ann Rheum Dis 2013;72:157-161
OA Treatment

Interventions that can impact the course:

• Education
• Exercise
• Weight reduction
• Medications
Severe osteoarthritis

Surgery:
Joint replacement, osteotomy

Non-surgical interventions:
NSAIDs, other drugs, physiotherapy, occupational therapy, orthoses, other aids

Information, advice, self-help:
Education, weight loss, exercise, lifestyle alterations, simple analgesics, topical agents

Mild osteoarthritis

Few

Some

All

Number of people
10% weight loss through diet and exercise = 50% reduction in knee pain from osteoarthritis (OA).

Figure 1: Skeletal Muscle Aging

Aging is associated with gradual loss of muscle mass and strength, a decline that begins as early as age 25.

Factors that contribute to skeletal muscle aging include the decreased proliferative ability of muscle cells and the adverse effects of oxidative stress, which can cause premature muscle aging.

There is more infiltration of fat into cells, and fast-twitch muscle fibres age at an accelerated pace compared to slow-twitch muscle fibres.
Exercise: General Principles

- Muscles are the major supporting structures of joints.
- Chose exercises that are convenient and enjoyable.
- Balance activity and rest - pacing.
- Avoid significant pain.
- Understand activity threshold.
Table 1. Current recommended OA drugs by AAOS, ACR, and OARSI\(^3,24,48–49\)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Recommendations</th>
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| Acetaminophen                | **AAOS:** Inconclusively recommended for symptomatic knee OA with 3 000 mg per day (moderately recommended in the 2008 edition with up to 4 000 mg per day)  
**ACR:** First-line drug up to 4 000 mg per day  
**OARSI:** An effective initial oral analgesic for mild-to-moderate OA pain up to 4 000 mg per day |
| Non-selective NSAIDs         | **AAOS:** Strongly recommended for symptomatic knee OA  
**ACR:** Conditionally recommended for hand, knee, and hip OA  
**OARSI:** Recommended for patients with symptomatic hip or knee OA at the lowest effective dose |
| Selective COX-2 inhibitors   | **AAOS:** Strongly recommended for symptomatic knee OA  
**ACR:** Conditionally recommended for hand, knee, and hip OA  
**OARSI:** Recommended for patients with symptomatic hip or knee OA at the lowest effective dose |
| Opioid analgesics (tramadol) | **AAOS:** Strongly recommended for symptomatic knee OA  
**ACR:** Conditionally recommend for hand, knee, and hip OA  
**OARSI:** Consider use for the treatment of refractory pain in patients with hip or knee OA |
| SNRIs (duloxetine)           | **AAOS:** Not included  
**ACR:** Conditionally recommended for patients \(\geq 75\)  
**OARSI:** Not included |
| Intra-articular corticosteroids | **AAOS:** Inconclusively recommended for symptomatic knee OA  
**ACR:** Conditionally recommended for hip and knee OA  
**OARSI:** For patients with moderate-to-severe pain who are not respond to oral analgesic and anti-inflammatory agents |
| Intra-articular hyaluronic acid | **AAOS:** No longer recommended (inconclusively recommended in the 2008 edition)  
**ACR:** No recommendation  
**OARSI:** May be useful in patients with knee or hip OA |

ACR, American College of Rheumatology; AAOS, American Academy of Orthopaedic Surgeons; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; SNRIs, serotonin-norepinephrine reuptake inhibitor.
Increasing degrees of selectivity for COX-2 are associated with augmented CV risk whereas increasing degrees of selectivity for COX-1 are associated with augmented gastrointestinal risk.
**Normal cartilage**
- Glucosamine in protein lattice framework
- Joint fluid moves in and out of the cartilage. The fluid binds to the glucosamine and provides elasticity
- Cartilage surface
- Normal joint fluid

**Abnormal cartilage**
- Lower levels of glucosamine in a poor protein lattice framework
- Low quality inflamed joint fluid moves in and out of poor quality cartilage. This fluid binds to the lower levels of glucosamine and provides less elasticity. Result is cartilage deterioration
- Inflamed/poor quality joint fluid
- Cracked Cartilage surface

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**Kirkland Signature**

**Joint Health**
Helps relieve joint pain associated with osteoarthritis

- Kirkland Glucosamine Chondroitin & MSM 500/400/300 mg
- 300 Tablets
Glucosamine and Chondroitin

- No evidence when administered p.o., IM, or IA of incorporation into the cartilage matrix.
- Trials: methodological issues, 50-80% respond—often rapidly.
- Effects: anti-inflammatory, stimulation of GAG synthesis.
- Conclusions: Modest benefit, equivalent to low dose NSAIDs, well tolerated, chondroprotection.
Stem Cells and Cloning: Advances and Applications
Figure 3 Examples of MSC therapy used for the treatment of joint lesions or preclinical models of OA

Barry, F. & Murphy, M. (2013) Mesenchymal stem cells in joint disease and repair


Barry, F. & Murphy, M. (2013) Mesenchymal stem cells in joint disease and repair
PRP action mechanisms

Osteoarthritis
- TNFα
- IL-1
- IL-1 R
- Metalloproteinases
- Chondrocyte

PRP action
- TNFα soluble receptor
- IL-1 receptor antagonist
- TGF-β1
- TIMPS
- Chondrocyte
- Metalloproteinases

Growth factors (PDGF, TGF-β, IGF, FGF-2)
- Osteoblast
  - Proliferation of osteoblasts
  - Collagen deposition
  - Osteoclast formation
  - Bone formation
  - Bone regeneration

Growth factors (PDGF, TGF-β, IGF, FGF-2)
- Synoviocyte
  - Hyaluronic acid production
Criteria for Referral to Orthopedic Surgery

1. Intractable pain
2. Loss of function and impaired activities of daily living
3. Unstable knee
4. Other factors: age, health status, weight, level of activity, functional limitations
Metallic replacement for head and neck of femur

Plastic and metallic replacement for acetabulum (hip socket)

Artificial Hip Joint

Artificial Knee Joint

Metallic replacement for bottom of femur (thigh bone)

Plastic replacement for patella (knee cap)

Plastic replacement for top of tibia (shin bone)
A 2016 AAOS guideline on surgical management of knee OA includes the following recommendations regarding total knee arthroplasty (TKA)

- Obese patients have less improvement in outcomes (strong supporting evidence)
- Patients with diabetes are at higher risk for complications (moderate evidence)
- Patients with select chronic pain conditions have less improvement in patient-reported outcomes (moderate)
- Patients with depression and/or anxiety symptoms have less improvement in patient-reported outcomes (limited)
- Patients with cirrhosis or hepatitis C are at higher risk for complications (limited)
- An 8-month delay to TKA does not worsen outcomes (moderate)