Knee Osteoarthritis Interventions

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IUMS

Osteoarthritis

- Osteoarthritis (OA) is the most common form of arthritis. Some people call it degenerative joint disease or “wear and tear” arthritis.
- Most common joint disease of humans
- Among the elderly, osteoarthritis (OA) is a leading cause of disability in developed countries
- Risk factors include age, major trauma, repetitive joint use, and obesity

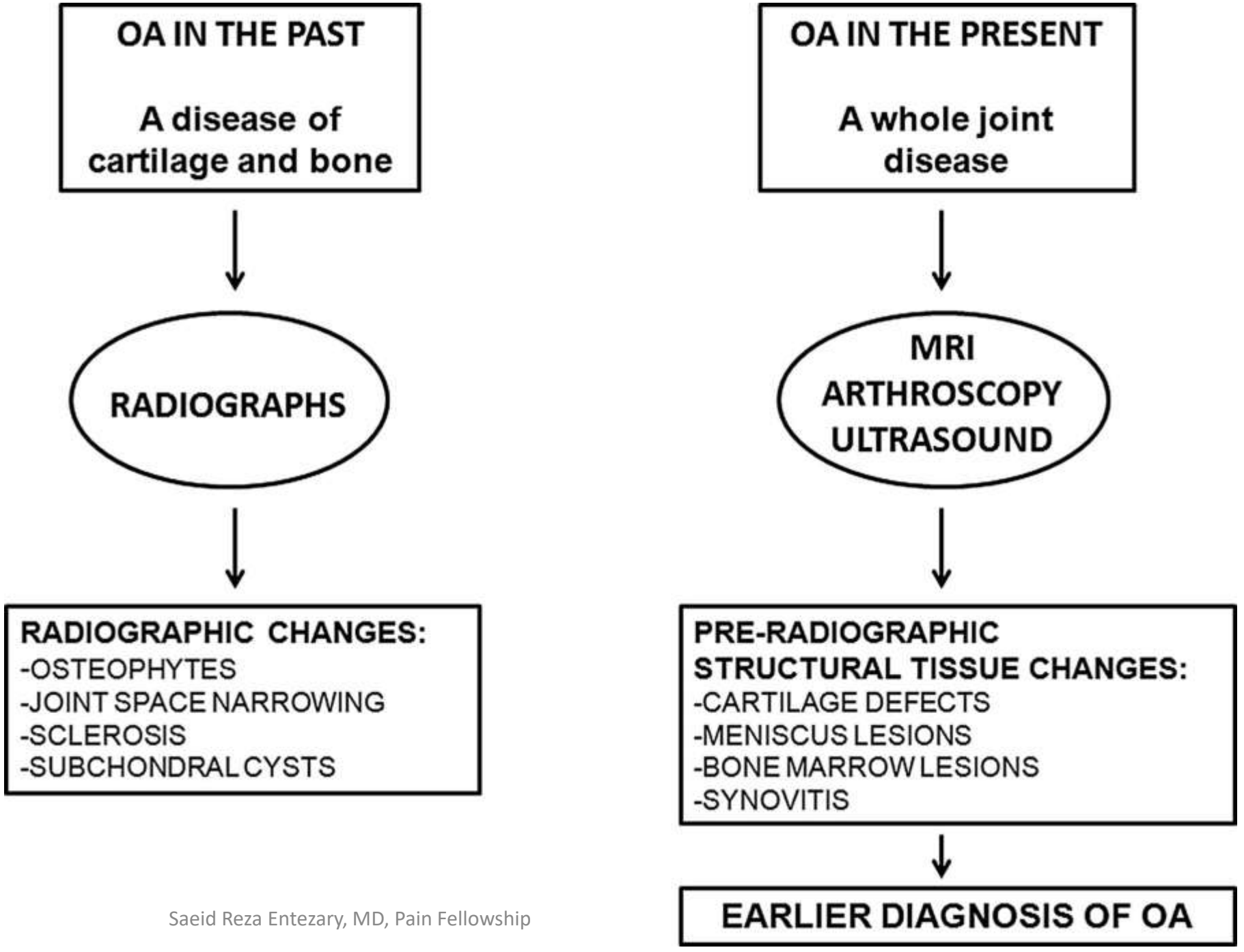
Pain

- Joint pain has been described as a deep ache localized to the involved joint
- Usually OA pain is aggravated by use and relieved by rest
- Stiffness of the involved joint may occur on arising in the a.m. or after a period of inactivity (pain usually lasts < 20 minutes)

Pain

- Articular cartilage is aneural. Joint pain may arise from stretching of nerve endings in the periosteum covering osteophytes.
- Pain may arise from microfractures in the subchondral bone or from medullary hypertension caused by distortion of blood flow through thickened subchondral trabeculae
- Synovitis may cause pain
- Phagocytosis of shards of cartilage and bone from the abraded joint surface or from cartilage release of soluble matrix macromolecules or crystals of calcium pyrophosphate or hydroxyapatite.
- Immune complexes containing antigens derived from cartilage matrix may be sequestered in collagenous joint tissue.

- May involve medial or lateral femoratibial compartment and or patellafemoral compartment
- Varus (bow-leg) deformity (medial compartment)
- Valgus (knock-knee) deformity (lateral compartment)
- Patellofemoral OA


OA IN THE PAST
A disease of cartilage and bone
RADIOGRAPHS
RADIOGRAPHIC CHANGES:
-OSTEOPHYTES
-JOINT SPACE NARROWING
-SCLEROSIS
-SUBCHONDRAL CYSTS
OA IN THE PRESENT
A whole joint disease
MRI
ARTHROSCOPY
ULTRASOUND
PRE-RADIOGRAPHIC STRUCTURAL TISSUE CHANGES:
-CARTILAGE DEFECTS
-MENISCUS LESIONS
-BONE MARROW LESIONS
-SYNOVITIS
EARLIER DIAGNOSIS OF OA

- The reviewed studies performed in humans show no increased risk for runners in developing OA of the knees when compared with controls.

- Older individuals with knee OA (not endstage) benefit from exercise (aerobic walking exercise and resistance training)

Risk factors of knee osteoarthritis

- Age
- Genetic susceptibility, People who have family members with OA are more likely to develop OA. People who have hand OA are more likely to develop knee OA.
- Obesity
- Female gender
- Trauma, ACL rupture and meniscal tear are two major risks factors for OA
- Repetitive knee trauma
- Muscle weakness
- Joint laxity
- Mechanical forces
- Kneeling
- Squatting

Physiopathology

- At the beginning, a hypertrophic repair phase can occur, resulting in softening of the articular cartilage due to increased water content secondary to glycosaminoglycan (GAG) loss.
- In this phase, anabolic activities and production of collagen type II and proteoglycan are actually increased.

- Chondrocytes appear in clusters as the result of their increased proliferation rate.

Physiopathology

- Subsequently, in the early phase of the disease, the amplification of catabolic activity occurs, associated with increased expression of inflammatory mediators, cartilage-degrading proteinases and stress response factors.
- These alterations lead to cartilage loss, from fibrillation of the superficial zone to more complex and deeper fissures.

- Collagen type II fragments from the damaged cartilage surface can induce inflammatory responses in the synovial membrane resulting in hyperplasia, lymphocytic infiltration and perivascular lymphoid aggregates.

Physiopathology

- In obesity an abnormal activation of neuroendocrine and pro-inflammatory pathways leads to an altered control of food intake, fat expansion and metabolic changes.

- Activated white adipose tissue increases the synthesis of pro-inflammatory cytokines, such as IL-6, IL-1, IL-8, TNF alpha, IL-18, but decreases the regulatory cytokines, such as IL-10.

- This observation supports the link between obesity and OA

Physiopathology

- The obesity gene and its product leptin may have important implications for the onset and progression of OA.

- Leptin was found in synovial fluids of OA joints which was correlated with BMI.
- Cytokines, biomechanical factors, and proteolytic enzymes lead to variable degrees of synovial inflamatory process which up-regulate metalloproteinases and blunt chondrocyte compensatory synthesis pathways required to restore the integrity of the degraded matrix.

Physiopathology

- Considerable evidence indicates that the menisci, ligaments, periarticular muscles and the joint capsule are also involved in the OA process.
- Even infrapatellar fat pad from patients with knee-OA contains inflammatory cells which can partly lead to pain in the anterior area of the knee OA.
- Extravasation from the immune cells of infrapatellar fat pad can lead to vasodilation and extravasation of the mediators that could in part be responsible for anterior pain in knee-OA.

Histology

- Loss of superficial chondrocytes
- Replication and breakdown of the tidemark
- Fissuring
- Cartilage destruction with eburnation of subchondral bone

Clinical features

- Persistent pain,
- Morning stiffness, less than 30 min
- Reduced function, are the three symptoms that are recommended for the diagnosis of knee OA by the EULAR.
- In addition
- Crepitus,
- Decreased ROM
- Bony enlargement are also very useful for diagnosis of knee OA.

Clinical features

- Pain is the most common symptom in knee OA
- Typically exacerbates by activity and relieves by rest.
- In the presence of the above six symptoms and signs the probability of having radiographic knee OA increases to 99%.
- In advanced cases synovities may appear and leads to pain at rest or night.

Clinical features

- Tenderness to palpation.
- Joint effusions, which typically exhibit a mild pleocytosis, normal viscosity, and modestly elevated protein.

- Crepitus during joint motion or walking is a common.
- Limitation of ROM are all common signs of OA of the knee.

- In advanced cases malalignment may be apparent (genu varrus or genu valgus)

Imaging

- Conventional plain radiographs is the first diagnostic procedure as usually requested to demonstrate the structure-pain relationship in knee OA.
- Conventional radiography predominantly visualizes bone
- MRI visualize all the structures of a joint, including soft tissue and cartilage, subchondral bone marrow lesions.

- Subchondral bone marrow abnormalities determined by MRI have recently been shown to be predictors of radiographic progression in patients with knee OA.

Association of Radiographic Features of Osteoarthritis of the Knee with Knee Pain

Data from the Baltimore Longitudinal Study of Aging

Margaret Lethbridge-Çejku, William W. Scott, Jr., Ralph Reichle, Walter H. Ettinger, Alan Zonderman, Paul Costa, Chris C. Plato, Jordan D. Tobin, and Marc C. Hochberg

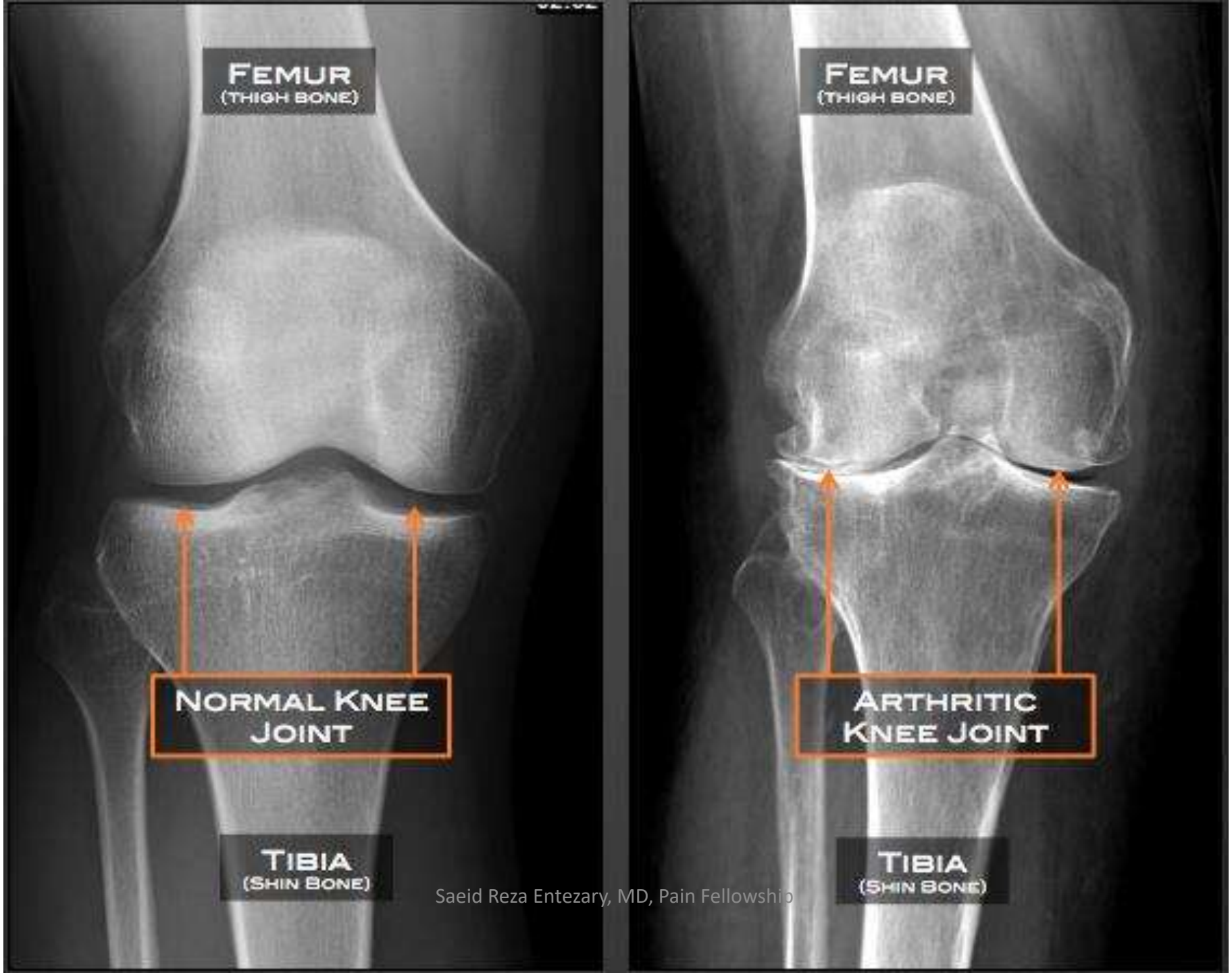
Arthritis Care and Research 1995 83

- Results
- Both ever never pain and current knee pain were significantly associated with the presence of definite knee OA (Kellgren-Lawrence grade).
- A direct relationship was found between all measures of severity of radiographic OA and knee pain.

Plain Radiography

- Identification of bone changes in early knee OA may not be possible due to low sensitivity of radiography.
- However when articular changes have been observed by plain radiography further imaging studies are unnecessary.
- The major radiographic features of OA include: Joint space narrowing, subchondral sclerosis, osteophytes, subchondral cysts.

- Chondrocalcinosis may be seen in 4.4% of patients which may increase by aging

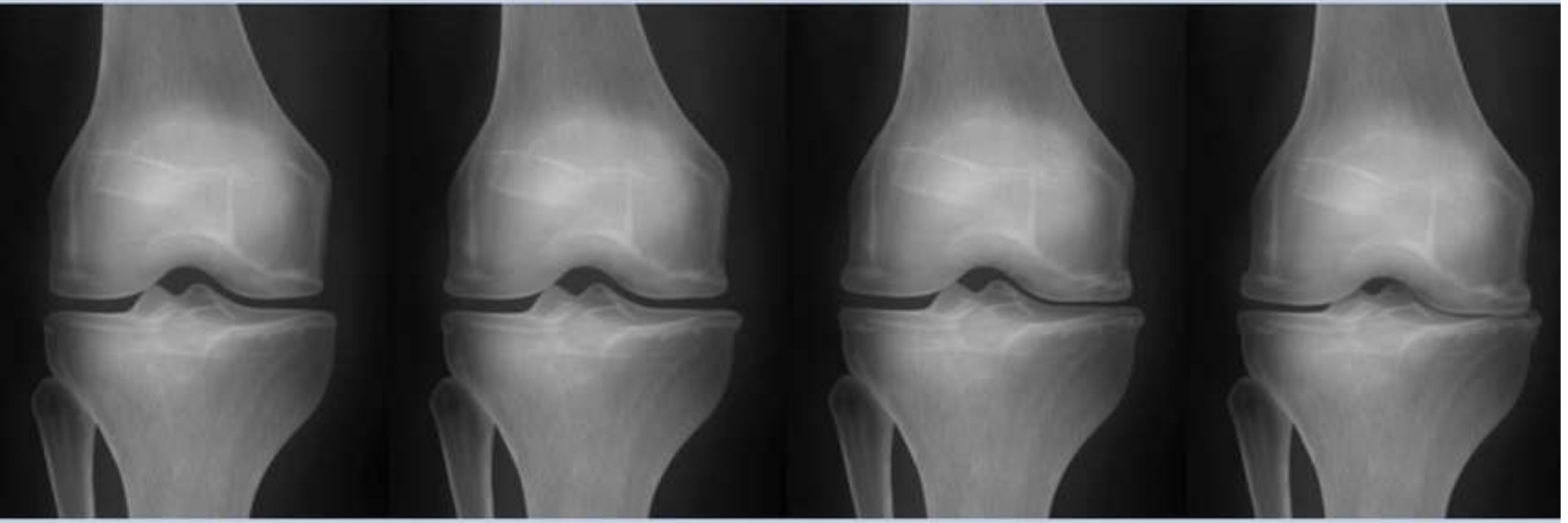


Radiographic findings

- Non-weight-bearing and weight-bearing radiographs of the knee in extension were found to be of limited value in assessing disease status, whereas all standing flexed knee positions reliably imaged joint space width and bone changes in the tibiofemoral joint.

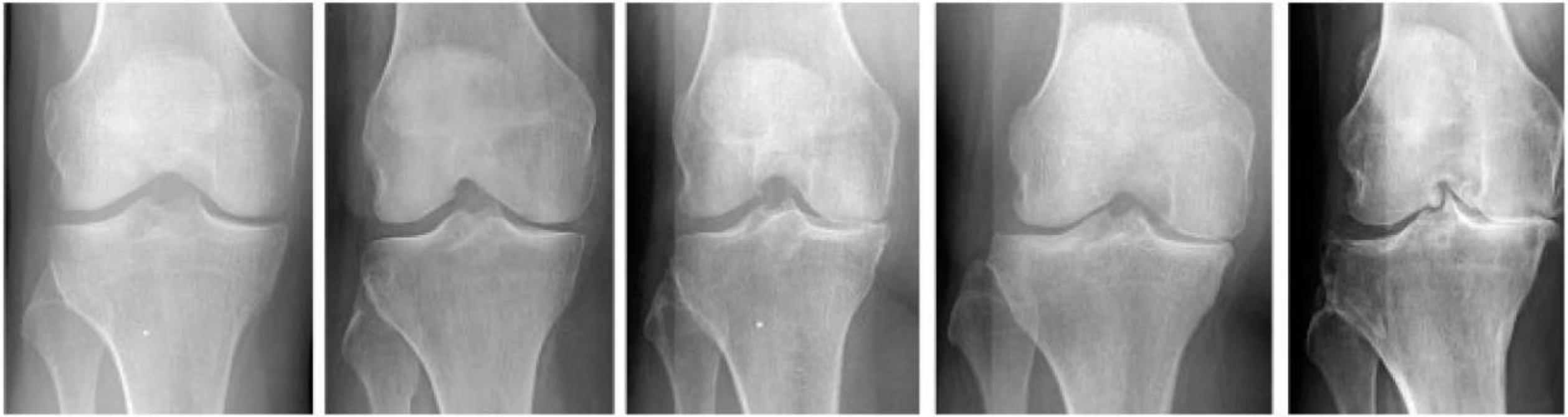
- The presence of osteophyte at the patellofemoral joint was more sensitive but less specific than at the tibiofemoral joint.
- Osteophyte is the radiographic feature that associates best with knee pain.

Kellgren-Lawrence (KL) grading scale



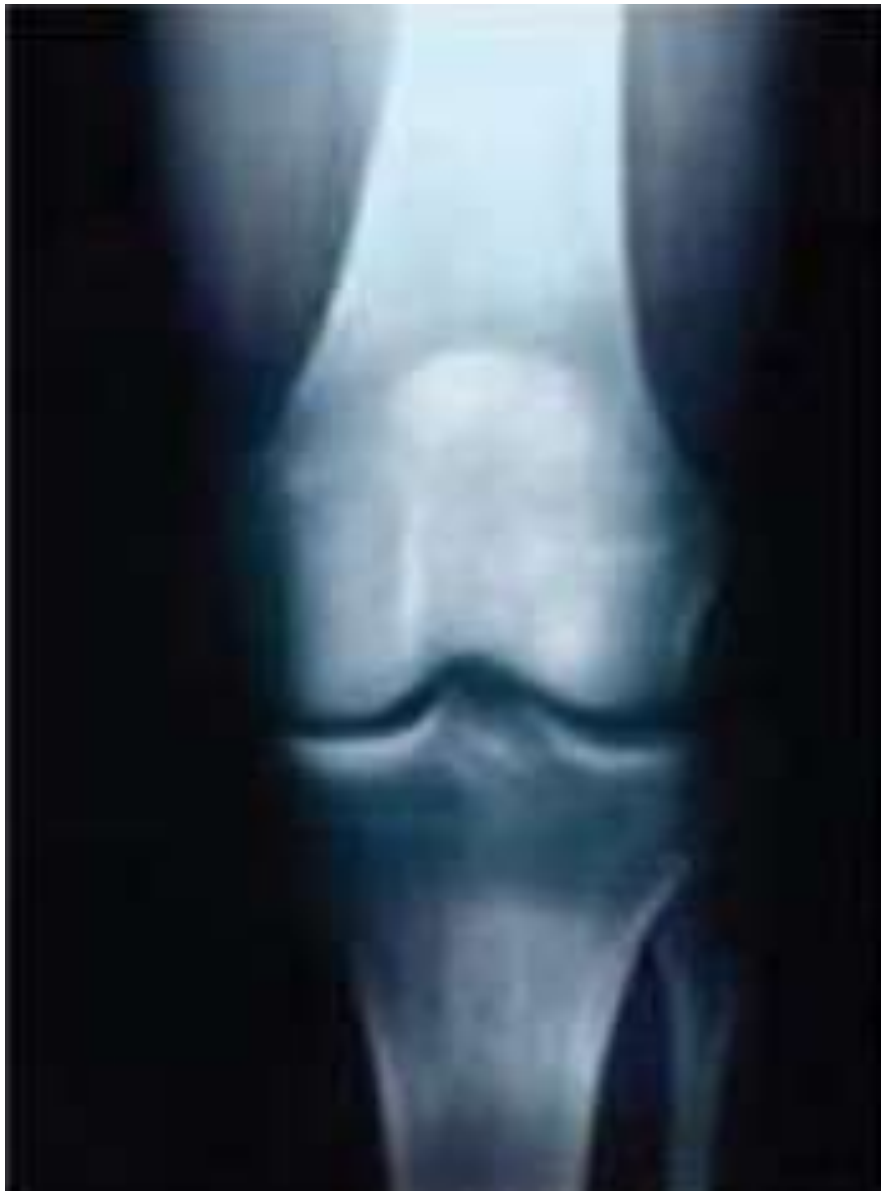
Grade 1 | Grade 2 | Grade 3 | Grade 4

CLASSIFICATION	Normal	Doubtful	Mild	Moderate	Severe
DESCRIPTION	No features of OA	Minute osteophyte: doubtful significance	Definite osteophyte: normal joint space	Moderate joint space reduction	Joint space greatly reduced: subchondral sclerosis

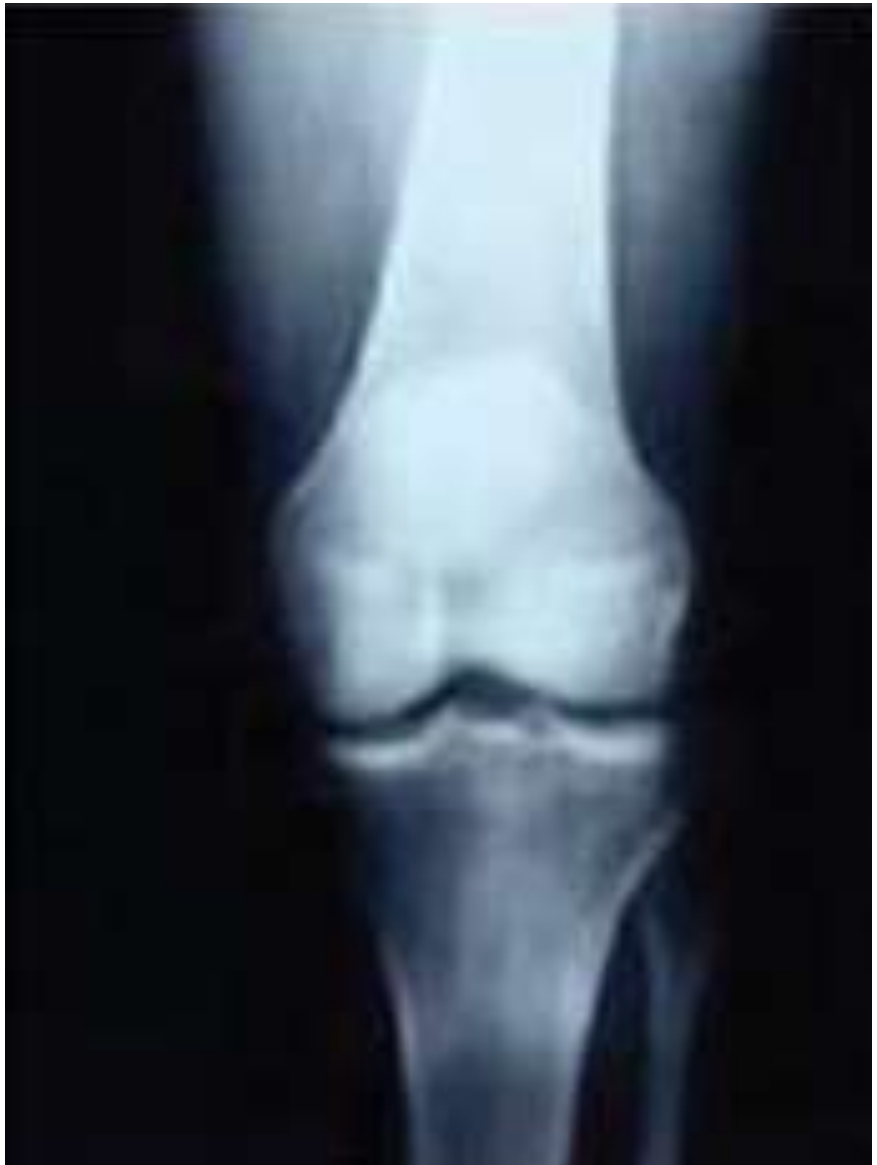


Grade 0 healthy joints.
Grade 1: doubtful, possibility of osteophytic lip &questionable JSN.
Grade 2: mild, osteophytes, possibility of JSN.
Grade 3: moderate, JSN, multiple osteophytes, and sclerosis.
Grade 4: severe, large osteophytes, marked JSN and severe sclerosis.

Grade 0
No joint space narrowing (JSN) or reactive changes



Grade 1
Possible osteophytic lipping + doubtful JSN



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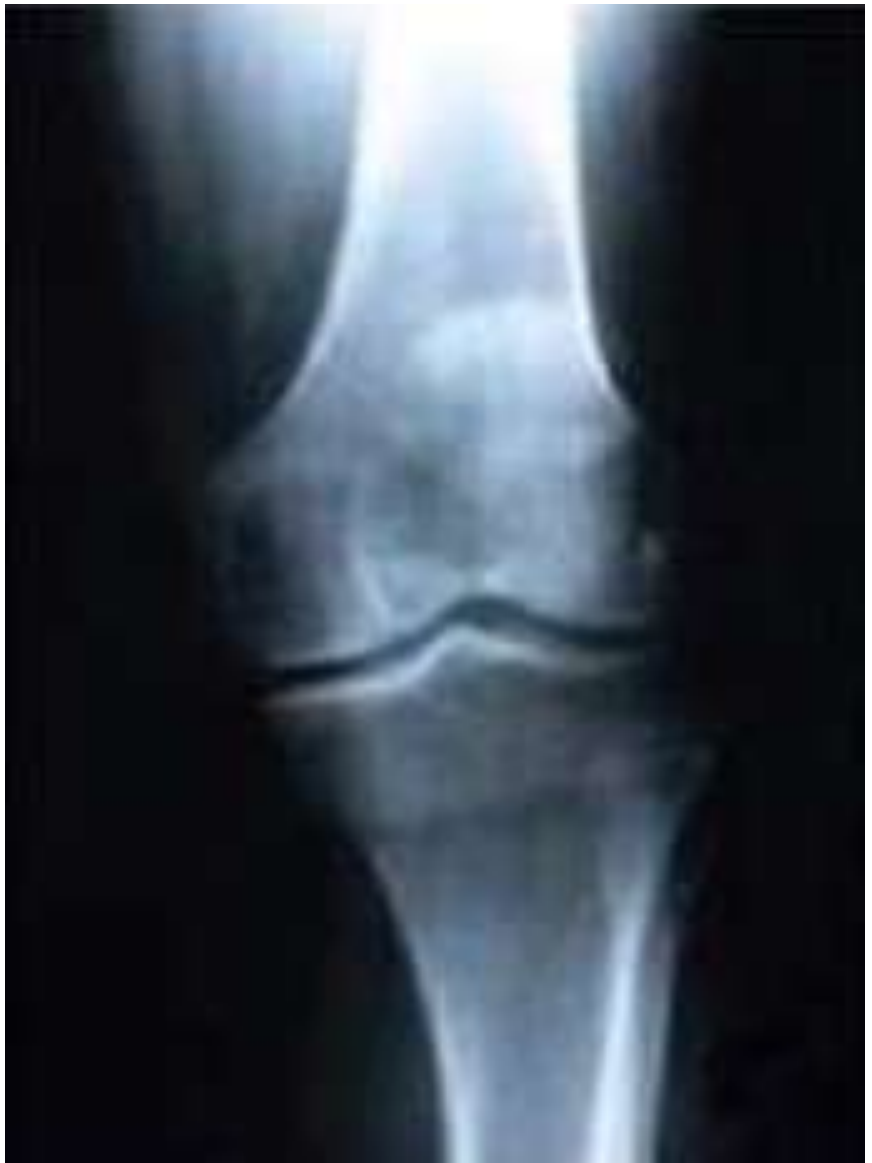
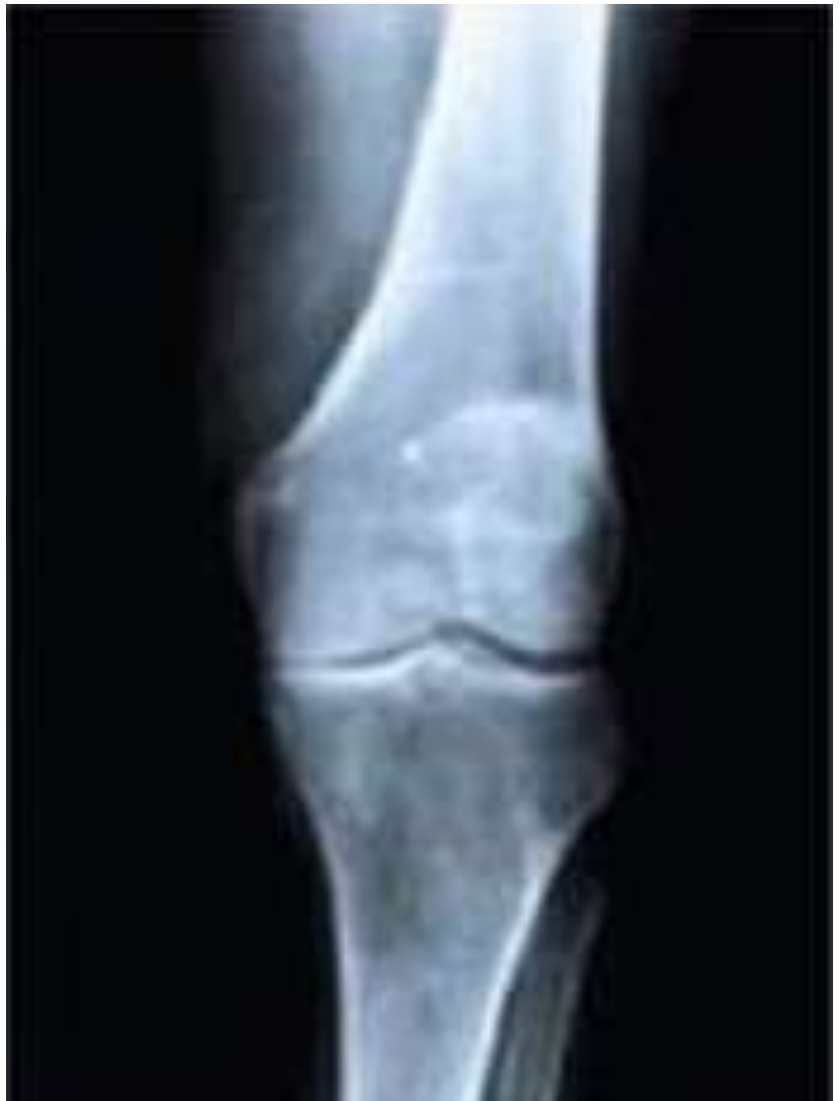
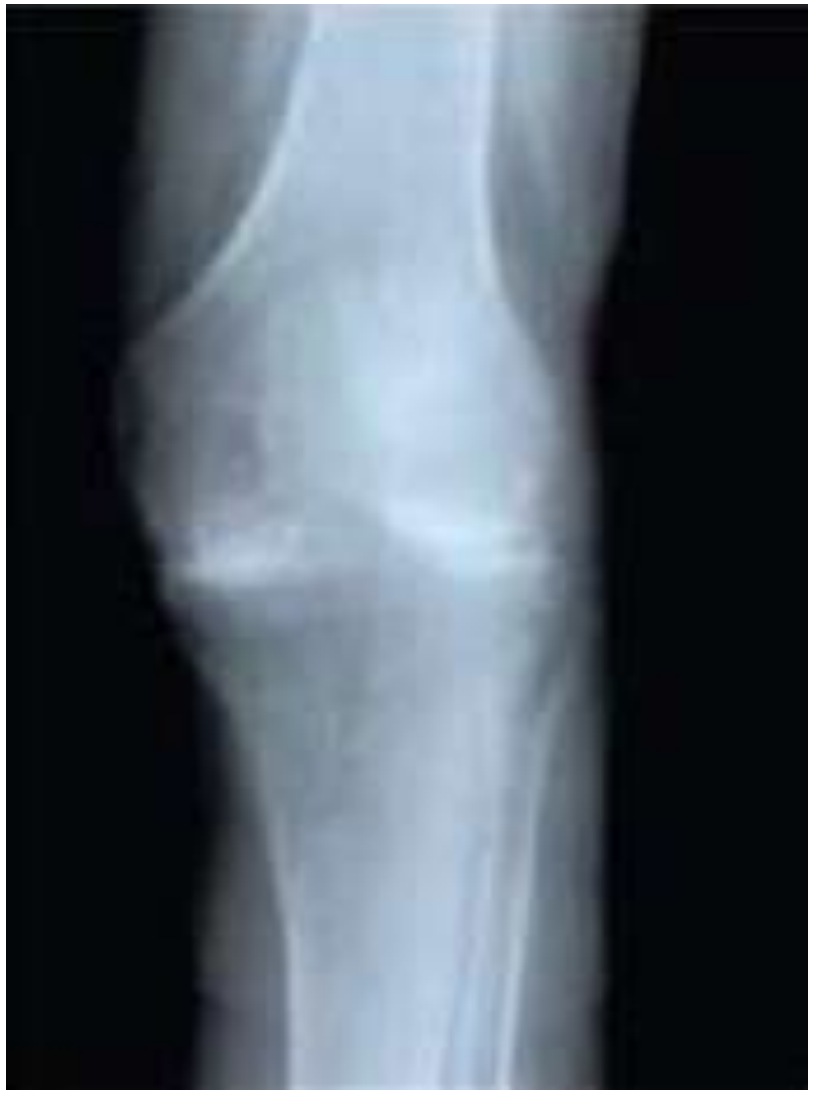
Grade 2
Definite osteophytes + possible JSN



Grade 3
Moderate osteophytes + definite JSN + some sclerosis + possible bone end deformity

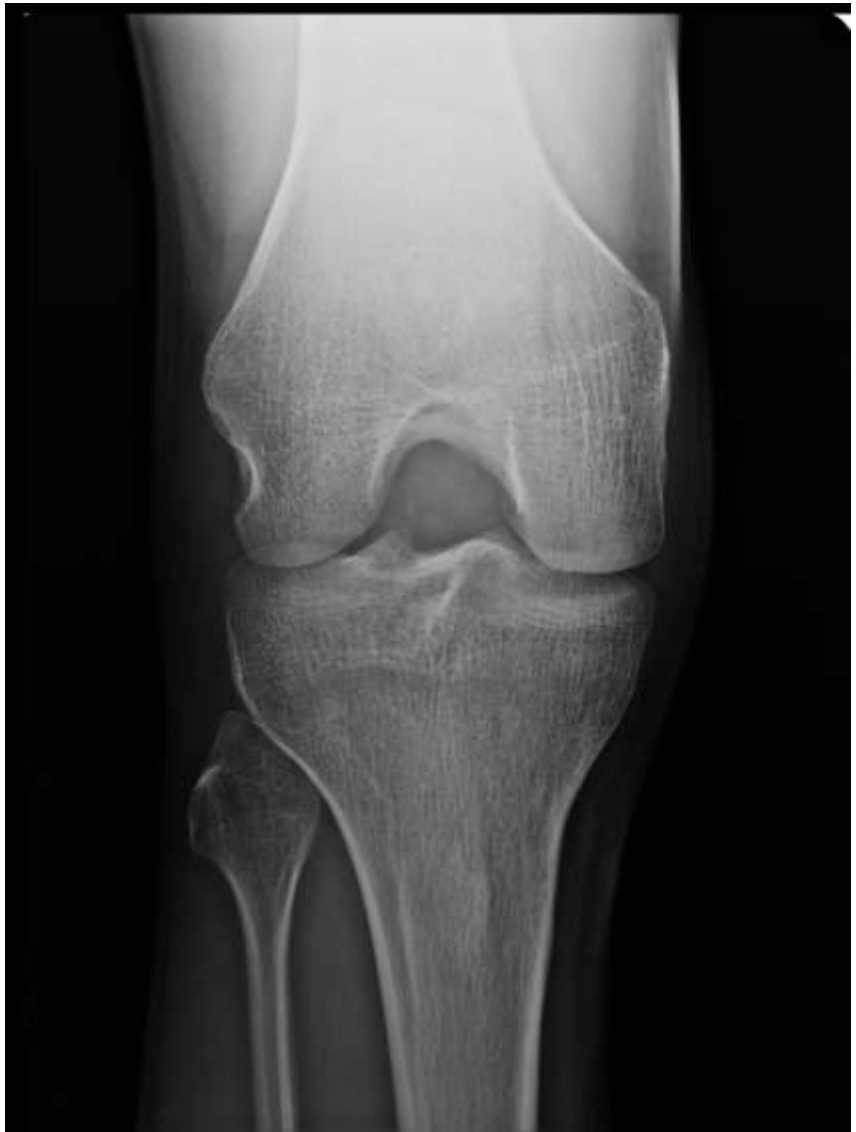


Grade 4
Large osteophytes + marked JSN + severe sclerosis + definite bone end deformity



sunrise view

PA view in 30 degrees of flexion



MRI findings in knee Osteoarthritis

- MRI is not necessary for most patients with suggestive symptoms of OA and/or typical plain radiographic features.

- However, MRI of the knee has a diagnostic role in patients with joint pain and symptoms such as locking, popping, or instability that suggest meniscal or ligamentous damage.

MRI findings in knee osteoarthritis

- Cartilage abnormalities,
- Osteophytes,
- Bone edema,
- Subarticular cysts,
- Bone attrition,
- Meniscal tears,
- Ligament abnormalities
- Synovial thickening,
- Joint effusion
- Intra-articular loose bodies
- Periarticular cysts

Boston Leeds Osteoarthritis Knee Score (BLOKS)

- The BLOKS scoring method assesses nine intra-articular regions and contains eight items, including features of bone marrow lesions, cartilage, osteophytes, synovitis, effusions and ligaments.

- The scaling for each feature ranges from 0-3.

MRI Osteoarthritis Knee Score (MOAKS)

- (MOAKS) is a semi-quantitative scoring tool that was developed from the Whole Organ Magnetic Resonance Imaging Score (WORMS) and Boston Leeds Osteoarthritis Knee Score (BLOKS) scoring tools. MOAKS has been shown to have very good to excellent reliability.
- Patella, femur, Tibia
- Bone marrow lesions and cysts
- Articular cartilage
- Hoffa's synovitis and synovitis-effusion
- Meniscus
- Ligaments/tendons
- Periarticular features (pes anserine bursitis, iliotibial band signal, popliteal (Baker's) cyst, infrapatellar bursa signal, prepatellar bursa signal, ganglion cyst)
- loose bodies

Laboratory findings

- Although mild synovitis may be seen in patients with knee OA but markers of inflammation such as ESR and CRP levels are usually normal.
- Synovial fluid in knee OA is of non-inflammatory type. Serum and synovial fluid levels of CRP in OA are markedly lower than inflammatory arthritis.
- Synovial fluid anti-cyclic citrullinated peptide antibody is negative in both serum and synovial fluid of patients with knee OA.
- In suspected cases of knee OA synovial fluid level of anti-CCP can be used for differentiation of OA from RA

TREATMENT

- Non-steroidal anti-inflammatory drugs
- Indications:
- First line treatment for all patients with symptomatic arthritis
- Technique:
- Topical and oral NSAIDS recommended
- Selection should be based on physician preference, patient acceptability and cost
- Duration of treatment based on effectiveness, side-effects and past medical history
- Outcomes
- AAOS guidelines: strong evidence for

Tramadol

- Treatment option for patients with symptomatic arthritis
- Weak opioid mu receptor agonist
- Good evidence for mid term (8-13 weeks) improvement in pain and stiffness over placebo

- Outcomes:

Prior AAOS guidelines recommended its use, but newer guidelines do NOT recommend its routine use

Rehabilitation, Education and Wellness activity

- First line treatment for all patients with symptomatic arthritis
- Technique
- Self-management and education programs
- Combination of supervised exercises and home program have shown the best results
- These benefits lost after 6 months if exercises are stopped
- Outcomes:
- AAOS guidelines strong evidence for

Weight Loss Programs

- Indications:
- Patients with symptomatic arthritis and BMI > 25

- Technique:
- Diet and low-impact aerobic exercise

- Outcomes:
- AAOS guidelines: moderate evidence for

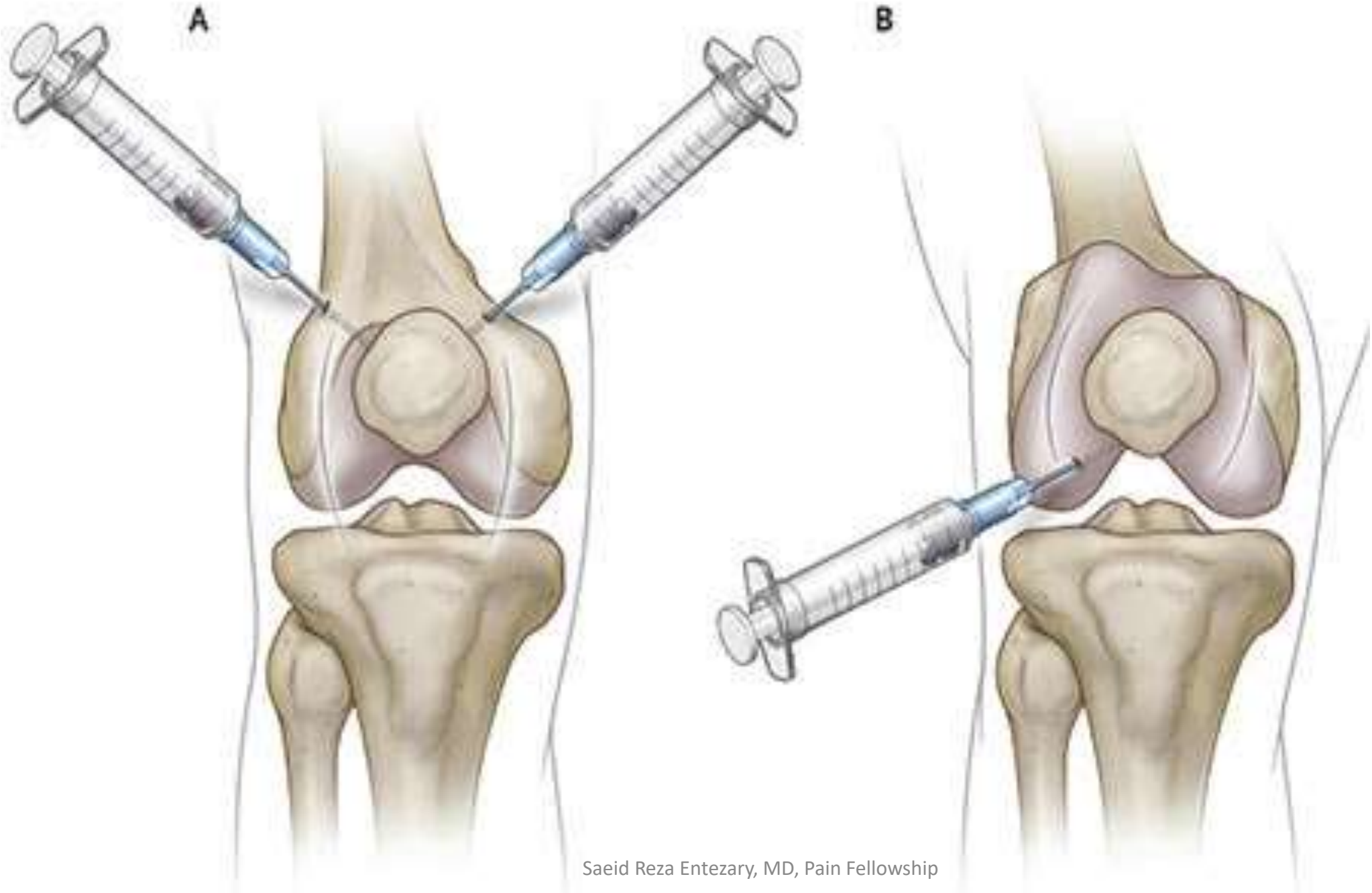
Bracing

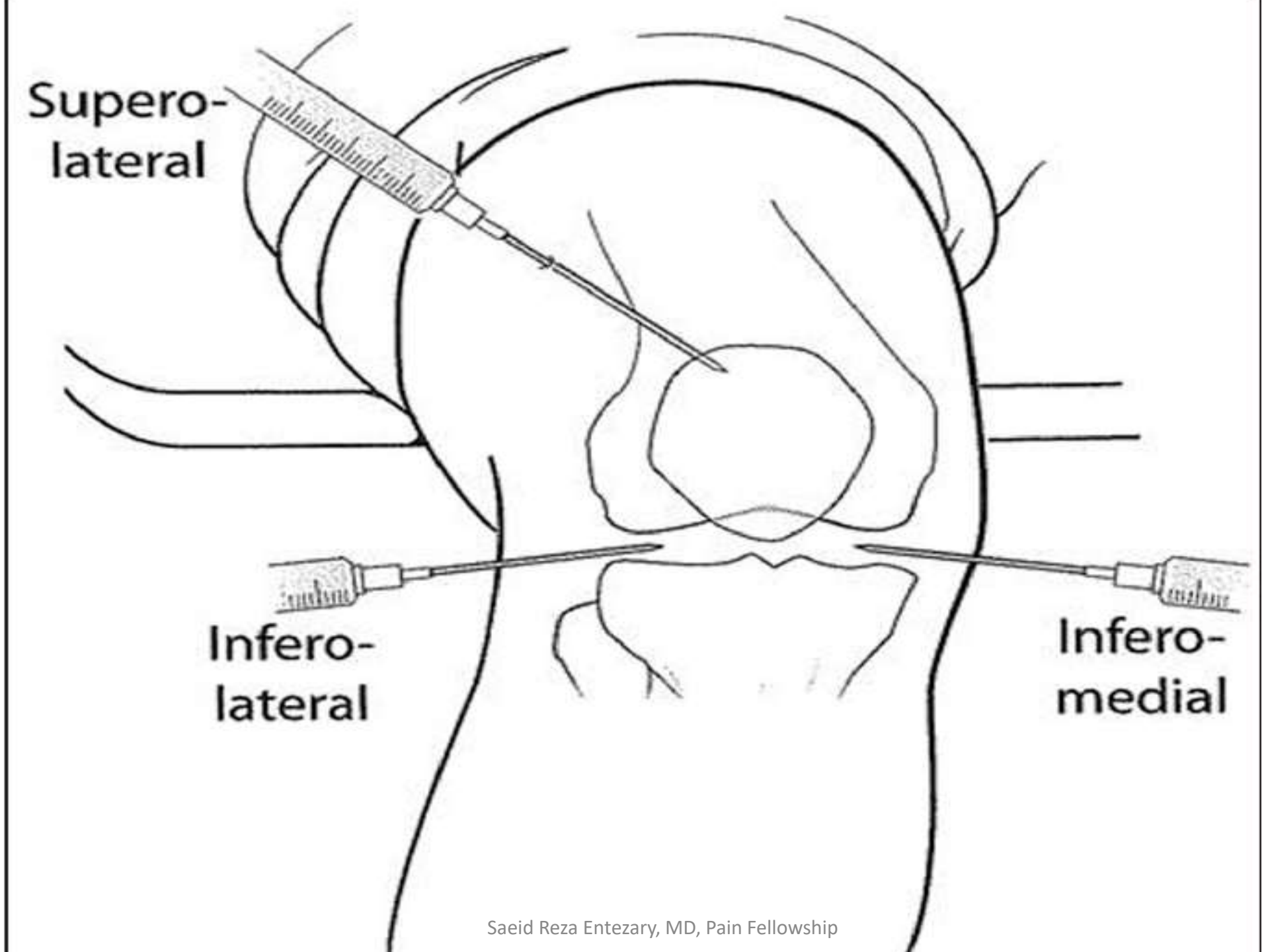
- Medial unloader for isolated medial compartment OA
- AAOS guidelines: moderate evidence for

Injections

- In addition to well-established treatment options such as hyaluronic acid (HA), cortico-steroids (CS) and oxygen-ozone therapy, many other promising products have been employed in the last decades such as **polydeoxyribonucleotide (PDRN)** and biologic agents such as **platelet-rich plasma (PRP)** and **mesenchymal stem cells (MSCs).**

- Moreover, ultrasound-guided **intra-meniscal injection** and X-ray-guided **subchondral injection** techniques have been introduced into clinical practice.


A
B


Supero-
lateral
Infero-
lateral
Infero-
medial

Corticosteroids (CS)

- Intra-articular injection of CS is the most common conservative approach. The rationale behind its use relies on its immunosuppressive activity in the knee joint acting at different levels of the inflammatory cascade.

- In particular, it acts by blocking the synthesis of pro-inflammatory signaling molecules, such as interleukin 1 (IL-1), leukotrienes, prostaglandins and catabolic proteins such as metaloproteinases.

Corticosteroids (CS)

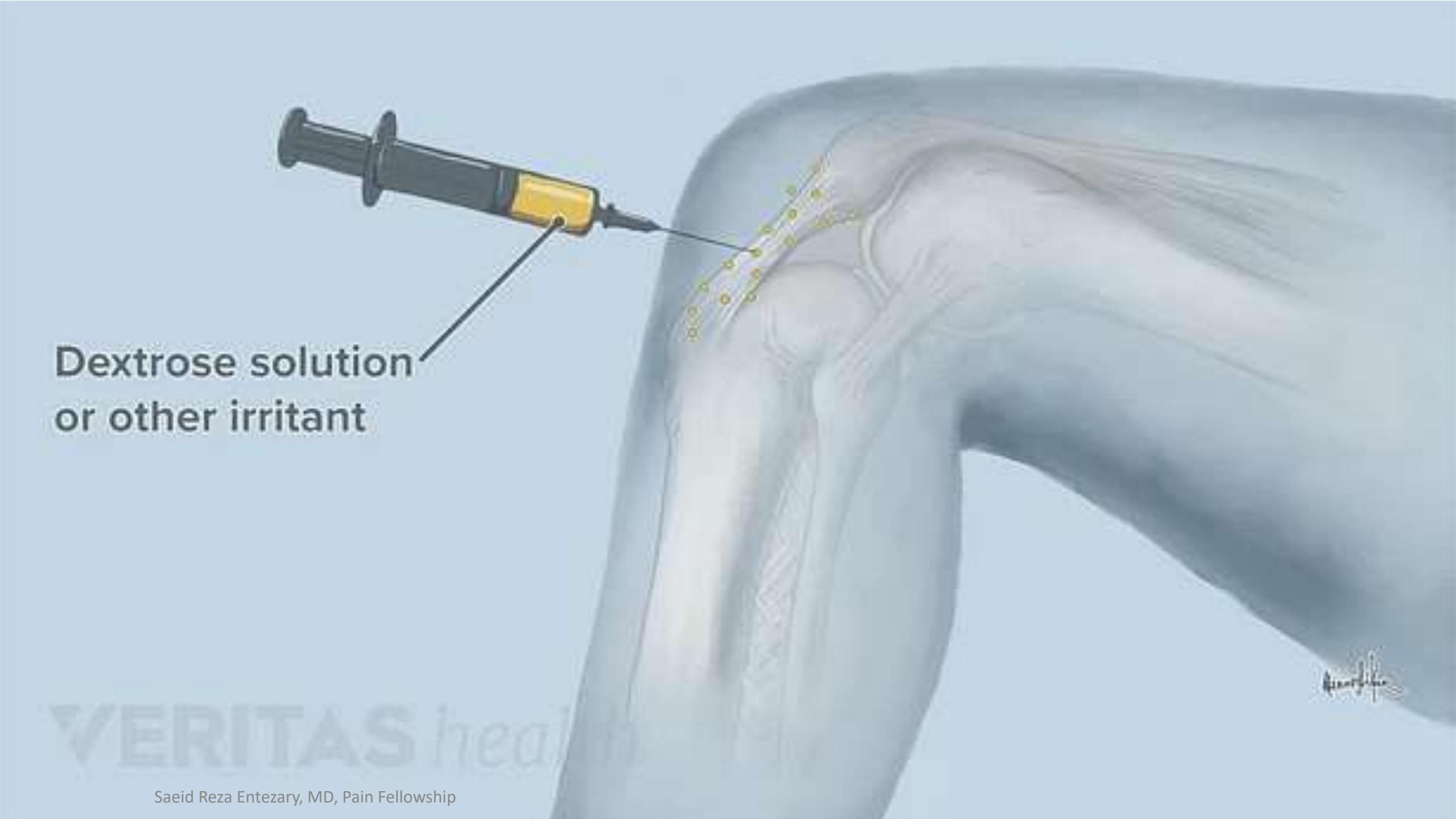
- The latest 2019 Osteoarthritis Research Society International (OARSI) guidelines have assigned to intra-articular CS injections a recommendation level of 1B (‘high consensus’), the same level as for HA.
- In particular, their use is suggested for short-term pain relief compared to hyaluronic acid, which instead requires a longer time to provide its more beneficial effects in terms of pain control (2–4 weeks).

- Synovitis patients with an inflammatory phenotype of OA, characterized by stiffness, joint swelling and effusion, are more likely to respond to CS compared to HA.

Prolotherapy

- The goal of prolotherapy is to stimulate natural tissue repair in the body. During treatment, a physician will inject an irritant, such as a dextrose solution, into the arthritic knee joint and surrounding tissues.
- Several injections (perhaps 15 or 20) will be made during one treatment session.

- Prolotherapy temporarily increases inflammation. The hope is that the additional inflammation will facilitate further healing.



Hyaluronic acid (HA)

- Hyaluronic acid (HA) is a glycosaminoglycan that provides joint lubrication and shock absorbency and acts as the backbone for the proteoglycans of the extracellular matrix. In normal adult knees, HA concentration ranges from 2.5 to 4.0 mg/ml, whereas in OA it decreases by 33–50%.

- Currently, no clinical trials indicate a clear advantage of one product over another, even though a higher MW allows optimal binding on cell surfaces

Hyaluronic acid (HA)

- There is no evidence to support that HA viscosupplementation affects OA progression. HA effects may last up to 26 weeks. The benefits in terms of pain relief and function improvement associated with HA have been recently rediscussed.

- Osteoarthritis Research Society International (OARSI) guidelines assigned a level of recommendation 1B to the use of HA in the treatment of knee OA.

Hyaluronic acid (HA)

- Intra-articular HA is particularly recommended for long-term treatment, and has demonstrated a more favourable safety profile than repeated corticosteroids injections.

- On the other hand, the American Academy of Orthopaedic Surgeons (AAOS), in light of inconclusive evidence, has neither endorsed nor discouraged HA use. However, the real benefits of HA in the early stages of joint degeneration need to be confirmed by specifically designed studies.

Polynucleotides

- Polydeoxyribonucleotide (PDRN) is composed by polymers of various chain lengths capable of binding large amounts of water molecules, hence capable of reorganizing the cartilage surface..

- PDRN effects seem to be related to viscoelastic properties, cell growth induction, collagen and cell migration and anti-inflammatory capabilities. Moreover, in animal models, not only symptomatic improvement has been reported, but also a decrease of proinflammatory factors, such as IL-6 and TNF-α.

Polynucleotides

- The PDRN preparation appears colourless, transparent, viscoelastic and it is provided in pre-filled glass sterile disposable syringes containing a solution of 2 ml (the concentration of polynucleotides is 20 mg/ml).

- PDRN intra-articular treatment has been shown to produce faster improvement of activities of daily living compared to HA

Polynucleotides

- According to a meta-analysis, intra-articular PDRN injections provided more significant pain reduction for up to two months after the procedure and equal functional improvements if compared to HA, thus reducing the frequency of injections.

- However, there are still no large-scale RCTs determining the effect of PDRN injections on knee OA.

Oxygen-ozone therapy

- The rationale behind the use of intra-articular ozone (O3) therapy arose from the assumption that chronic oxidative stress plays an important role in OA. Clinical experiences and research have considered O3 as a powerful anti-inflammatory, immune-modulatory substance.

- Due to its high reactivity, it may be able to reduce oxidative stress, stimulate fibroblastic joint repair and may promote new cartilage growth

Oxygen-ozone therapy

- It can be safely administered intra-articularly as an O3-O2 gas mixture. When dissolved into the synovial fluid, it can generate reactive oxygen species (ROS) and lipid oxidation products that may inhibit proteolytic enzymes.

- Indeed, O3 therapy leads to a localized increase in oxygen delivery by promoting vasodilation and angiogenesis.

Oxygen-ozone therapy

- Despite controversial results, O3 therapy has shown better results in terms of pain relief, joint function and quality of life compared to placebo or corticosteroids injections.
- In some trials HA treatment was clinically superior to O3 therapy and therefore oxygen-ozone therapy still lacks a large consensus.

- In terms of safety profile, O3 proved to be a safe procedure with almost zero adverse events: O3 is bacteriostatic, fungicidal, and viricidal, therefore the infection risk is minimal.

Platelet-Rich Plasma (PRP)

- The rationale behind the PRP injection relies on the ability of it to release biologically active proteins that are able to promote tissue healing; especially when the target tissue has low healing potential as cartilage.
- This beneficial effect of PRP is exerted by means of a number of growth factors released by platelets as insulin-like growth factor (IGF), tissue growth factor (TGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), vascular endothelium growth factor (VEGF) and fibroblast growth factor (FGF).

Platelet-Rich Plasma (PRP)

- In particular, PRP effects can be ascribed to its effect on the Wnt/β-pathway, which is implicated in OA development.
- The Wnt family of proteins plays a central role in inflammation signalling cascades stimulating the catabolic molecules such as metalloproteinases, which are responsible for cartilage degradation and progressive degeneration of all the articular tissues.
- Moreover, the Wnt pathway is significantly involved in Type II collagen degradation and chondrocyte apoptosis.

Platelet-Rich Plasma (PRP)

- Many RCTs, have demonstrated its safety and overall clinical benefits.

- Looking at high-quality studies, the majority have shown that PRP is superior to hyaluronic acid (HA), especially in the case of low-grade articular degeneration, whereas in severe OA less satisfactory outcomes have been documented, with results quite similar in comparison to viscosupplementation.

Platelet-Rich Plasma (PRP)

- A potential explanation for these contradictory results might be the high variability of PRP products.

- An example of PRP's formulation variability is the amount of leukocytes present. In fact, both leukocyte-rich PRP and leukocyte-poor PRP products are available. Nevertheless, comparison between these two formulations has been performed showing no inter-product differences; similarly, no clear evidence exists on the ideal number of injections and their timing to maximize the clinical results

Autologous Conditioned Serum (ACS) (Orthokine)

- Interleukin-1 (IL-1) is one such pro-inflammatory cytokine, suspected to play a prominent role in the pathophysiology of OA.

- ACS is a serum isolated from whole blood, incubated and then separated with centrifugation. There are IL-1 receptor antagonists (IL-1ra) and anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 in this serum.
- The effectiveness of ACS and PRP treatments can last up to two years. After two years, the effectiveness of both treatments decreases. Comparing the two treatments, ACS treatment showed better results on VAS and KOOS scores compared to PRP treatment.

Mesenchymal Stem Cells (MSCs)

- Intra-articular injections of stem cells associated to a pool of immune-modulatory and anti-inflammatory stromal molecules.

- Many adult tissues are populated by MSCs (adipose tissue, muscles, dermis, periosteum, synovial membrane, synovial fluid, etc.), but, in clinical practice, they are usually harvested from either bone marrow or adipose tissue.

Mesenchymal Stem Cells (MSCs)

- Even if many issues are still to be verified, MSCs, given their capacity to differentiate in mesenchymal derived tissue such as osteoblasts, chondrocytes and adipocytes, may have not only an anti-inflammatory, pro-angiogenetic and anti-apoptotic function, but also a reparative or regenerative role.

- Their effects are consequences of direct cell–cell interaction and secretion of factors.

Mesenchymal Stem Cells (MSCs)

- Similar to PRP, MSCs affect Wnt/β-catenin expression, thus controlling OA progression. However, differentiation potential is dependent on several factors such as architectural extracellular and inter-cellular segmental characterization, environmental factors, growth factors, and adequate pool of MSCs.

- In addition, having low expression of antigen-presenting molecules, MSCs are non-immunogenic; moreover, cartilage tissue, due to lack of vascular and lymphatic system, is particularly immune-privileged.

Mesenchymal Stem Cells (MSCs)

- In clinical practice, MSCs can be used as a cell suspension, after expansion in culture or enzymatic digestion, or they can be concentrated directly in the operating room (OR), which is currently the favoured approach due to the stringent regulations and higher costs affecting the procedures undergoing extensive manipulation in the lab.
- Expanded MSCs allow a more reproducible treatment but a two-step procedure is needed with an increase in costs, manipulation-related infection risks and invasiveness. This is why in both the USA and Europe ‘minimally manipulated’ MSCs, such as bone marrow aspirate concentrate (BMAC) and adipose-derived stromal vascular fraction (SVF) are the most exploited strategies for clinical application.

Bone Marrow Aspirate Concentrate (BMAC)

- BMAC is commonly obtained from the iliac crest using needle aspiration and concentration through centrifugation (one or multiple) occurring directly in the OR to obtain a product for immediate use.

- With regard to clinical outcomes, even if BMAC has been shown to have a positive effect on function and pain, its regenerative effects and superiority compared to viscosupplementation and corticosteroids are still to be proved.

Adipose-Derived Stromal Vascular Fraction (SVF)

- SVF contains 300-fold more MSCs when compared to BMAC, and is composed of a heterogenous cell population: preadipocytes, vascular endothelial cells, smooth muscle cells and pericytes (ASCs), leucocytes, and erythrocytes.

- SVF has proved to be a safe treatment with positive clinical consequences and a radiological and histological improvement compared to BMAC.

Adipose-Derived Stromal Vascular Fraction (SVF)

- SVF products differ in terms of preparation methods:
- originally SVF was obtained by enzymatic digestion with collagenase and trypsin,

- But then minimally manipulative methods were developed, exploiting mechanical forces such as centrifugation or microfragmentation in order to obtain a readily injectable product.

Potential contraindications

- In the case of PRP, low basal platelet count (< 150,000/mm3),
- The presence of haematological diseases, coagulopathies (both congenital or acquired) or chronic anti-aggregant or steroidal therapy may impair or reduce the biologic efficacy of PRP.
- PRP and MSCs should be also avoided in cases of recent diagnosis of malignancies, in particular hematologic ones.

- Debated about rheumatic diseases???

Combined therapies

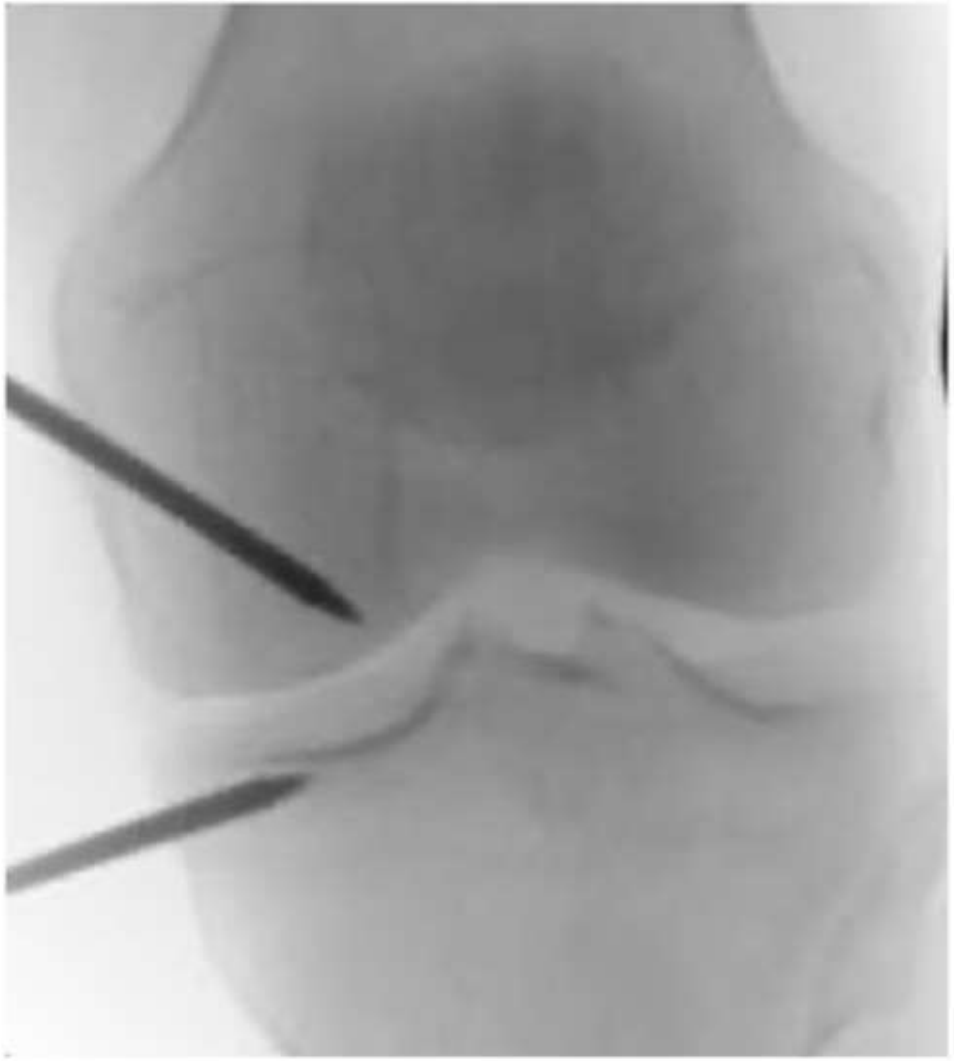
- Another attempted strategy is a combination therapy, based on a single intra-articular administration of multiple substances.
- A recent meta-analysis showed that combination of CS and HA were superior to HA alone in the reduction of pain both in the short and long-term outcomes.
- Similar results were found in a study comparing PRP and HA against HA and PRP alone.
- Preliminary results on a PRP + MSCs combination showed significant reduction of symptoms up to 12 months after the procedure.

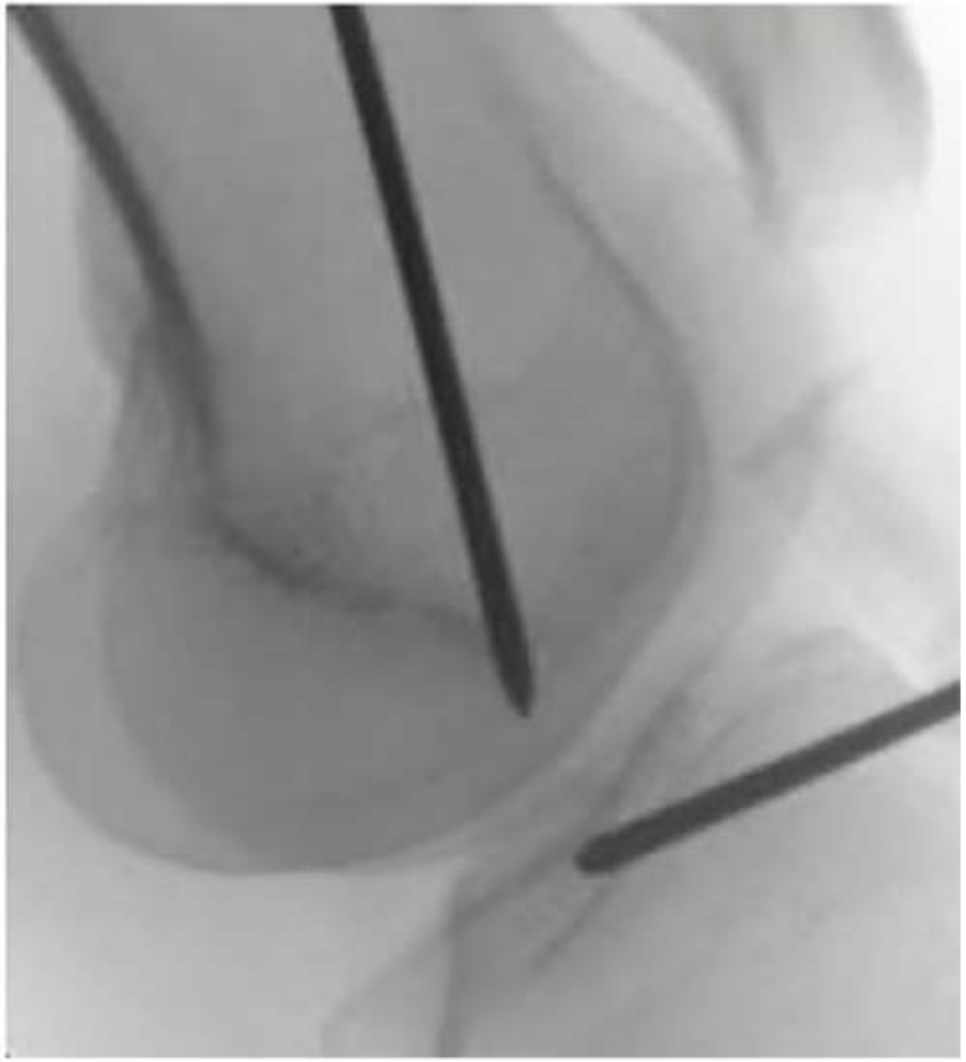
Subchondral Injections

- Minimally invasive intra-osseous delivery under fluoroscopic guidance of products such as PRP, MSCs or as calcium phosphate [Subchondroplasty] .

- The rationale behind this procedure stems from an increasing interest in the role of the subchondral bone in OA.

Subchondral injections





Intra-Meniscal Injections

- Recently attempts to target selectively the meniscal tissue with intra-meniscal injections. Among them, PRP, due to its anti-inflammatory and regenerative effects, has recently been spreading in clinical practice.
- Guenon et al (cadavric) performed an ultrasound-guided intra-meniscal, meniscal wall and intra-articular injection procedure, demonstrating that intra-meniscal PRP treatment is feasible, safe and efficient.
- Gerard A Malanga et al, prolonged clinical and functional improvement was observed.

Micro-Fragmented Adipose Tissue (MFAT)

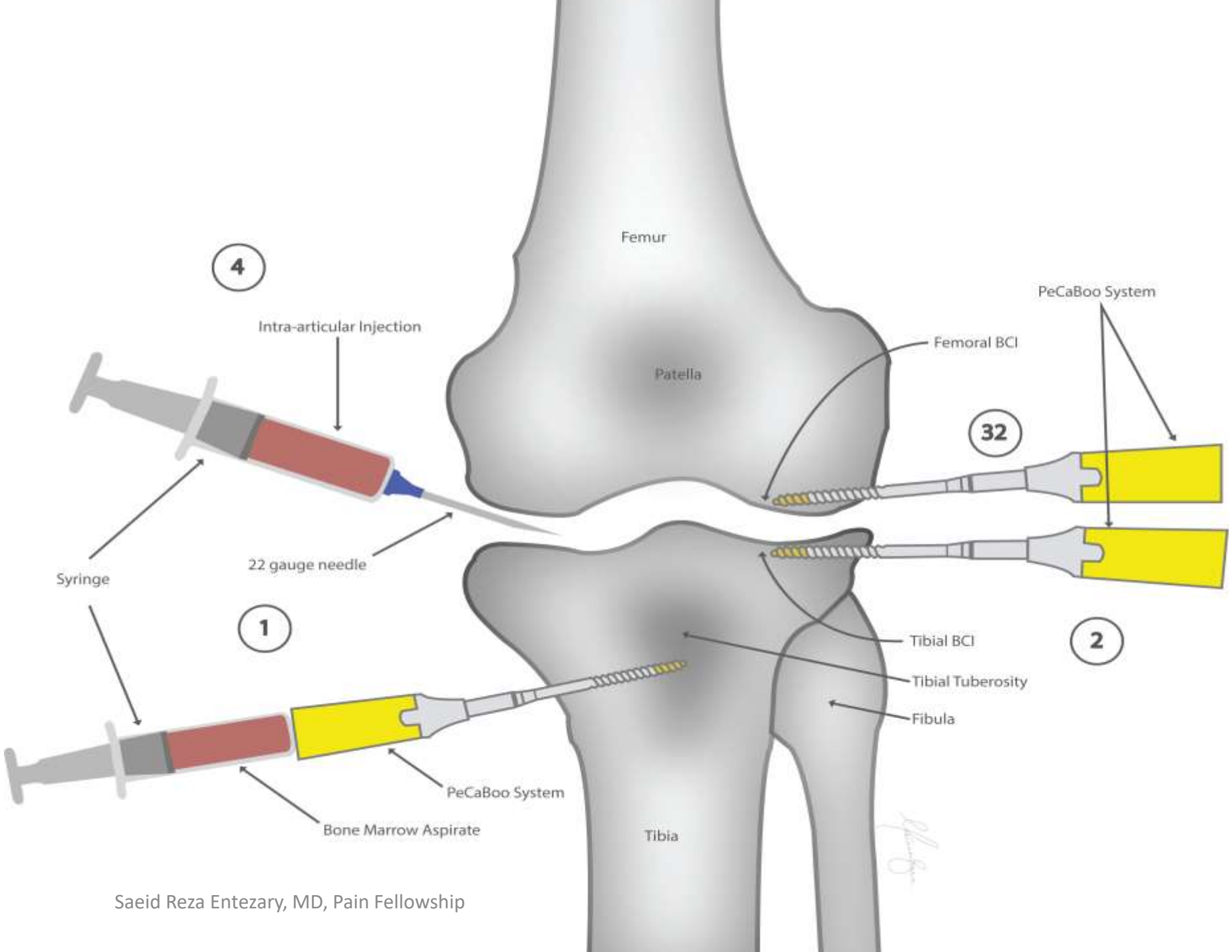
- Micro-fragmented adipose tissue (MFAT) rich in SVF, may also be used for intra-meniscal injections.
- It acts as trophic mediator by secreting a variety of cytokines and growth factors, inhibiting fibrosis and apoptosis, enhancing angiogenesis and stimulating the differentiation of tissue-intrinsic reparative or stem cells.

- MFAT may not only work as biological vehicle but also as an adipose tissue filler for meniscus regeneration.

Carboplasty

- Carboplasty combines the beneficial biochemical properties of bone marrow aspirate (BMA) and the mechanical properties of bone decompression using the percutaneous cartilage bone interface optimization system.
- The term “carboplasty” comes from “cartilage” and “bone”.

- The main objective of this technique is to treat OA by addressing the problem directly in the BCI while decompressing bone edema. This technique involves the application of tibial BMA in the femoral and tibial BCI as well as intra-articularly



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Future perspectives

- A strong limitation of the injective techniques is still the limited longevity of a sufficient drug dose inside the joint in order to exert a durable therapeutic effect. To overcome this limit, numerous new nano-technological approaches have been developed and are currently under testing.
- Another new experimental approach is represented by gene delivery. The concept is to deliver intra-articularly viral vectors with cDNAs coding for therapeutic proteins such as TGF-β1, IL-1Ra, interferon-beta (IFN-β), aiming at a sustained, endogenous drug delivery system.

- The recombinant human fibroblast growth factor 18 (rhFGF-18, Sprifermin): it has been investigated both in vitro and in rat models showing its ability to expand hyaline cartilage-producing chondrocytes leading to an overall increase in cartilage volume.

Future perspectives

- Among the cartilage catabolism inhibitors, we should mention IL-1 receptor antagonist (IL-1Ra): its use as an intra-articular injectable was found to be safe in humans and effective in reducing cartilage degeneration and synovial inflammation in animal models. Moreover, monoclonal antibodies directed against nerve growth factor (NGF) (tanezumab, fulranumab, and fasinumab) have also been suggested as potentially therapeutic in OA.
- Indeed, anti-NGF injections for knee OA were found to be superior in pain reduction compared to a placebo.