Advances in Osteoarthritis Since the Founding of OARSI

Marc C. Hochberg, MD, MPH, MACP, MACR
Professor of Medicine and Epidemiology and Public Health
Head, Division of Rheumatology and Clinical Immunology
Vice Chair, Department of Medicine
Director, Medical Care Clinical Center
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- Stock ownership
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OARSI: 25th Anniversary

- Initially registered under French law in 1990
- Charles Joel Menkes, 1st president
- Roy D. Altman, 1st Editor of OA&C
- Inaugural Congress held in Paris in 1992

Dr. and Mrs. Menkes dancing at the Inaugural OARSI Congress, 1992
Methods

• Email survey of current and past Presidents of OARSI requesting list of top 5 advances in OA since formation of OARSI (1990)
  • Thanks to Ms. Diann Stern
• Responses received from all but 2 persons
• Top 10 responses chosen for presentation
Top Ten List

• Feature of David Letterman’s Late Night TV show since 18 Sept 1985
  • Started on NBC before switching to CBS in 1993
• Probably inspired by the “Top Ten” records of the week on “American Bandstand” hosted by Dick Clark (1956-89)
#10 Genetics of OA

- Candidate genes based on mutations in structural proteins of articular cartilage

- Genome-wide association studies
  - TREAT-OA Consortium, arcOGEN, others
  - OAI, JoCo OA Project, GOGO

- Epigenetics

#9 OA Cohorts

- Osteoarthritis Initiative
  - “http://www.oai-ucsf.edu”
- Rotterdam Study
- Cohort Hip and Cohort Knee (CHECK)
- ROAD Study
- Chingford Study
#8 Recommendations

- American College of Rheumatology (ACR)
- European League of Associations of Rheumatology (EULAR)
- National Institute for Clinical Excellence (NICE)
- Osteoarthritis Research Society International (OARSI)
- Chronic OA Management Initiative (COAMI) of U.S. Bone and Joint Initiative

#7 Clinical trials methodology

- OARSI Recommendations for conduct and reporting of clinical trials

- Standardized imaging techniques
  - PA Semi-flexed knee radiographs
  - AP Pelvis radiographs

- OARSI Atlas of Individual Radiographic Features
#7 Clinical trials methodology

- Standardized outcome measures
  - Knee and Hip
  - Hand
- Responder criteria
#6 Biomarkers

- **GREES Recommendations**

- **NIH OA Biomarkers Network (BIPED Classification)**

- **OARSI Biomarker Panel**

- **ESCEO Biomarker Recommendations**

- **FNIH Study**
Sources of Biomarkers in OA
#5 Animal models of OA

**Small and Medium animals**

- Rabbits
  - Partial meniscectomy
- Guinea pigs
  - Hartley albino pigs
- Rats and mice
  - Naturally occurring
  - Genetically modified
  - Post-surgical
  - Post-IA injections

**Large animals**

- Nonhuman primates
- Sheep and goats
  - Medial meniscectomy
- Dogs
  - ACL Transection Model
    - Pond MJ, Nuki G: 1973
  - ACL Transection with dorsal root ganglionectomy

ANIMAL MODELS OF OA

INDUCED MODELS

SURGICAL MODELS
- Meniscal tear:
  - G. pigs: 3w*, 6w§
  - Rats: 3w*, 6w§
- Menisectomy:
  - Mice: 8w*
  - Rats: 1w*
  - Dogs: 3m*
- Articular groove:
  - Dogs: 3w*, 10w§
- Transarticular impact (1,800-2,400N):
  - Dogs: 6m* (3,000N)
  - Dogs: 6m§
- Ovariectomy:
  - Rats: 9w*, 15w*

CHEMICAL MODELS
- Partial meniscectomy lateral:
  - Rabbits: 6w* (4w MRI)
  - Mice: 3-4w*
  - Dogs: 1-3m*
- Monosodium iodoacetate (IA ini):
  - Rats: 1-3d*, 2w§
- Panain (IA ini):
  - Rats: 4w*
  - Mice: 1-3d*, 3w†
- ACL transaction:
  - Mice: 8w‡
  - Rats: 8w§
  - Rabbits: 4w*, 8-12w§
  - Dogs: 3m*
  - PCL: MCL:
    - Rabbits: 12w‡ + removal of MM:
      - Mice: 4w||
      - Rats: 1w*
      - + removal of MM/MLM:
        - + transection of PCL, MCL/ACL:
          - Mice: 2w||

SPONTANEOUS MODELS
NATURALLY OCCURRING OA
- G. pigs: 3m*, 6m†, 18m‡
- Mice: 6m*, 15m§
- C. macaques: >10y†, <15y§
- Hip:
  - Dogs (LR): >2y§

GENETIC MODELS
Depending on the influence of the overexpression or deletion of each investigated gene

#4 Magnetic resonance imaging

- Visualizes all the tissues of the joint in 3 dimensions and detects pathologic changes earlier than conventional X-ray
- Semi-quantitative scoring systems for knee OA
  - WORMS, BLOKS, KOSS, MOAKS, ...
- Quantitative measurement of cartilage thickness and volume
- Various features predict total knee arthroplasty
- Proposed as an outcome measure in trials of DMOADs

MRI Definition of Knee OA

- Systematic review
  - Clinimetric properties of MRI in knee OA
- Delphi exercise
  - OARSI Knee OA Imaging Workgroup
- Validation in subset of 160 OAI participants

- Group A
  - Definite osteophyte
  - Full thickness cartilage loss

- Group B
  - Subchondral BML
  - Meniscal subluxation, maceration or tear
  - Partial thickness cartilage loss
  - Bone attrition

#3 Role of inflammation in OA

- Prostaglandins and eicosanoids
  - Rationale for use of NSAIDs
- Synovitis
- Cytokines, especially IL-1, and NF-KB signalling
- Relationship to obesity, metabolic syndrome and adipokines
- Role of innate immune system
  - Toll-like receptors (TLRs) and complement
  - Damage-associated and pathogen-associated molecular patterns
An hypothesis for the role of inflammation in the pathogenesis of OA according to the phenotype.

Relationship of OA to Metabolic Syndrome

Immune-mediated inflammation in OA

#2 Improved understanding of cartilage metabolism

- Mechanisms of cartilage homeostasis
  - Degradation (catabolism) of matrix
    - Matrix metalloproteinases (collagenases and gelatinases), including MMP-1, -2 and -13
    - Aggrecanases, including ADAMTS-4 and -5
  - Synthesis (anabolism) of matrix
    - Aggrecans
    - Collagens and non-collagenous proteins
    - Role of growth factors, including BMPs
- Role of chondrocyte activation, proliferation, senescence and apoptosis

#1 All of the tissues are involved in the OA process

- “… the name osteoarthritis is a misnomer insofar as it implies an inherently inflammatory process, … the more accurate term [is] degenerative joint disease.”

- “…wear and tear processes play a central role in initiating the degenerative process in cartilage.”
Degenerative Joint Disease is a misnomer and should be discarded from the lexicon
#1 All of the tissues are involved in the OA process

- OA is not a cartilage centric disease
Heliocentrism vs. geocentrism

• Geocentric model proposed by Aristotle and standardized by Ptolemy 2nd c.)
• Copernicus (16th c.) presented model of heliocentric system that was expanded upon by Galileo and Kepler.
OA: OARSI Definition

- OA is a progressive disease representing the failed repair of joint damage that, in the preponderance of cases, has been triggered by abnormal intra-articular stress.
- All of the tissues of the joint are involved, including the articular cartilage, subchondral bone, ligaments, menisci (when present), periarticular muscles and peripheral nerves.
- OA may be initiated by an abnormality in any of these tissues. Thus, OA is not a disease merely of cartilage but is a failure of the synovial joint.

Thank you for your attention