New Directions in Osteoarthritis Research

Kananaskis October 22, 2015

Nick Mohtadi MD MSc FRCSC

No conflicts of interest related to this presentation

Osteoarthritis: Disease? Fact of Life?

- Strong family history of Osteoarthritis
  - Both parents and both brothers
  - Knee and hip replacements
- ACL injuries in three generations in our family
  - Sports or genetics or both?

BENCH TO BEDSIDE AND BACK

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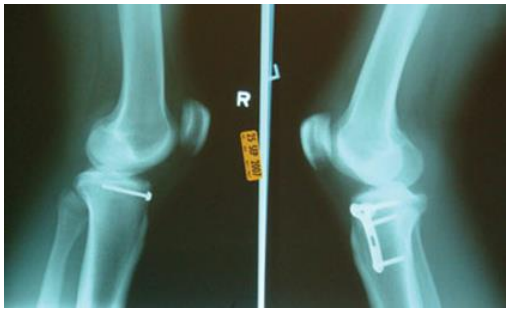
BENCH AND BEDSIDE

- Cy Frank in the orthopaedic world was considered a basic science researcher

- Full-time clinician
  - Clinical research
  - Outcomes development
  - Clinical trials



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BENCH TO BEDSIDE AND BACK

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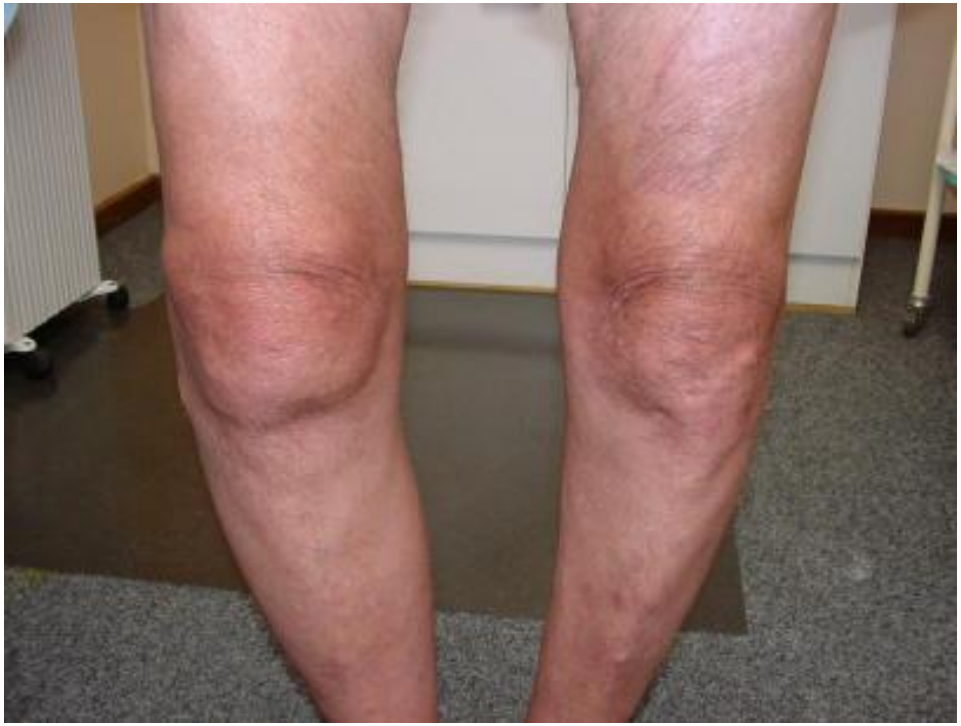
Management of OA Using the ACL deficient knee as the model

- Define OA
- Factors leading to OA in the ACL deficient knee
- Treatment
  - Microfracture
  - Osteotomy
  - Stem Cells?



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DEFINE OA

- Clinically
  - Stiffness
  - Pain
  - Swelling

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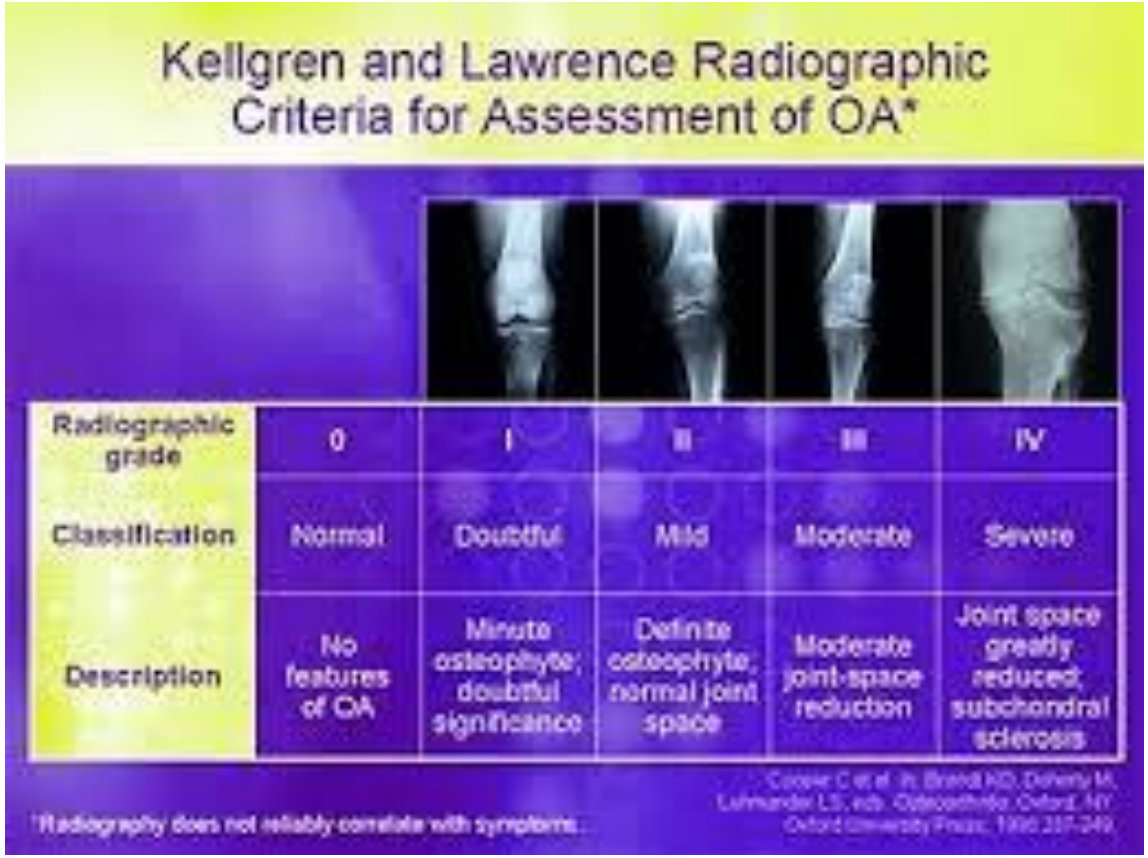
DEFINE OA

- Radiologically
  - Osteophytes
  - Sclerosis
  - Subchondral Cysts
  - Joint space narrowing



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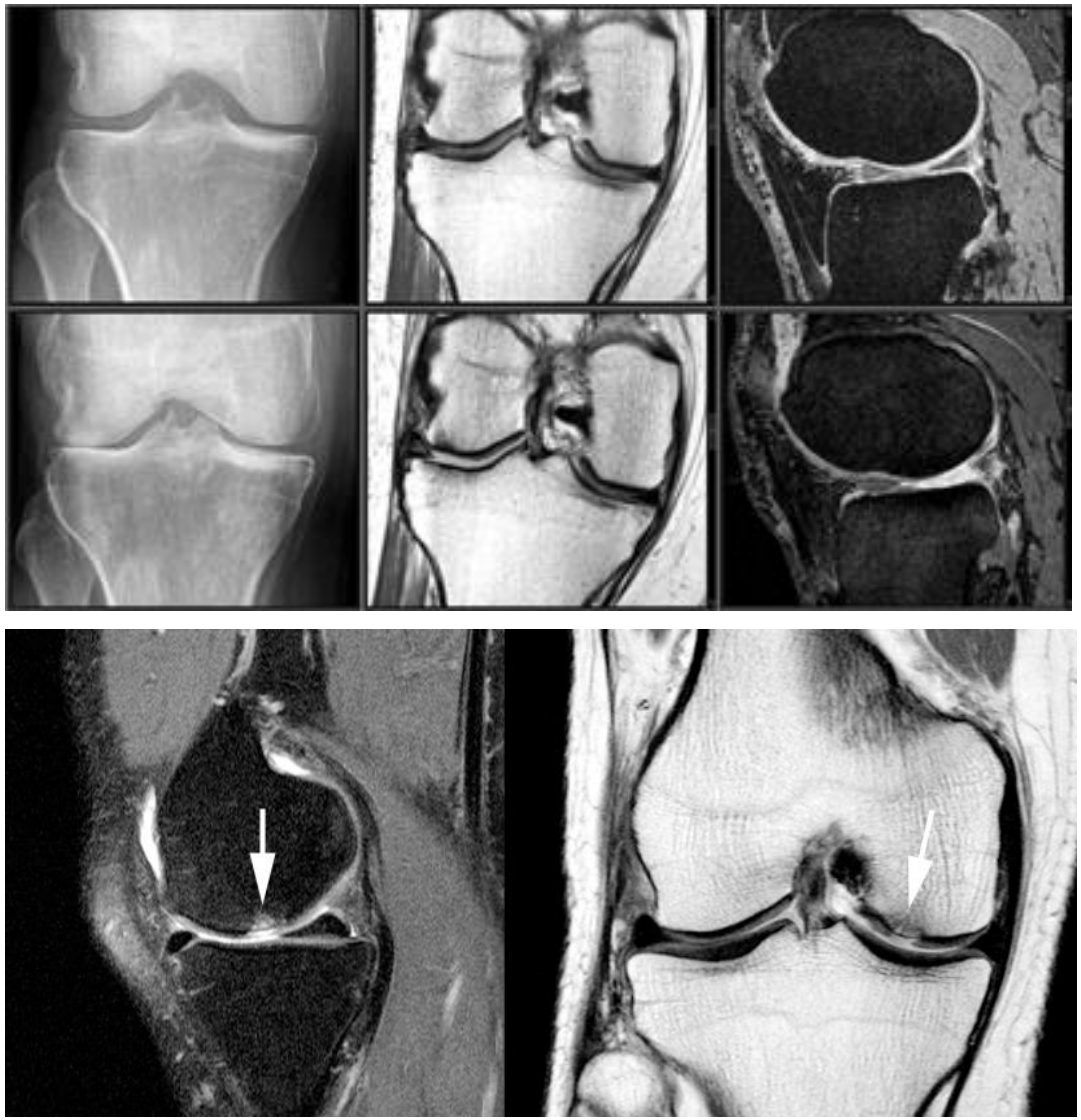
DEFINE OA

- MRI
  - Chondrosis



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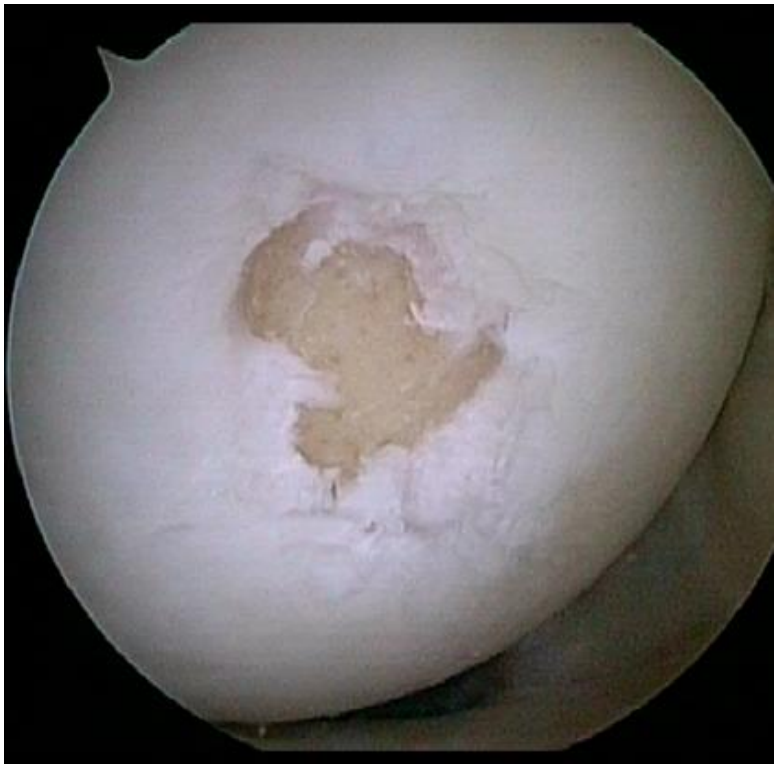
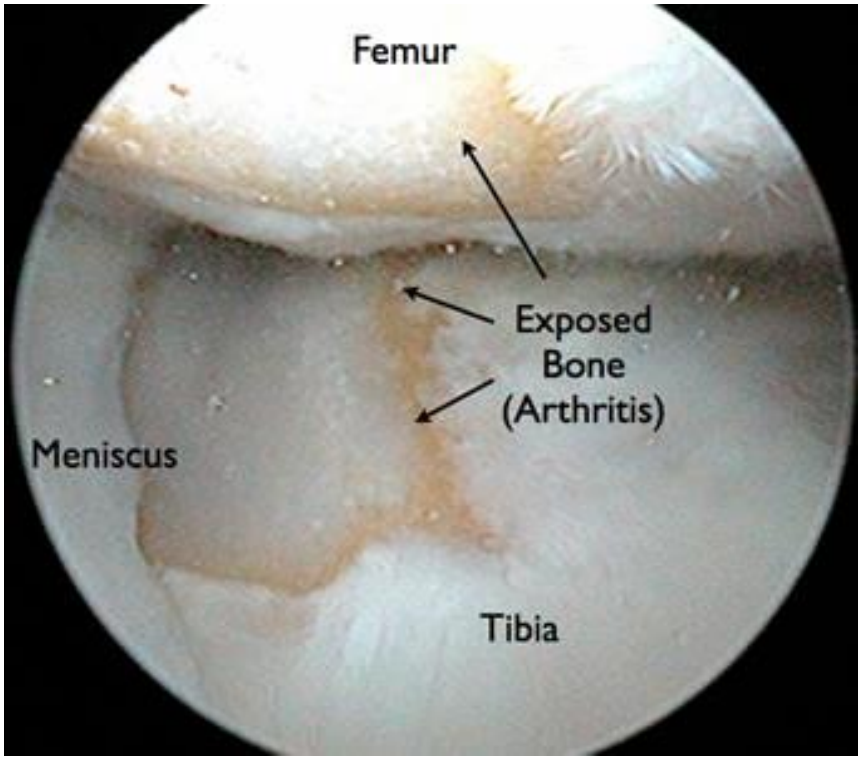
DEFINE OA

- Arthroscopically





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OA: ACR

"A heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins". Clinically, the condition is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation."

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OA: NICE

"Osteoarthritis is characterized pathologically by localized loss of cartilage, remodeling of adjacent bone and associated inflammation. A variety of traumas may trigger the need for a joint to repair itself. Osteoarthritis includes a slow but efficient repair process that often compensates for the initial trauma, resulting in a structurally altered but symptom-free joint. In some people, because of either overwhelming trauma or compromised repair, the process cannot compensate, resulting in eventual presentation with symptomatic osteoarthritis; this might be thought of as 'joint failure'. This explains the extreme variability in clinical presentation and outcome that can be observed between people, and also at different joints in the same person."

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OA: OARSI

"Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness."

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OA: CDC

"Osteoarthritis is a disease characterized by degeneration of cartilage and its underlying bone within a joint as well as bony overgrowth. The breakdown of these tissues eventually leads to pain and joint stiffness. The joints most commonly affected are the knees, hips, and those in the hands and spine. The specific causes of osteoarthritis are unknown, but are believed to be a result of both mechanical and molecular events in the affected joint. Disease onset is gradual and usually begins after the age of 40."

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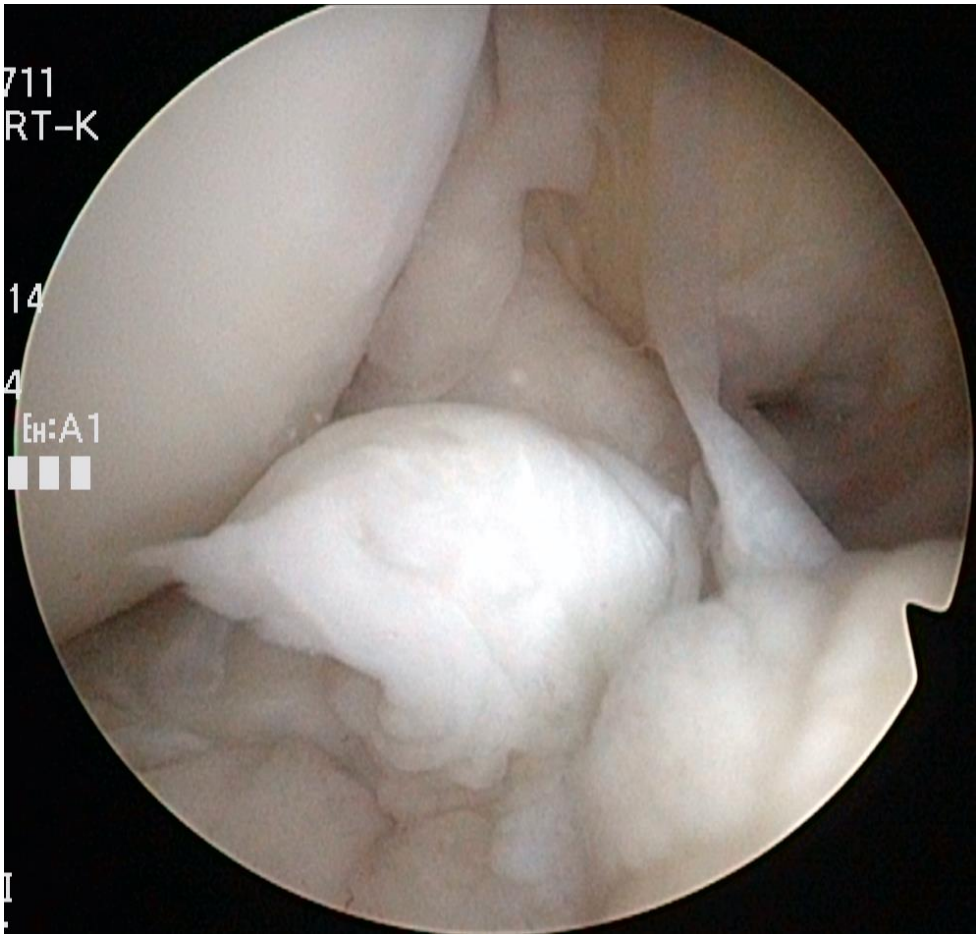
RISK FACTORS FOR OA IN THE ACL DEFICIENT KNEE

- ACL tear
- Genetics
- Meniscal tears
- Chondral injury/Bone bruising
- Knee Alignment



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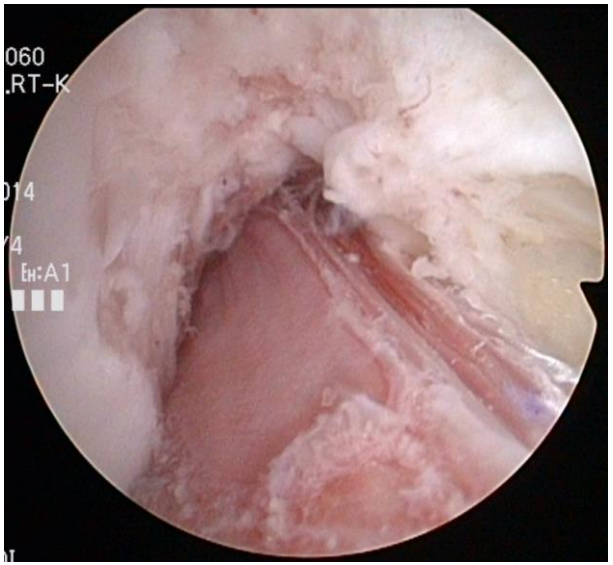
FACTORS LEADING TO OA
ACL TEAR

- Knee joint subluxation
  - Tibia is translated anteriorly/rotationally
  - Axial load
- ACL healing?
  - Always heals but not well
    - Mechanism of injury
    - 10% of the time healing is consistent with a relatively stable knee
- ACL reconstruction



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GENETICS

- Major risk factor in determining risk of getting an ACL tear
  - Predictor of OA

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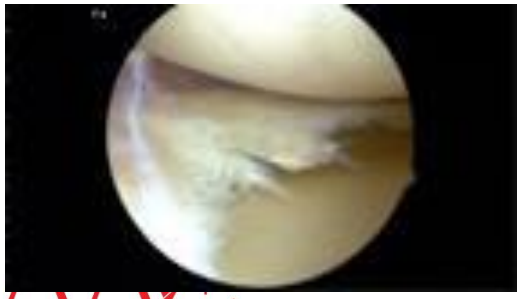
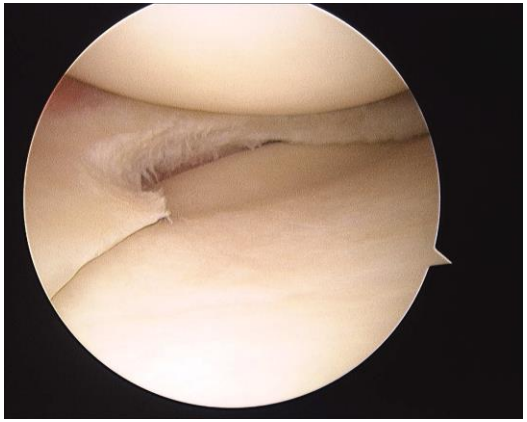
MENISCAL TEARS

- Bad thing to have at a young age i.e. whan people tear their ACLs
  - Repairing a meniscal tear is the most important thing that I do as a knee surgeon
  - Risk increase with Varus knee and medial meniscal tear
  - Even greater with a valgus knee and a lateral meniscal tear





MENISCAL TEARS

Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review

Belle L van Meer,[1] Duncan E Meuffels,[1] Wilbert A van Eijsden,[1] Jan A N Verhaar,[1] Sita M A Bierma-Zeinstra,[1,2] Max Reijman[1]

- Medial meniscal injury/meniscectomy after ACL rupture increased the risk of OA development. In contrast, it seems that lateral meniscal injury/meniscectomy has no relationship with OA development.

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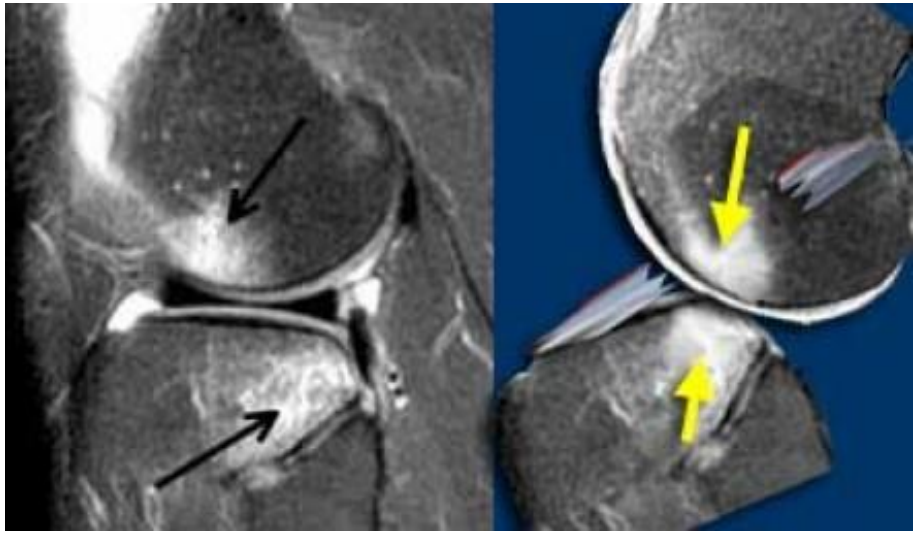
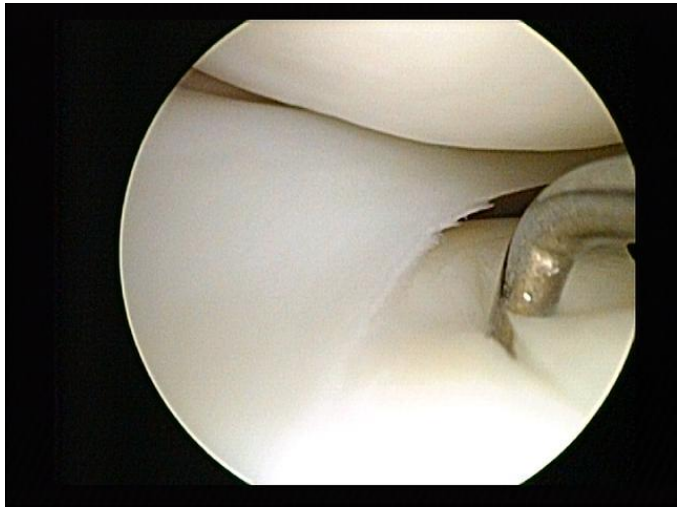
BONE BRUISING/CHONDRAL INJURY

- ? Precursor for OA
  - Depends on the location of the injury
  - Posterolateral tibial plateau
  - Anterocentral lateral femoral condyle





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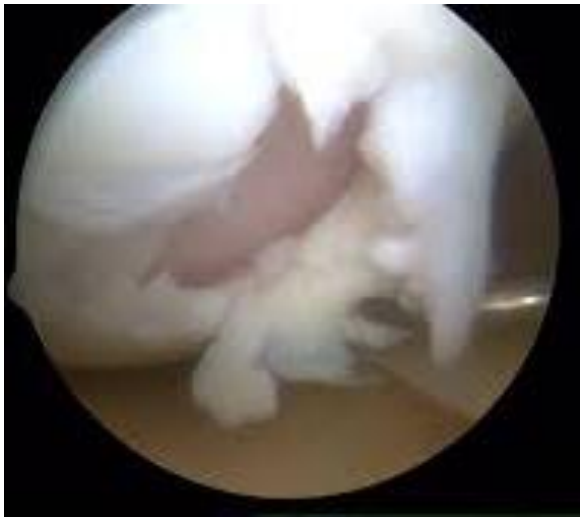
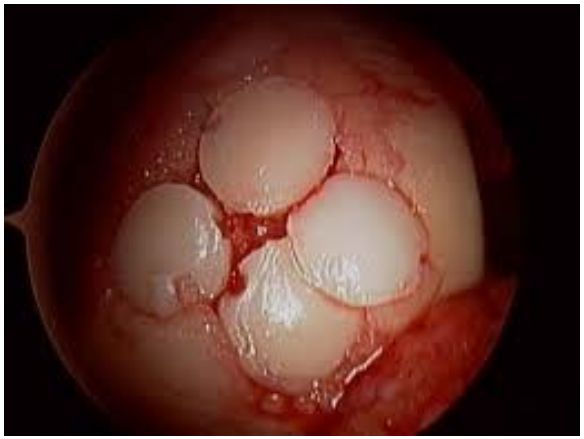
CHONDRAL DEFECTS

- Osteochondral autografts/allografts
  - +/-ACL surgery or re-alignment surgery
- Autologous Chondrocyte Implantation
  - +/-ACL surgery or re-alignment surgery





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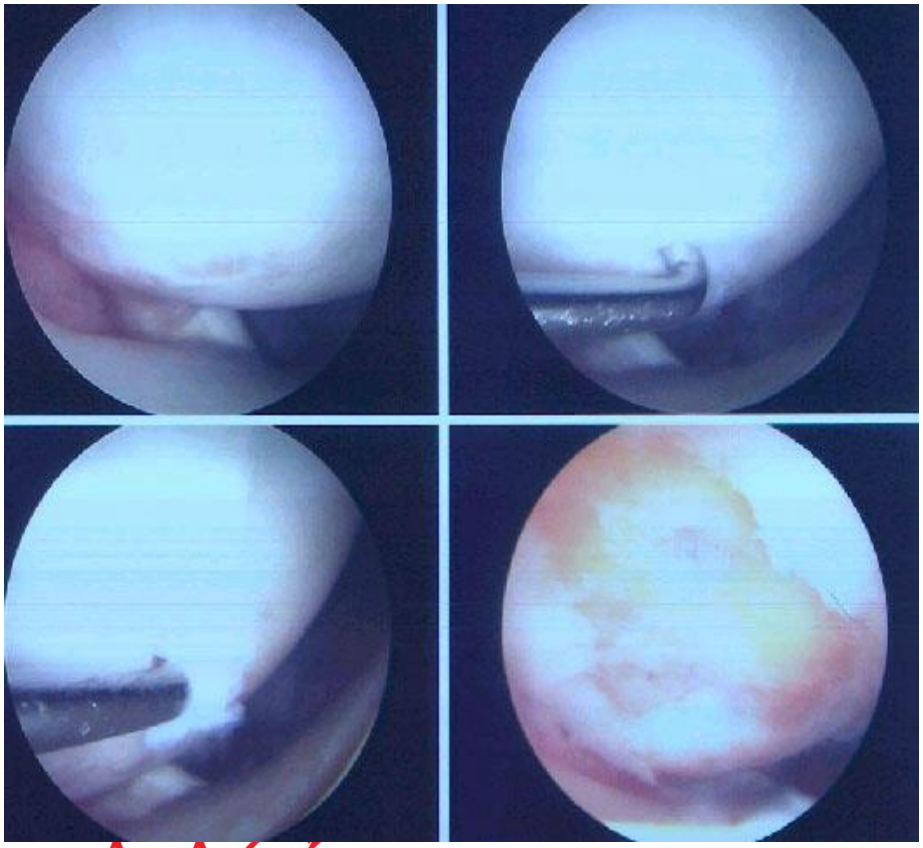
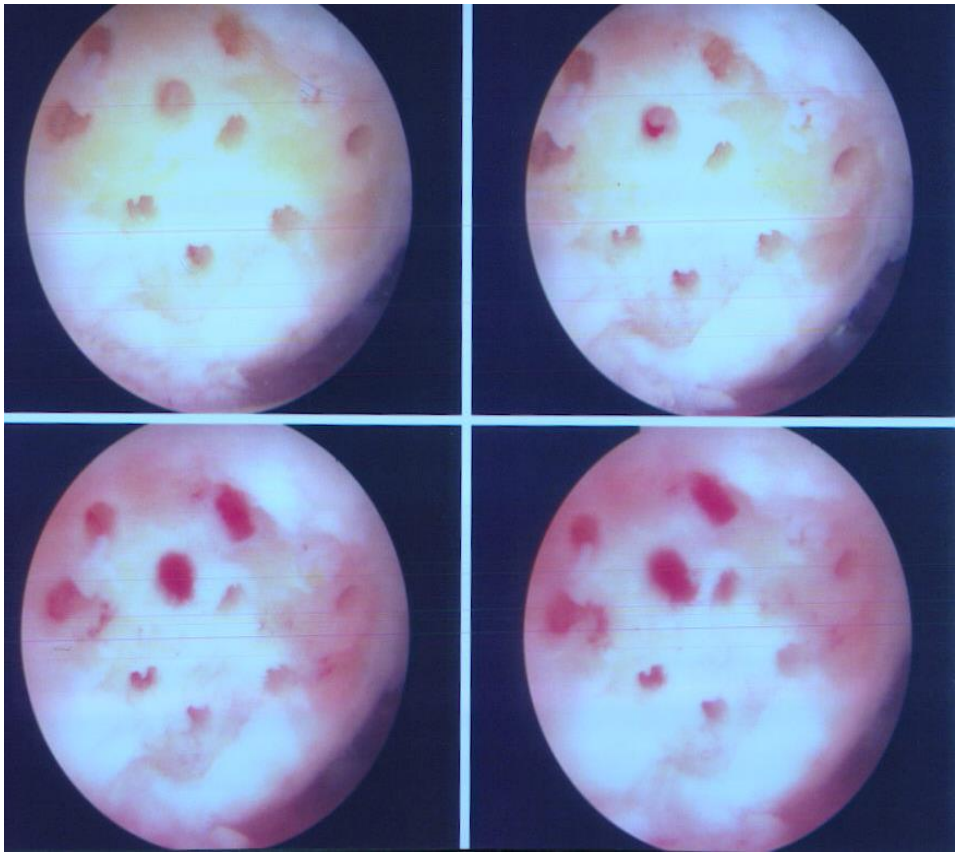
CHONDRAL DEFEFTS TREATMENTS

- Microfracture





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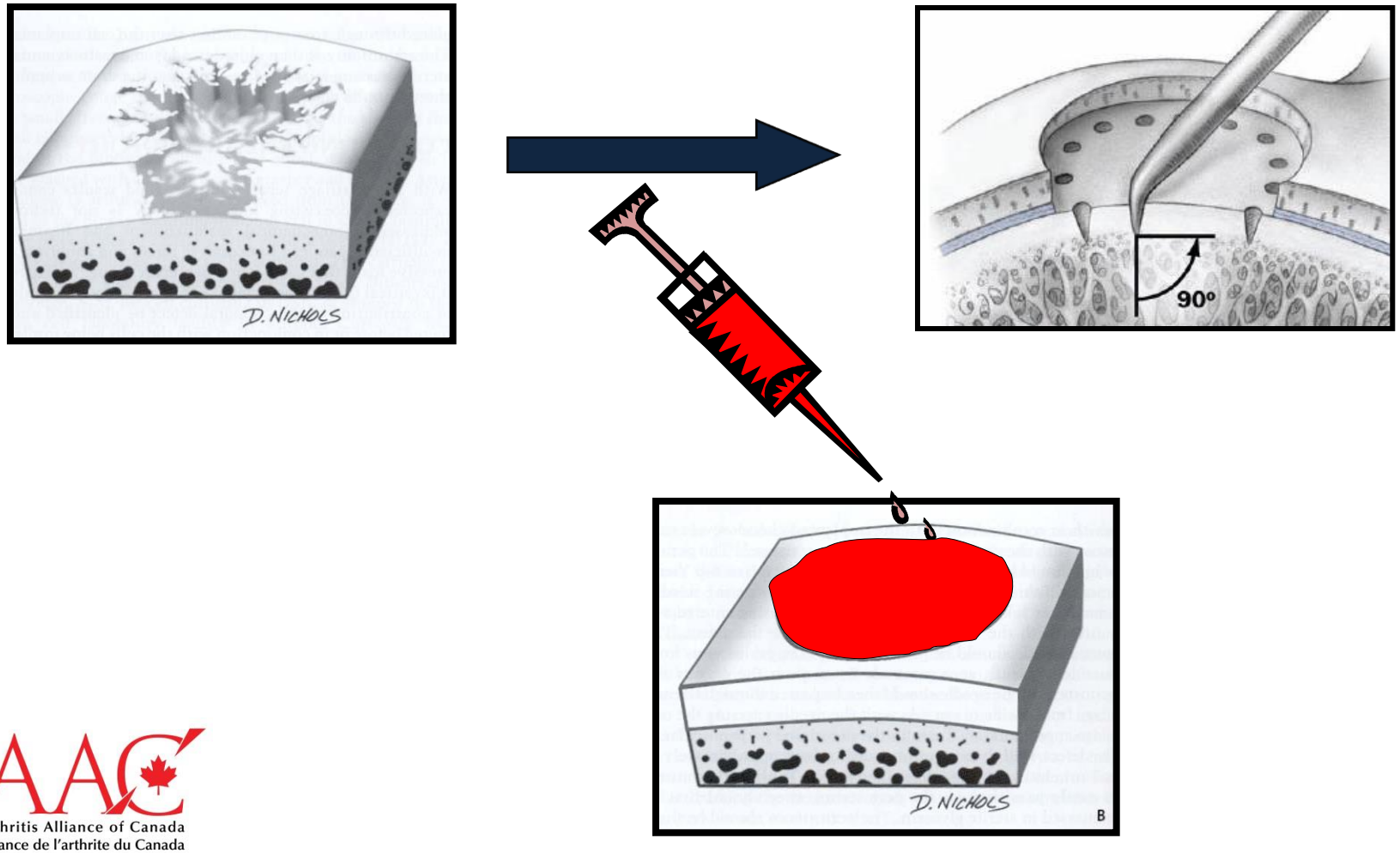
CHONDRAL DEFECTS

- BST CarGel



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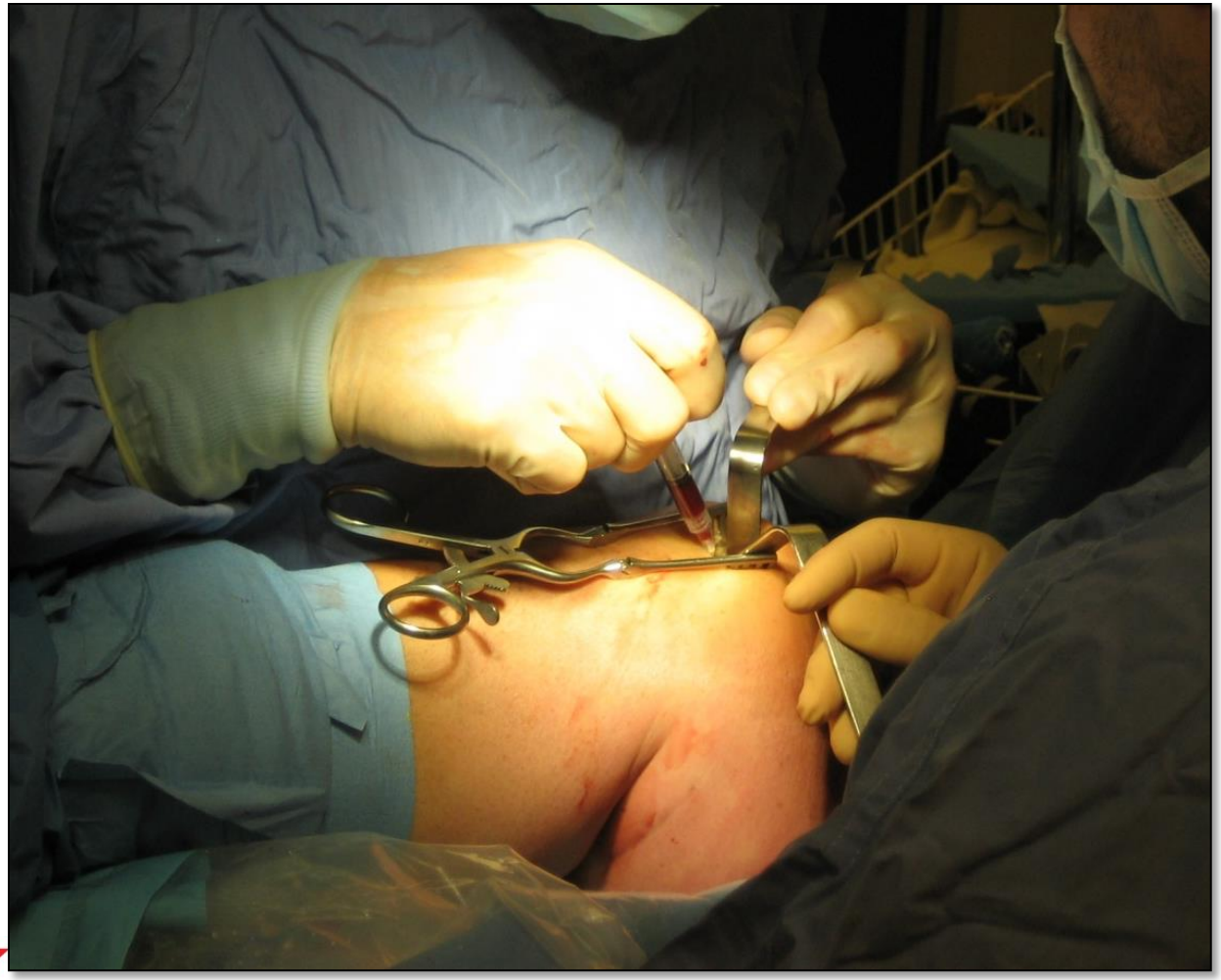
CHONDRAL DEFECTS



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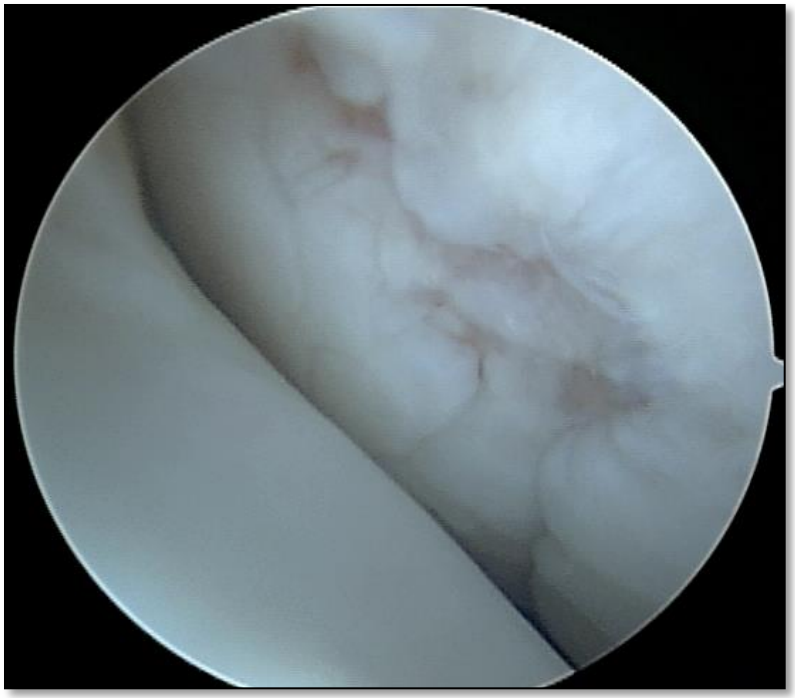
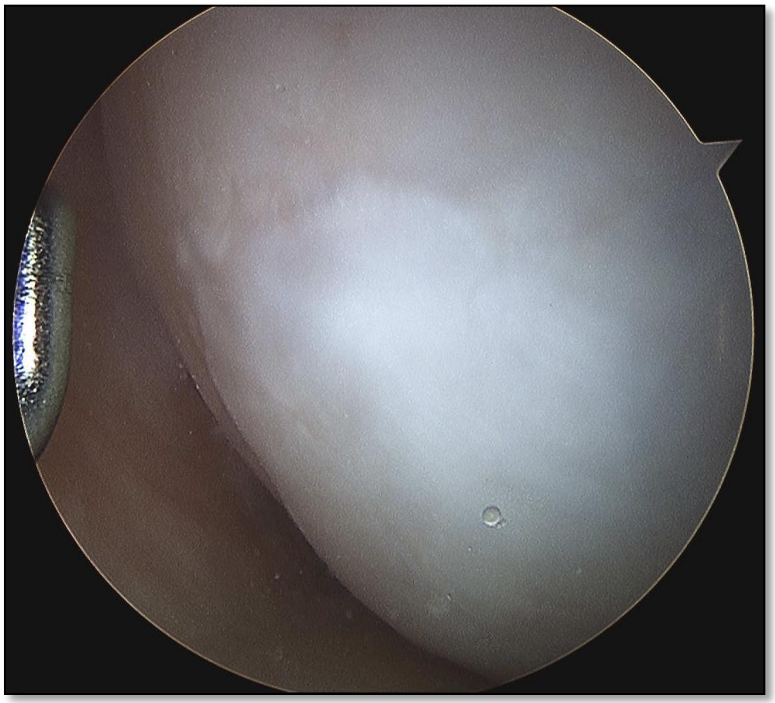
CHONDRAL DEFECTS

- BST CarGel





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CHONDRAL DEFECTS

BST-CarGel® Treatment Maintains Cartilage Repair Superiority over Microfracture at 5 Years in a Multicenter Randomized Controlled Trial
Cartilage 2015, Vol. 6(2) 62–72
Matthew S. Shive, William D. Stanish, Robert McCormack, Francisco Forriol, Nicholas Mohtadi, Stéphane Pelet, Jacques Desnoyers, Stéphane Méthot, Kendra Vehik, and Alberto Restrepo

- At 5 years, BST-CarGel® treatment resulted in sustained and significantly superior repair tissue quantity and quality over microfracture alone. Clinical benefit following BST-CarGel® and microfracture treatment were highly significant over baseline levels.

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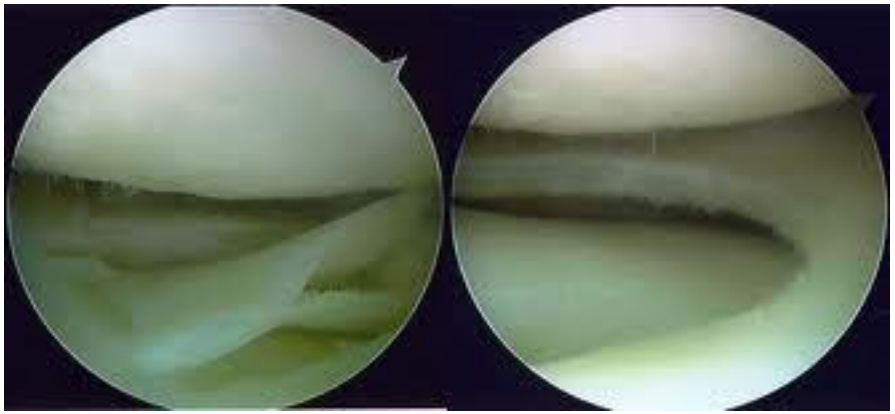
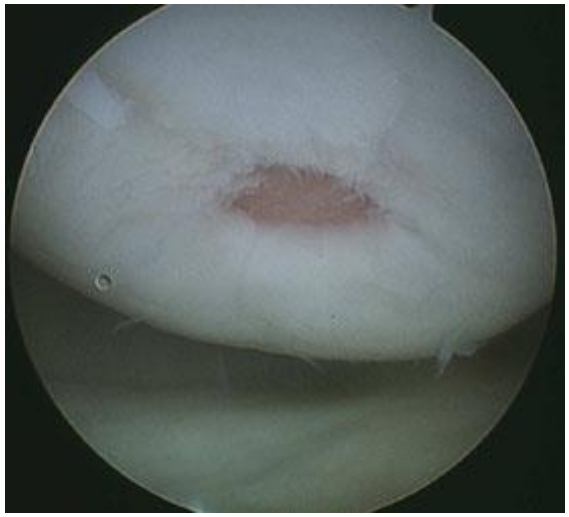
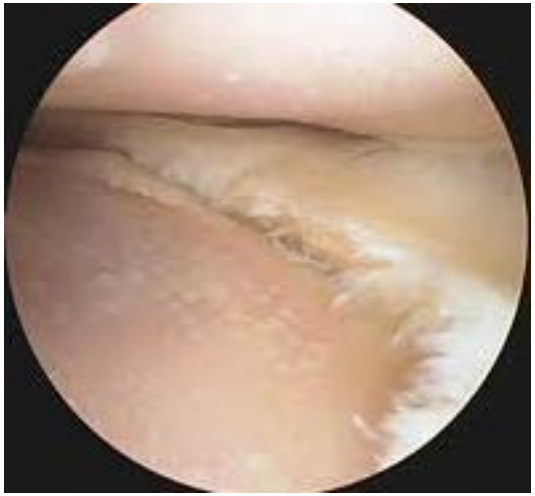
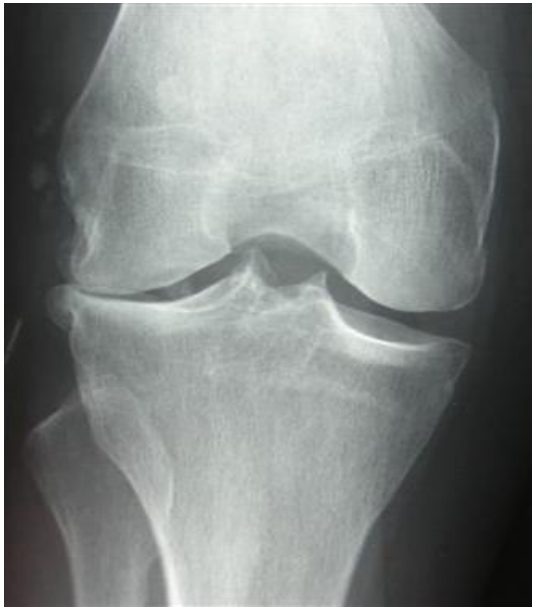
PROGRESSION TO OA









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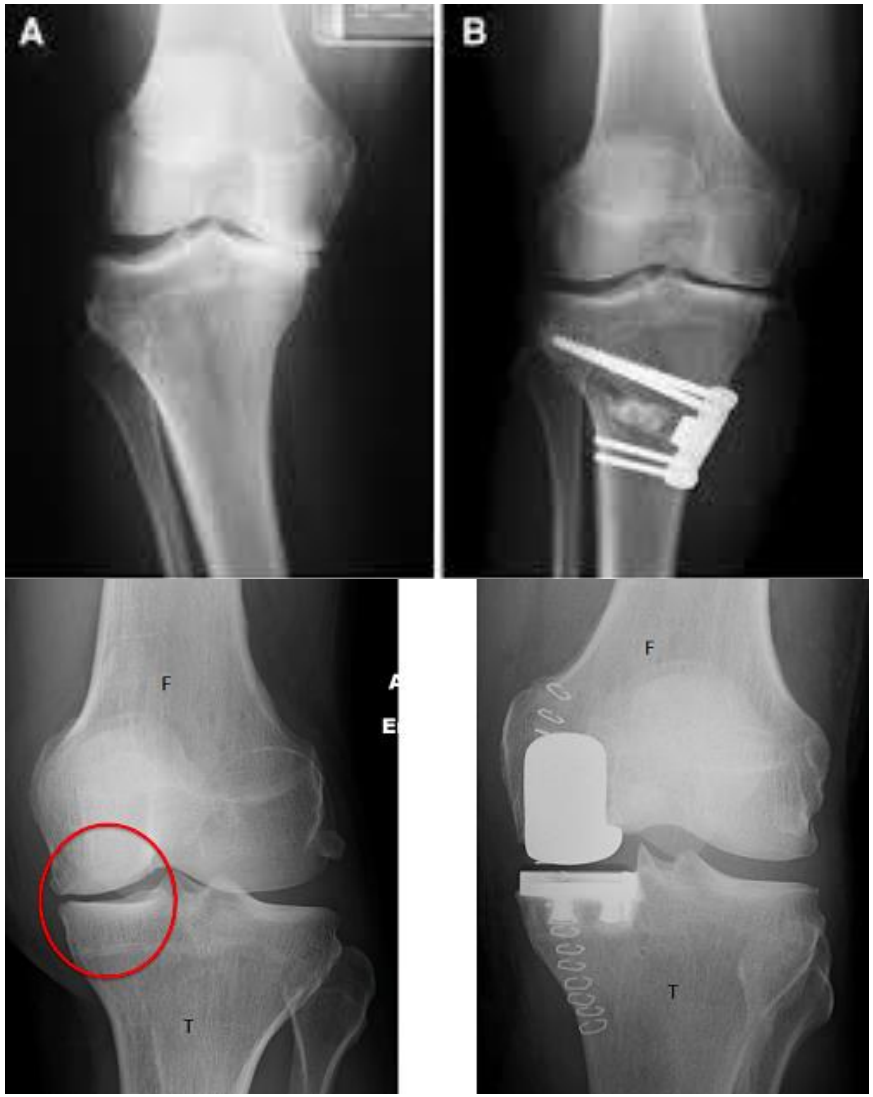
TRUE OA

- Osteotomy
- Arthroplasty



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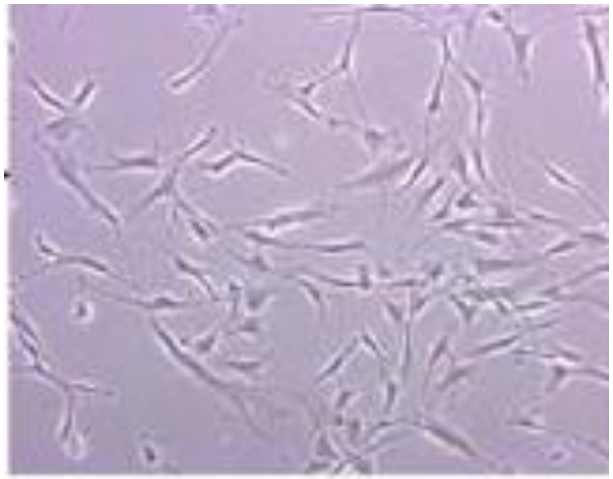
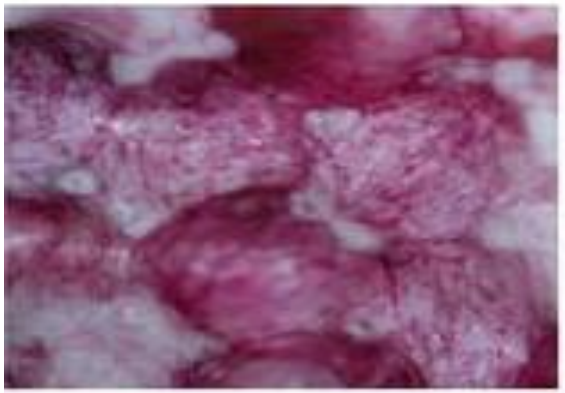
STEM CELLS

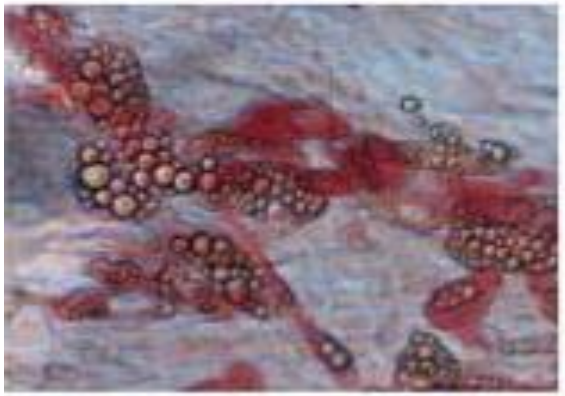
- Embryonic
- Adult autologous
- Adult Allogeneic



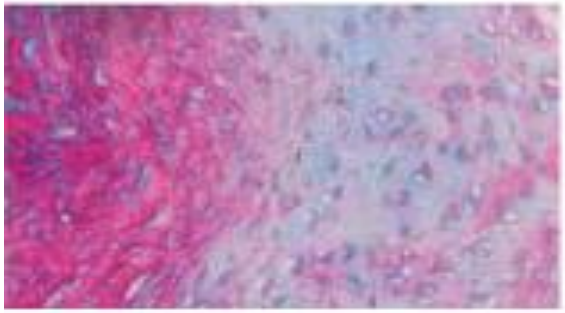
MSC



Bone



Fat



Cartilage

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STEM CELLS

- Clinical trials
  - What is the model in the knee that will allow us to investigate the use of stem cells?
  - ACL OA knee
  - Localized chondral injury
  - Generalized OA knee
  - Unicompartmental OA
    - Medial
    - Lateral
    - Patellofemoral

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CLINICAL STEM CELL RESEARCH

Matrix-Induced Autologous Chondrocyte Implantation versus Multipotent Stem Cells for the Treatment of Large Patellofemoral Chondral Lesions: A Nonrandomized Prospective Trial

Cartilage
2015, Vol. 6(2) 82–97

DOI: 10.1177/1947603514563597
cart.sagepub.com
SAGE

Alberto Gobbi[1], Sanyam Chaurasia[1], Georgios Karnatzikos[1], and Norimasa Nakamura[2]

- 6 years 67 patients: 37 were included
  - 24 had concomitant surgical procedures
- 19 MACI (Matrix-induced Autologous Chondrocyte Implantation)
- 18 BMAC (Bone Marrow Aspirate Concentrate)

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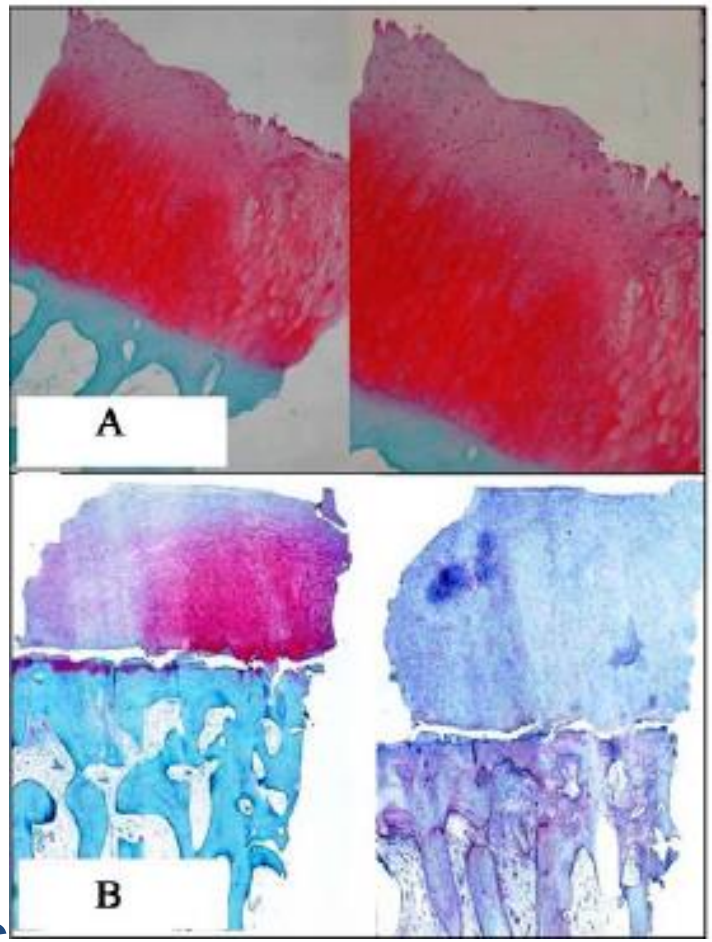
CLINICAL STEM CELL RESEARCH

- MACI with Hyaluronic acid (HA) scaffold
- BMAC with Hyaluronic acid (HA) scaffold
- Both groups better than baseline
- No difference but BMAC slightly better according to MRI filling, subjective scores



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STEM CELL TREATMENT OF OA

Comparative Matched-Pair Analysis of the Injection Versus Implantation of Mesenchymal Stem Cells for Knee Osteoarthritis

Yong Sang Kim,* MD, Oh Ryong Kwon,* MD, Yun Jin Choi,* MD, Dong Suk Suh,* MD, Dong Beom Heo,* MD, and Yong Gon Koh,*† MD
Investigation performed at the Center for Stem Cell & Arthritis Research, Department of Orthopaedic Surgery, Yonsei Sarang Hospital, Seoul, Korea

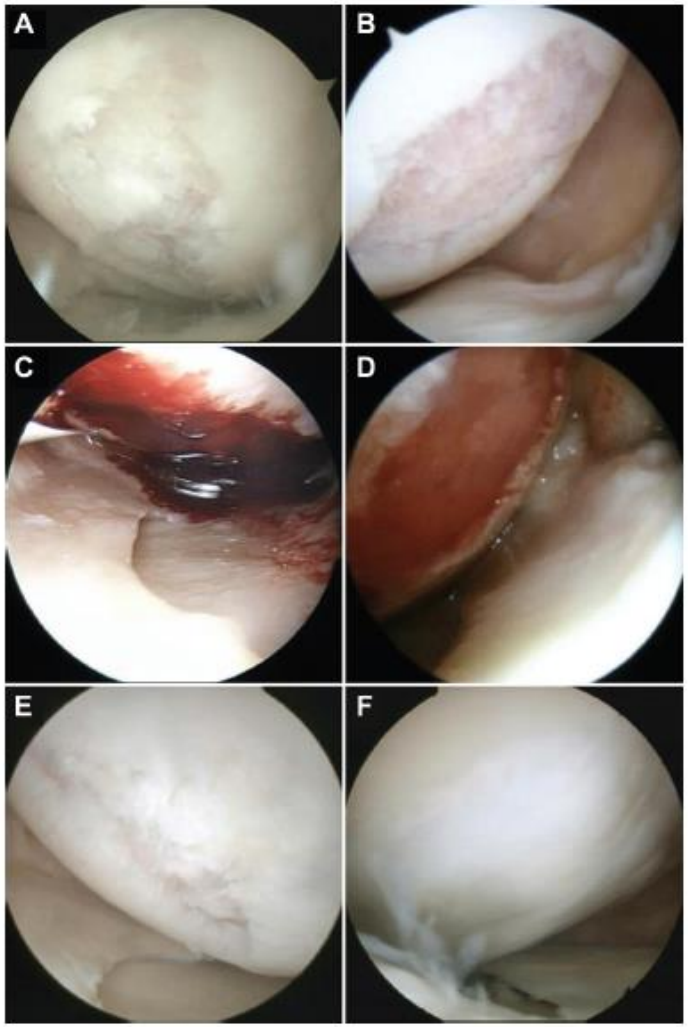

Figure 2. Arthroscopic images of (A, C, E) 57-year-old and (B, D, F) 59-year-old women. (A, B) Intraoperative arthroscopic surgery showed a cartilage lesion with osteoarthritic changes in the femoral condyles. (C) Arthroscopic visualization of the injection of mesenchymal stem cells (MSCs) with platelet-rich plasma into the lesion site. (D) An arthroscopic view after the implantation of MSCs at the lesion site. (E) Second-look arthroscopic surgery showed poor regeneration of cartilage in the MSC-injected site (International Cartilage Repair Society [ICRS] grade IV). (F) Second-look arthroscopic surgery showed complete coverage of the lesion with cartilage after MSC implantation (ICRS grade I).

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STEM CELL TREATMENT OF OA

"from an **orthopedic patient's perspective**, the ultimate goal will remain the utilization of **MSCs** and progenitors in simple, safe, and reproducible strategies for the augmentation of bone, cartilage, and tendon repair to address the pressing, clinical, unmet need of many. **Tissue engineering could** provide suitable, efficacious, alternative therapies for **orthopedic applications** such as **nonunion fracture, healing of critical-sized segmental defects, and regeneration of articular cartilage in degenerative joint disease."**

"The **biological understanding** of stem cells is improving at an extraordinary rate but much **greater developments in our understanding** of **MSC** and osteoprogenitor biology are of **paramount importance** if stem cell therapies are **ever to become routine clinical practice."**

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SUMMARY

- Need to ensure that we are using the same language to define and describe “Osteoarthritis”
- Ultimately clinical trials are needed
- Concerted and coordinated effort
  - Match the science with the patients
- **Bench with the bedside and back**

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