INTRODUCTION

Musculoskeletal diseases are now the second greatest cause of disability in all regions of the world, with osteoarthritis (OA) showing the greatest increase in the last 20 years. [1,2] Quality of life studies suggest that the impact of OA is comparable to that of cardiac, neurological and pulmonary diseases in terms of effect on daily functioning and health –related quality of life. [3-5]

Osteoarthritis (OA), also known as degenerative joint disease, is the most frequent chronic musculoskeletal disease and the leading cause of disability in elderly persons. Traditionally OA has been considered as a disease of articular cartilage, but the disease is manifest in all joint structures; cartilage, subchondral bone, synovium,capsule and ligaments. [6,7]

OA is defined by focal lesions of the articular cartilage, combined with a hypertrophic reaction (sclerosis) in the subchondral bone and new bone formation (osteophytes) at the joint margins. More recently, OA has been relabelled as a whole organ disease, because pathologic abnormalities such as periarticular muscle weakness, lax ligaments, low-grade synovitis and meniscal degeneration are frequently present in these patients. [8]

Osteoarthritis may be classified as primary or secondary according to its cause or major predisposing factor; both types have in common altered cartilage physiology. Primary osteoarthritis is the most common type and has no identifiable etiology or predisposing cause. Secondary osteoarthritis, although it has an identifiable underlying cause, is pathologically indistinguishable

Although the etiology of osteoarthritis is incompletely understood, the accompanying biochemical, structural, and metabolic changes in joint cartilage have been well documented. It is now known that cytokines, mechanical trauma, and altered genetics are involved in its pathogenesis, and that these factors can initiate a degradative cascade that results in many of the characteristic alterations of articular cartilage in osteoarthritis. [9,10]

Prevalence

The exact incidence and prevalence of osteoarthritis is difficult to determine because the clinical syndrome of osteoarthritis (joint pain and stiffness) does not always correspond with the structural changes of osteoarthritis (usually defined as abnormal changes in the appearance of joints on radiographs). This area is becoming more complex with sensitive imaging techniques such as magnetic resonance imaging which demonstrate more frequent structural abnormalities than detected by radiographs. [11]

Osteoarthritis at individual joint sites (notably knee, hip and hand) demonstrates consistent age-related increases in prevalence. However symptomatic osteoarthritis is not an inevitable consequence of ageing. Although prevalence of osteoarthritis rises in frequency with age, it does affect substantial numbers of people of working age. The number of people with osteoarthritis is increasing as the population ages, and as the prevalence of risk factors such as obesity and poor levels of physical fitness also continues to rise. [11]

The prevalence of osteoarthritis depends on the precise definition used and the region of interest. Forty-eight percent of knees at autopsy have histologic evidence of osteoarthritis, whereas only 10% of these patients previously reported any clinical manifestations of knee osteoarthritis. The knee is the most clinically significant site affected—the prevalence increases with age so that 53% of women older than 50 years and 33% of men older than 55 years have radiographic knee osteoarthritis. [(12)]

Gender plays a role in both radiographic and symptomatic OA. The prevalence of knee OA is higher in women than in men although the radiographic prevalence is similar while hip OA seems more frequently observed in men. Hand OA is more frequent in women. In patients older than 55 years, the prevalence of radiographic hand OA is 90% in women and 80% in men. [(13)]

Radiographic osteoarthritis

Although joint pain is more common than radiographic osteoarthritis, much radiographic osteoarthritis occurs in the absence of symptoms. The prevalence of radiographic osteoarthritis, like symptoms, is also dependent on the particular images acquired and definitions used. [(14)]

The prevalence of radiographic osteoarthritis is higher in women than men, especially after age 50 and for hand and knee osteoarthritis. Radiographic osteoarthritis of the knee affects about 25% of community populations of adults aged 50 years and over. [(14)]

Ethnic differences in radiographic osteoarthritis prevalence have been more difficult to distinguish, especially in studied African-American groups, but recent reports349 comparing Chinese and US populations have demonstrated much lower levels of hip osteoarthritis in the Chinese, although levels of knee and hand osteoarthritis generally were similar despite varying patterns.

The relationship between symptomatic and radiographic osteoarthritis

Although symptoms and radiographic changes do not always overlap, radiographic osteoarthritis is still more common in persons with a longer history and more persistent symptoms. There is a consistent association at the knee, for example, between severity of pain, stiffness, and physical function and the presence of radiographic osteoarthritis.130 Concordance between symptoms and radiographic osteoarthritis seems greater with more advanced structural damage. [(15)]

Half of adults aged 50 years and over with radiographic osteoarthritis of the knee have symptoms Of the 25% of older adults with significant knee joint pain, two-thirds have radiographic disease. The prevalence of painful, disabling radiographic knee osteoarthritis in the UK populations over 55 has been estimated at approximately 10%. The prevalence of symptomatic radiographic osteoarthritis is higher in women than men, especially after age 50. Within the knee joint of symptomatic individuals, the most common radiographic osteoarthritis pattern of involvement is combined tibiofemoral and patellofemoral changes. Although there are few good studies, symptomatic radiographic hand osteoarthritis has been reported in less than 3% of populations, while rates of symptomatic radiographic hip osteoarthritis have varied from 5 to 9%.[(16)]

Classification of Osteoarthritis

I. Idiopathic

A. Localized OA

1. Hands: Herberden's and Bouchard nodes (nodal), erosive inter-phalangeal arthritis (non nodal), 1st carpometacarpal joint.(17)

2. Feet: hallux valgus, hallux rigidus, contracted toes (hammer/cock up toes), talonavicular.

3. Knee:

a. Medial compartment
b. Lateral compartment
c. Patellofemoral compartment

4. Hip:

a. Eccentric (superior)
b. Concentric (axial, medial)
c. Diffuse

5. Spine:

a. Apophyseal joint
b. Intervertbral joints (discs)
c. Spondylosis (osteophytes)
d. Ligamentous (hyperostosis, Forestier's disease. Diffuse idiopathic skeletal hyperostosis).

6. Other single sites, e.g., glenohumeral, acromioclavicular, tibiotalar, sacroiliac, temporomandibular.

B. Generalized OA includes 3 or more of these areas listed above.

II. Secondary

Because osteoarthritis may follow almost any established joint disorder, osteoarthritis is considered to be primary if it is idiopathic and secondary in cases of previous injury or disease of the target joint. It is not always easy to distinguish between primary and secondary osteoarthritis, however, because a significant proportion of subjects who develop secondary osteoarthritis have some predisposition to osteoarthritis that may operate independent of the prior condition. An interview and a physical examination may help the physician to identify an etiology. Along with these clinical features, radiographs can help diagnose some secondary osteoarthritis conditions, such as chondrocalcinosis and Paget's disease. (18)

Etiologies of secondary osteoarthritis (OA) [19]

A. Post Traumatic

- Major joint trauma
- Fracture through a joint or osteonecrosis
- Joint surgery (e.g. meniscectomy)
- Chronic injury (occupational arthropathy)

B. Congenital or developmental diseases

1. Localized

(a) Hip diseases: e.g Legg-Calve-Perthes diseases, congenital hip dislocation, slipped capital femoral epiphysis, shallow acetabulum.

(b) Mechanical and local factors: e.g obesity, unequal lower extremity length, extreme valgus/varus deformity, hypermobility syndromes, scoliosis.

2. Generalized

(a) Bone dysplasia: e.g. epiphysal dysplasia, spondylo-apophyseal dysplasia, osteonychondystrophy.

(b) Metabolic diseases: e.g. ochronosis, Gaucher's disease, haemoglobinopathy, Ehler-Danlos disease, haemochromatosis.

C. Calcium deposition disease

- Calcium pyrophosphate deposition disease (CPPD)
- Apatite arthropathy
- Destructive arthropathy (shoulder, knee)

D. Other bone and joint disorders:

e.g. avascular necrosis, RA, gouty arthritis, septic arthritis, paget's disease, osteopetrosis and osteochondritis.

E. Other diseases

- Endocrinal diseases: e.g. diabetes mellitus, acromegaly, hypothyrodism, hyperparathyroidism.
- Neuropathic arthropathy (Charcot joints).

Etiologic Factors in Osteoarthritis

Major factors that affect the degree of risk for developing osteoarthritis include age, gender, joint location, obesity, genetic predisposition, joint malalignment and trauma.

Age

Age is the risk factor most strongly correlated with osteoarthritis. Osteoarthritis is the most common chronic disease that develops in later life. More than 80% of individuals older than 75 years are affected, and osteoarthritis increases progressively with age at all joint sites. Radiologic changes of osteoarthritis increase as individuals age, although these changes do not always correlate with clinical symptoms or disability. Although an age-related disease, osteoarthritis is not an inevitable consequence of aging. [20]

Age-related morphologic and structural changes in articular cartilage include fraying, softening, and thinning of the articular surface; decreased size and aggregation of matrix proteoglycans; and loss of matrix tensile strength and stiffness. These age-related tissue changes are most often caused by a decrease in chondrocytes' ability to maintain and repair the tissue, as chondrocytes themselves undergo age-related decreases in mitotic and synthetic activity, exhibit decreased responsiveness to anabolic growth factors, and synthesize smaller and less uniform large aggregating proteoglycans and fewer functional link proteins. [20]

There also seems to be a direct correlation between chondrocyte apoptosis and cartilage degradation leading to osteoarthritis. Age seems to be an independent factor that predisposes articular chondrocytes to apoptosis because the expression levels of specific proapoptotic genes (Fas, Fas ligand, caspase-8, and p53) is higher in aged cartilage.[21]

Gender

Women are about twice as likely as men to develop osteoarthritis. Although women have a lower prevalence of osteoarthritis than men before age 50 years, there is a marked increase in prevalence among women after age 50, particularly in the knee. Women have a greater number of joints involved and are more likely to exhibit clinical symptoms of morning stiffness, joint swelling, and nocturnal pain.[22]

The gender differences in osteoarthritis incidence after age 50 may be the result of postmenopausal estrogen deficiency. Articular chondrocytes possess functional estrogen receptors (ERs), suggesting that these cells can be regulated by estrogen. [23]

Joint location

Although osteoarthritis occurs most commonly in weight-bearing joints. Joint-specific, age-related viability in articular cartilage may explain why osteoarthritis is more common in hip and knee joints with increasing age, but occurs rarely in the ankle. Alterations in chondrocyte responsiveness to cytokines also seem to vary depending on the joint. Studies show that knee joint chondrocytes exhibit more interleukin (IL)-1 receptors

than ankle joint chondrocytes, and that knee chondrocytes express mRNA for matrix metalloproteinase (MMP)-8, whereas ankle chondrocytes do not. [24]

Obesity

Obesity is another important risk factor for osteoarthritis. Greater body mass index in women and men has been shown to be associated with increased risk of knee, but not hip osteoarthritis. [25]

Particularly in elderly obese individuals, heavy physical activity is an additional risk factor for the development of knee osteoarthritis, whereas light-to-moderate activity does not seem to increase risk for knee osteoarthritis and may alleviate symptomatic knee osteoarthritis by reducing body mass index. [26]

Genetic predisposition

Structural genes are important for the maintenance and repair of articular cartilage and for the regulation of chondrocyte proliferation and gene expression. In some cases (e.g., chondrodysplasias), structural genes are the identifiable causes of osteoarthritis. Several candidate genes encoding for structural proteins of the extracellular matrix of the articular cartilage have been associated with early-onset osteoarthritis. Although likely of limited importance in most cases of osteoarthritis, the discovery of a point mutation in the cDNA coding for type II collagen in several generations of a family with spondyloepiphyseal dysplasia and polyarticular osteoarthritis has focused attention on this area. [27]

In addition to the point mutation in type II collagen, which was identified in the family mentioned in the previous paragraph, inherited forms of osteoarthritis may be caused by mutations in several other genes that are expressed in cartilage, including genes encoding types IV, V, and VI collagens and cartilage oligomeric matrix protein (COMP). It was reported more recently that mice deficient in the type IX collagen gene developed age-dependent, osteoarthritis-like changes in the knee and temporo-mandibular joints.[28,29]

Joint malalignment and trauma

Joint malalignment or trauma may lead to rapid development of osteoarthritis, or it may initiate a slow process that results in symptomatic osteoarthritis years later. Probably as a result of progressive reduction in periarticular blood flow and the resultant decrease in rate of remodeling at the osteochondral junction, joints become increasingly congruent with age.[30] Altered joint geometry may interfere with nutrition of the cartilage, or it may alter load distribution, either of which may result in altered biochemical composition of the cartilage, regardless of age. Local factors, such as stresses related to joint use and joint deformity, also influence the development of osteoarthritis.[31]

Pathology of osteoarthritis

Normal cartilage

Cartilage is composed of extracellular matrix (ECM) which contains collagen (mainly type II and also types IX and XI) and proteoglycans. Among the proteoglycans, agrecan is a central core protein bearing numerous glycosaminoglycan chains of chondroitin sulfate and keratan sulfate which are themselves associated with hyaluronic acid. These molecular complexes have the property to retain water. This association of agrecan complex and collagen gives the cartilage its functional properties such as compressibility and elasticity. The chondrocyte is the only one cell type present in the ECM. Chondrocytes are able to live in hypoxia. Nutriments come from the synovial fluid and from subchondral bone, maintaining its cellular activities. [32]

Normal articular cartilage is a specialized tissue characterized macroscopically by its milky, shelled-almond (hyaline) appearance. It is an avascular tissue nourished by diffusion from the vasculature of the subchondral bone and from the synovial fluid. Articular cartilage is more than 70% water, and it is hypocellular compared with other tissues; chondrocytes constitute only 1% to 2% of its total volume. Most of the dry weight of cartilage consists of two components: type II collagen and the large aggregating proteoglycan, aggrecan. Several "minor" collagens and small proteoglycans also seem to play a role in cartilage-matrix organization, however. [32,33]

Despite its thinness (≤7 mm) and apparent homogeneity, mature articular cartilage is a heterogeneous tissue with four distinct regions: (1) the superficial tangential (or gliding) zone, (2) the middle (or transitional) zone, (3) the deep (or radial) zone, and (4) the calcified cartilage zone, which is located immediately below the tidemark and above the subchondral bone. In the superficial zone, the chondrocytes are flattened, and the matrix comprises thin collagen fibrils in tangential array, associated with a high concentration of the small proteoglycan decorin and a low concentration of aggrecan. The middle zone, composing 40% to 60% of the cartilage weight, consists of rounded chondrocytes surrounded by radial bundles of thick collagen fibrils. In the deep zone, the chondrocytes frequently are grouped in columns or clusters. In this region, the collagen bundles are the thickest and are arranged in a radial fashion. [34,35] **Figure (1)**

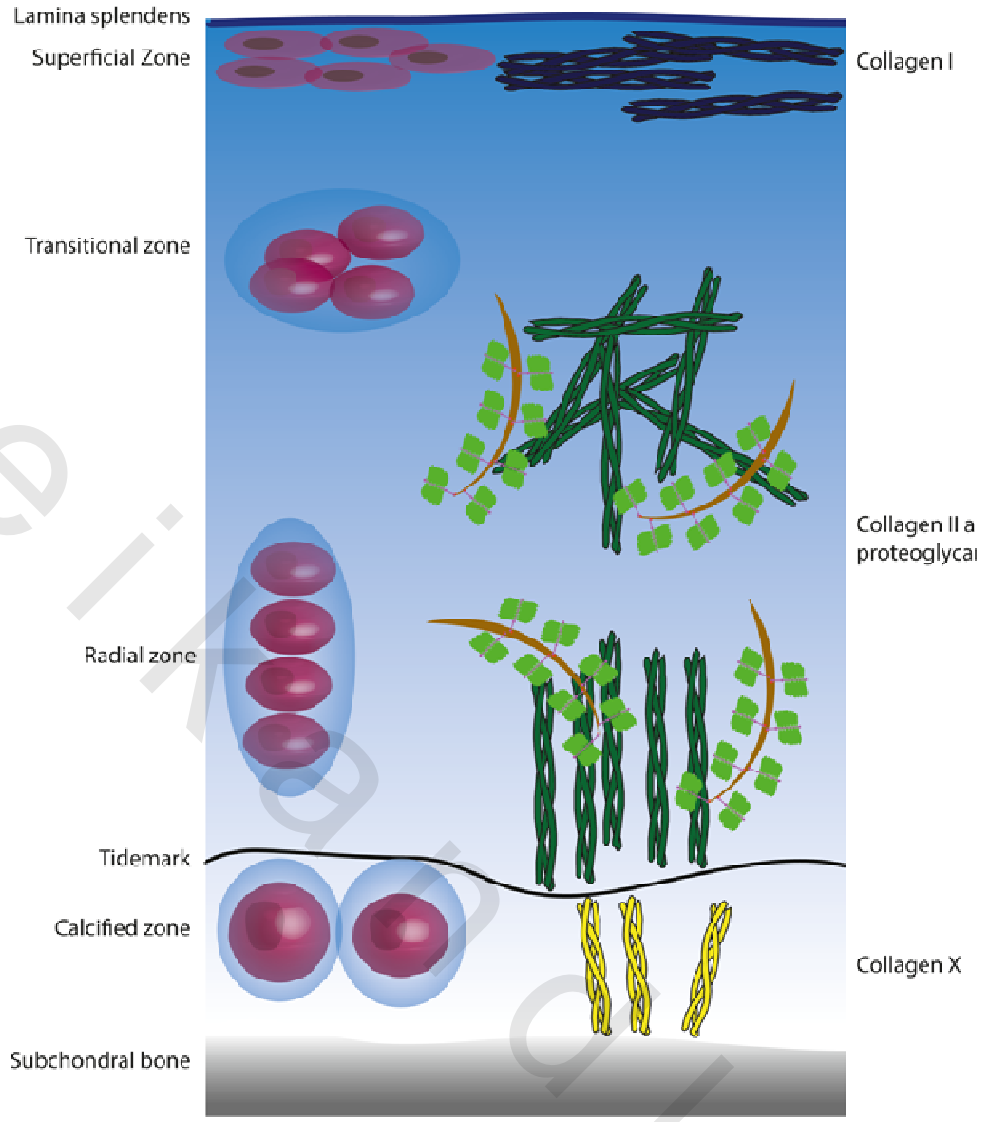

Figure (1): Illustration showing a cross section of articular cartilage from the subchondral bone up to the superficial layer facing the joint cavity.

Passage of normal cartilage to aging cartilage

Aging cartilage is characterized by the occurrence of disruption of the collagen network leading to fissures A prominent feature of aging cartilage is the accumulation of advanced glycation end products (AGE) leading to protein modification by non enzymatic glycation. The presence of AGE leads to an alteration of biomechanical properties. Moreover, AGE can bind to specific receptors present on the surface of chondrocytes, called receptor of advanced glycation end products (RAGE), The AGE/RAGE system is involved in the catabolic activity of the chondrocytes.[36]

In conclusion, aging cartilage contains less water, which alters the biochemical properties, diminished chondrocytes number and lower synthesis of ECM components quantitatively and qualitatively.

Osteoarthritis joint

The macroscopic alterations of an osteoarthritic joint are ***(Figure 2)***:

- Reduced joint space related to cartilage thickening.
- Subchondral bone with hypertrophic reaction (sclerosis), new bone formation (osteophytes) at the joint margin and neoangiogenesis from the subchondral bone into the cartilage (physiologically avascular). [37]
- Inflammation of the synovial membrane.

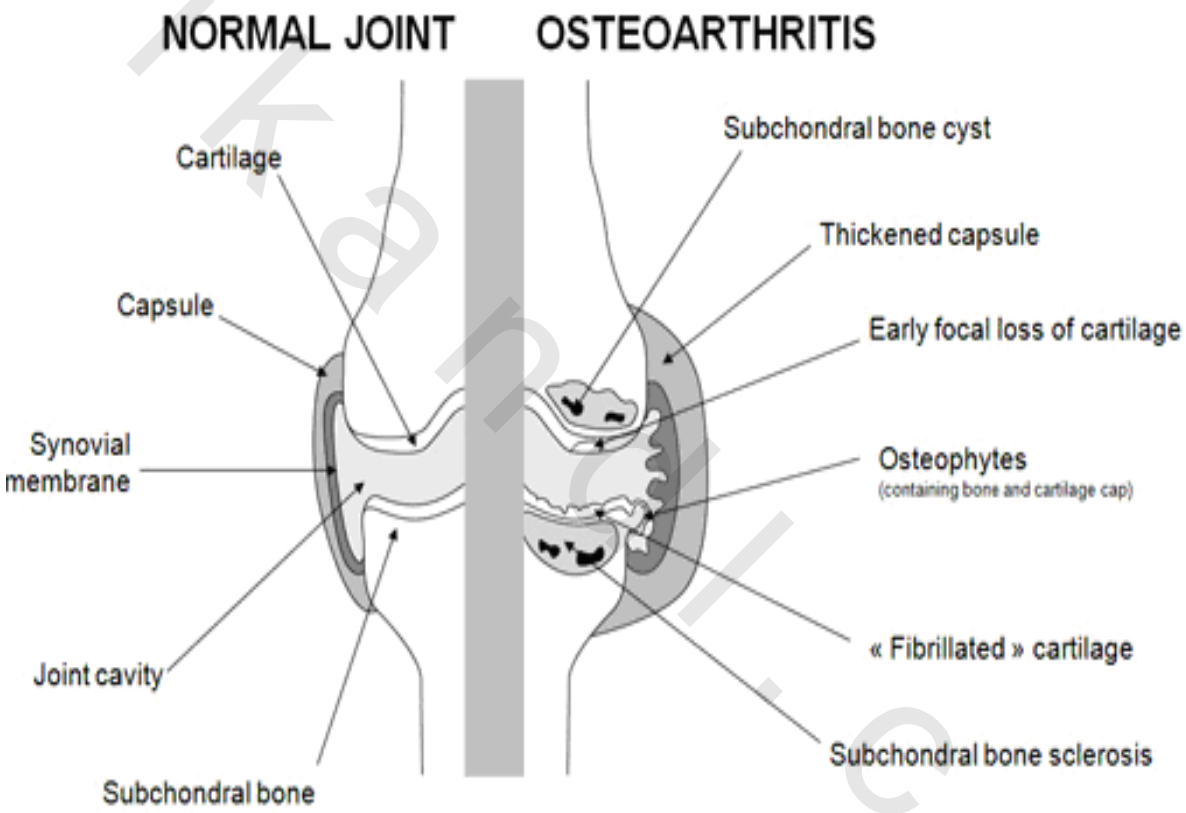

Figure (2):Pathology of osteoarthritis

Pathogenesis

The main load on articular cartilage—the major target tissue in OA—is generated by the contraction of the muscles that stabilize or move the joint. Although cartilage is an excellent shock absorber in terms of its bulk properties, at most sites it is too thin to serve as the sole shock-absorbing structure in the joint. Additional protective mechanisms are provided by the subchondral bone and periarticular muscles. (38)

Joint Protective Mechanisms include: joint capsule and ligaments, muscle, sensory afferents, and underlying bone. Joint capsule and ligaments serve as joint protectors by providing a limit to excursion, thereby fixing the range of joint motion.

Synovial fluid reduces friction between articulating cartilage surfaces, thereby serving as a major protector against friction-induced cartilage wear. This lubrication function depends on the molecule lubricin, a mucinous glycoprotein secreted by synovial fibroblasts whose concentration diminishes after joint injury and in the face of synovial inflammation. (39-42)

The ligaments, along with overlying skin and tendons, contain mechanoreceptor sensory afferent nerves. These mechanoreceptors fire at different frequencies throughout a joint's range of motion, providing feedback by way of the spinal cord to muscles and tendons. As a consequence, these muscles and tendons can assume the right tension at appropriate points in joint excursion to act as optimal joint protectors, anticipating joint loading. (43)

Muscles and tendons that bridge the joint are key joint protectors. Their contractions at the appropriate time in joint movement provide the appropriate power and acceleration for the limb to accomplish its tasks. Focal stress across the joint is minimized by muscle contraction that decelerates the joint before impact and assures that when joint impact arrives, it is distributed broadly across the joint surface.(44)

OA develops in either of two settings:

(1) The biomaterial properties of the articular cartilage and subchondral bone are normal, but excessive loading of the joint causes the tissues to fail; or

(2) The applied load is reasonable; but the material properties of the cartilage or bone are inferior.

Although articular cartilage is highly resistant to wear under conditions of repeated oscillation, repetitive impact loading soon leads to joint failure. This fact accounts for the high prevalence of OA at specific sites related to vocational or avocational overloading. In general, the earliest changes occur at the sites in the joint that are subject to the greatest compressive loads. (45)

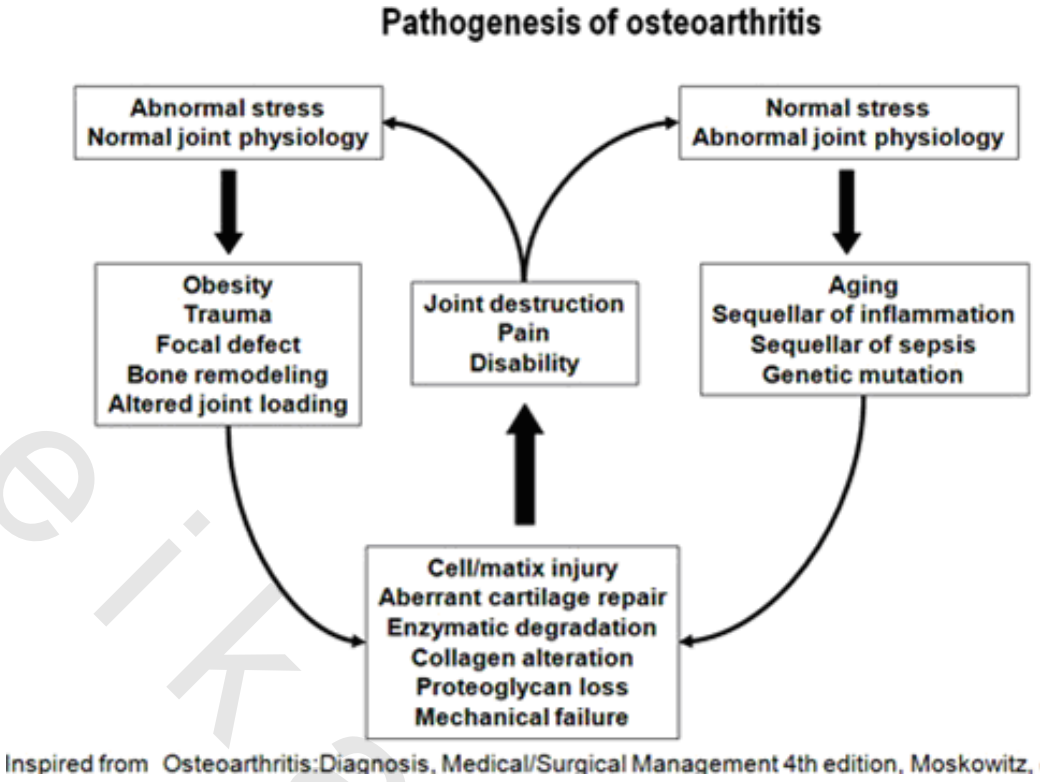

Figure (3): pathogenesis of osteoarthritis

Inflammatory molecules produced by articular cartilage

Cytokines and Chemokines

A characteristic feature of established osteoarthritis is the increased production of proinflammatory cytokines, such as IL-1β and TNF-α, by articular chondrocytes. IL-1β and TNF-α exert comparable catabolic effects on chondrocyte metabolism, decreasing proteoglycan collagen synthesis and increasing aggrecan release via the induction of degradative proteases. [46] IL-1β and TNF-α also induce chondrocytes and synovial cells to produce other inflammatory mediators, such as IL-8, IL-6, nitric oxide, and prostaglandin E_2. The actions of both cytokines are mediated partly by the activation of the transcription factor nuclear factor κB, which increases further their own expression and that of other catabolic proteins, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), creating an autocatalytic cascade that promotes self-destruction of articular cartilage (Fig.4) [47]

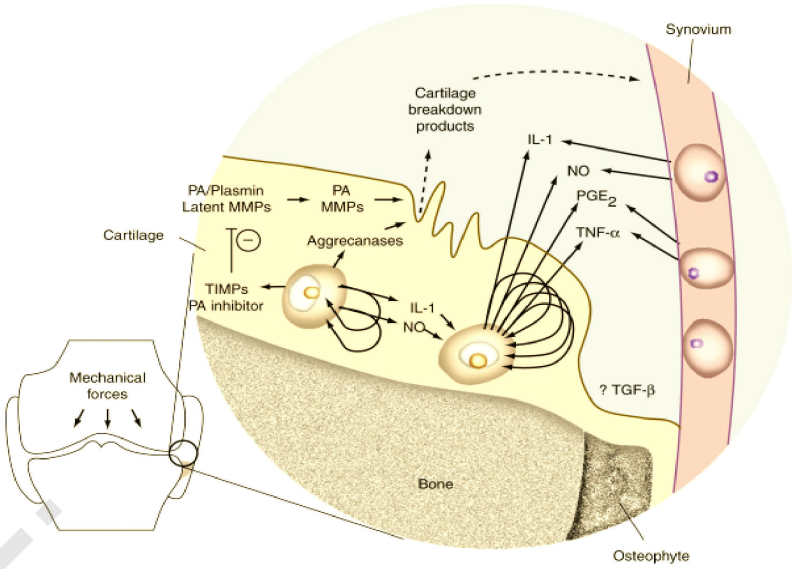

Figure (4): Schematic of pathogenic mechanisms of osteoarthritis

http://mulla.pri.ee/Kelley's%20Textbook%20of%20Rheumatology,%208th%20ed./HTML/676.htm

IL-6 is a multifunctional cytokine that plays a central role in both innate and acquired immune responses. IL-6 is the predominant mediator of the acute phase response, an innate immune mechanism that is triggered by infection and inflammation.

IL-6 is believed to be one of the major factors in joint destruction, being a pleiotropic pro-inflammatory cytokine that is markedly upregulated at times of tissue inflammation. A significant increase in the level of IL-6 mRNA has been detected in OAaffected cartilage, and the IL-6 levels in the serum and synovial fluid have been reported to be elevated among OA patients. [48]

In addition, human recombinant IL-6 has been shown to enhance human recombinant IL-1β-induced proteoglycan degradation and to inhibit chondrocyte proliferation. [49]

Interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) are of special interest in the elderly, because both cytokines induce production of IL-6 and because they haveprofound effects on body metabolism, body composition, and the acute-phase response [50-52], all of which are altered with increasing age.

TNFα has been shown to regulate energy expenditure in humans during inflammation and is associated with low lean body mass, which is an important marker of physiologic status and a major predictor of survival, strength, and functional status in the elderly and causes hepatic production of acute-phase proteins such as C-reactive protein (CRP). [53]

Increased circulating levels of CRP and IL-6 have been found to be predictors of reduced physical mobility and incident mobility limitation in the elderly. [54,55]

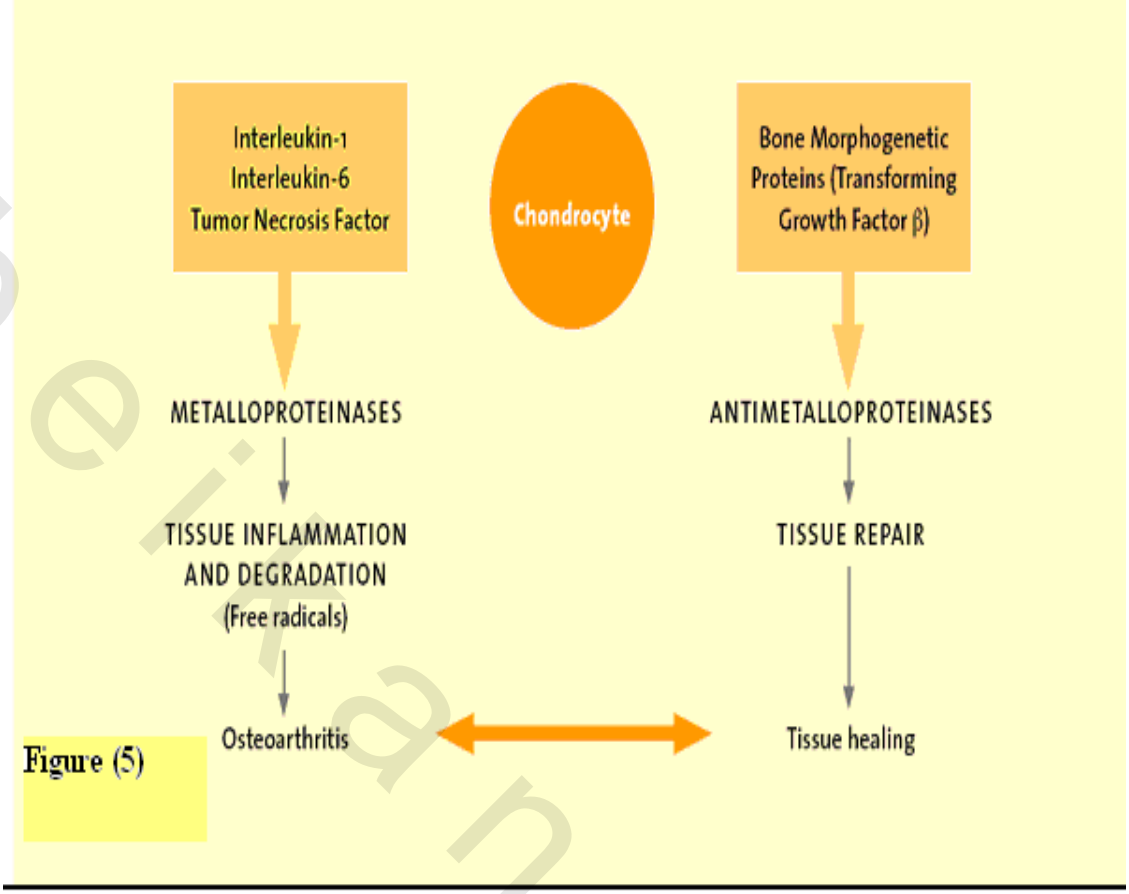

Figure (5): Effects of cytokines on chondrocyte.

http://www.nature.com/nrrheum/journal/v9/n7/images/nrrheum.2013.44-f1.jpg

Proteinases

There is increased expression of fibronectin, osteonectin, and osteopontin in osteoarthritis cartilage compared with normal cartilage. In addition, proteolytic processes generate fragments of extracellular matrix proteins, including fibronectin and type II collagen, which seem to exert catabolic and proteolytic activities. [56]

Nitric Oxide

Nitric oxide exerts multiple effects on chondrocytes that promote articular cartilage degradation, including:

(1) Inhibition of collagen and proteoglycan synthesis.
(2) Activation of metalloproteinases.
(3) Increased susceptibility to injury by other oxidants (e.g., hydrogen peroxide).
(4) Apoptosis. [57,58]

Transforming Growth Factor-β_1

In most respects, TGF-α acts as a counter regulatory molecule that opposes the effects of inflammatory mediators in cartilage. TGF-β_1 has been shown to down regulate proteolytic MMP-1, MMP-13, IL-1, and TNF receptors on osteoarthritis chondrocytes. [59] TGF-β_2 selectively suppresses the cleavage of type II collagen by collagenases in osteoarthritis cartilage in culture and limits MMP and proinflammatory cytokine expression.[60]

Hyaluronic Acid

Hyaluronic acid has been investigated as a marker of cartilage degradation that can be detected in synovial fluid and serum, but it also seems to play a role in limiting the progression of arthritis. [61]

Prostaglandins

The expression of inducible COX-2 is increased in osteoarthritis chondrocytes, which spontaneously produce prostaglandin E_2 ex vivo.[62] The effects of prostaglandins on chondrocyte metabolism are complex and include enhanced type II collagen synthesis, activation of metalloproteinases, and promotion of apoptosis. In cartilage explants, IL-1β induces COX-2 expression, and prostaglandin E_2 production coordinates with proteoglycan degradation. COX-2 inhibition prevents IL-1β-induced proteoglycan degradation, which can be reversed by the addition of prostaglandin E_2 to cultures.[63]

Knee osteoarthtitis

Anatomy of The Knee

Bones

The knee joint complex consists of the femur, the tibia, the fibula, and the patella. The distal end of the femur expands and forms the convex lateral and medial condyles, which are designed to articulate with the tibia and the patella. The proximal end of the tibia, the tibial plateau, articulates with the condyles of the femur. On this flat tibial plateau are two shallow concavities that articulate with their respective femoral condyles and are divided by the popliteal notch. Separating these concavities, or articular facets, is a roughened area where the cruciate ligaments attach and from which a process commonly known as the tibial spine arises.(64)

The patella is the largest sesamoid bone in the human body. It is located in the tendon of the quadriceps femoris muscle and is divided into three medial facets and a lateral facet that articulate with the femur The lateral aspect of the patella is wider than the medial aspect. The patella articulates between the concavity provided by the femoral condyles. Tracking within this groove depends on the pull of the quadriceps muscle and patellar tendon, the depth of the femoral condyles, and the shape of the patella.(65)

Articulations

The knee joint complex consists of four articulations between the femur and the tibia, the femur and the patella, the femur and the fibula, and the tibia and the fibula.

Menisci

The menisci are two oval (semilunar) fibrocartilages that deepen the articular facets of the tibia, cushion any stresses placed on the knee joint, and maintain spacing between the femoral condyles and tibial plateau. The consistency of the menisci is much like that of the intervertebral disks. They are located medially and laterally on the tibial plateau, or shelf. The menisci transmit one-half of the contact force in the medial compartment and an even higher percentage of the contact load in the lateral compartment. The menisci help stabilize the knee, especially the medial meniscus, when the knee is flexed at 90 degrees.(66)

Medial Meniscus: The medial meniscus is a C-shaped fibrocartilage, the circumference of which is attached firmly to the medial articular facet of the tibia and to the joint capsule by the coronary ligaments. Posteriorly,it is also attached to fibers of the semimembranous muscle.

Lateral Meniscus: The lateral meniscus is more O-shaped and is attached to the lateral articular facet on the superior aspect of the tibia. The lateral meniscus also attaches loosely to the lateral articular capsule and to the popliteal tendon. The ligament of Wrisberg is the part of the lateral meniscus that projects upward, close to the attachment of the posterior cruciate ligament.

Stabilizing Ligaments

The major stabilizing ligaments of the knee are the cruciate ligaments, the collateral ligaments, and the capsular ligaments.

The cruciate ligaments account for a considerable amount of knee stability. They are two ligamentous bands that cross one another within the joint capsule of the knee. The anterior cruciate ligament (ACL) attaches below and in front of the tibia; then, passing backward, it attaches laterally to the inner surface of the lateral condyle. The posterior cruciate ligament (PCL), the stronger of the two, crosses from the back of the tibia in an upward, forward, and medial direction and attaches to the anterior portion of the lateral surface of the medial condyle of the femur. (66)

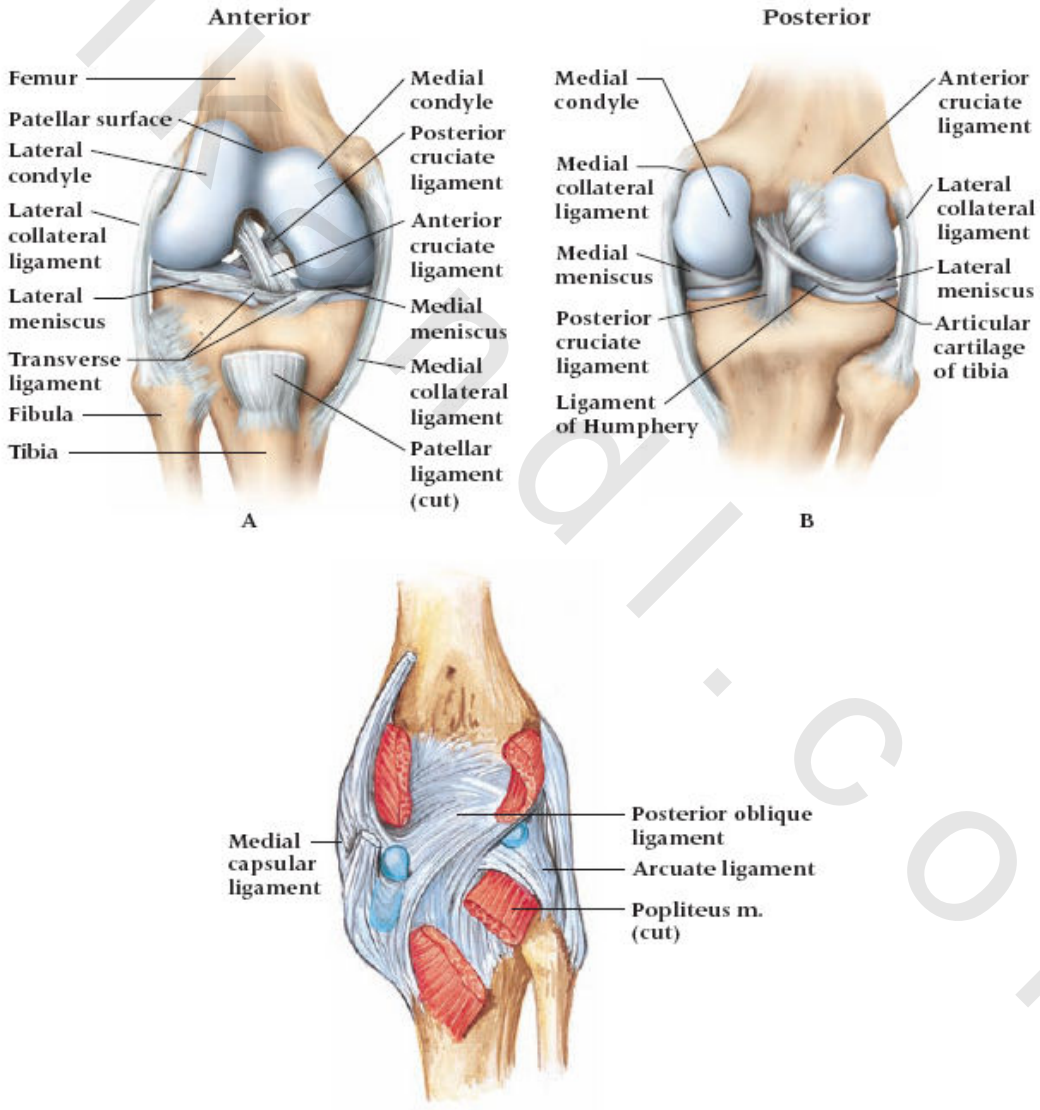

Figure (6): Anatomy of knee joint

http://www.eorthopod.com/knee-anatomy/topic/58

http://www.kindance.com/home/anatomy-tuesday-the-knee

Knee Osteoarthritis

Osteoarthritis can involve the medial tibiofemoral, the lateral tibiofemoral, and the femoropatellar compartments. The lateral tibiofemoral compartment is involved mainly in women who have a genu valgum deformity. The precise location of pain can indicate which compartment of the joint is involved. Patients also sometimes report knee instability—the knee "gives way." This instability is likely linked to decreased muscle strength rather than true meniscus damage.Posterior pain can be due to an abundant effusion. Physical examination for knee osteoarthritis should begin by investigating the gait, using a slow walk to check for an extension defect. Thereafter, any misalignment (genu valgus or genu varus) should be sought, and the presence of bone swelling should be noted.(67)

A popliteal (Baker's) cyst communicating with the joint space is common and may be complicated less often by distal vascular thrombosis. Acute cyst rupture may mimic venous thrombus and should be considered in "Doppler negative" leg swelling in the acute setting. Local tenderness along the joint line is characteristic of femorotibial osteoarthritis.(68) Crepitus is detected on passive motion of the patella or knee flexion-extension testing. The range of motion may be normal or limited by structural alterations or abundant effusion. Periarticular structure examination may reveal anserine bursitis or infrapatellar or prepatellar bursitis. Trochanteric bursitis also can cause pain radiating through the tensor fascia lata and iliotibial band to the lateral part of the knee. An acute tear of the anterior cruciate ligament may cause pain, but is unusual in middle-aged subjects. A positive Lachman's test may be elicited. The circumference of the quadriceps muscle should be noted to detect any atrophy.(69) Finally, the hip should be examined routinely because it may refer pain to the knee.

The syndrome of femoropatellar osteoarthritis is very specific: Pain occurs mainly during climbing or descending stairs; pain during walking on level ground is usually a symptom originating in the femorotibial compartment. Involvement of the femoropatellar compartment can cause anterior or posterior pain or both. Femoropatellar pain is produced by the patella pressing on the femoral condyles, or after patella subluxation or blocking elevation of patella during quadriceps contraction when the knee is extended. Femoropatellar osteoarthritis is usually better tolerated than femorotibial osteoarthritis, but severe disability is possible. The femoropatellar compartment is investigated using a specific x-ray axial view with variable degrees of knee flexion. (70)

Clinical manifestations

Symptoms are often initially insidious and can be highly variable, depending on the joint affected, the severity of joint involvement, and the number of joints affected.

Pain:

Pain is the first and predominant symptom of osteoarthritis that sends a patient to the general practitioner. Pain typically is worsened by activities such as long distance walking for weight-bearing joints and is alleviated by rest, in contrast to inflammatory disorders. (71)

Pain begins within a few minutes of starting an activity and may persist for hours after the activity has ceased. The pain sometimes can have an onset several hours after physical activities, especially in young patients. Although osteoarthritis pain is unusual during the night or at rest, there are exceptions, including in patients with mild osteoarthritis using joints for several hours especially during sport, in advanced osteoarthritis with destructive arthropathy, and in an acute inflammatory flare of osteoarthritis mimicking inflammatory arthropathy. Associated bursitis also can be a source of pain. Pain intensity and joint damage on radiographs are poorly correlated. Finally, there is no agreement as to whether a decrease in atmospheric pressure or a change in the weather increases osteoarthritis pain. (72)

Sources of Pain

Because cartilage is aneural, cartilage loss in a joint is not accompanied by pain. Thus, pain in OA likely arises from structures outside the cartilage. Innervated structures in the joint include the synovium, ligaments, joint capsule, muscles, and subchondral bone. Most of these are not visualized by the x-ray, and the severity of x-ray changes in OA correlates poorly with pain severity.(73)

Sources of pain include synovial inflammation, joint effusions, and bone marrow edema. Modest synovitis develops in many but not all osteoarthritic joints. Some diseased joints have no synovitis, whereas others have synovial inflammation that approaches the severity of joints with rheumatoid arthritis. The presence of synovitis on MRI is correlated with the presence and severity of knee pain. (74)

Capsular stretching from fluid in the joint stimulates nociceptive fibers there, inducing pain. Increased focal loading as part of the disease not only damages cartilage but probably also injures the underlying bone. As a consequence, bone marrow edema appears on the MRI; histologically, this edema signals the presence of microcracks and scar, which are the consequences of trauma. These lesions may stimulate bone nociceptive fibers. Also, hemostatic pressure within bone rises in OA, and the increased pressure itself may stimulate nociceptive fibers, causing pain..(73)

Lastly, osteophytes themselves may be a source of pain. When osteophytes grow, neurovascular innervation penetrates through the base of the bone into the cartilage and into the developing osteophyte. Pain may arise from outside the joint also, including bursae near the joints.

Stiffness and Loss of Movement and Function:

Stiffness also may occur in the morning, after a period of inactivity, or particularly in the evening. Morning stiffness generally resolves after less than 10 minutes, in contrast to the prolonged (usually >30 minutes) stiffness seen in inflammatory disorders.

Loss of movement and function reflected in limited range of motion observed at physical examination is sometimes the main reason for a visit to the practitioner. Patients report limitations in their ability to perform day-to-day activities, such as kneeling for knee osteoarthritis. (75) Osteoarthritis also can hamper stair climbing, walking, and performing household chores. Limited joint function is caused by several mechanisms, including pain, decreased motion related to reduced joint space, diminished muscle strength, and

instability. Joint proprioceptor sensitivity may be altered; its relationship to disability is less clear as yet, but is probably not caused by pain alone. [76]

Lastly, symptomatic osteoarthritis may be associated with depression and disturbed sleep, which are additional contributors to disability. Osteoarthritis, wherever it occurs, typically causes pain, alters function, and leads to a significant deterioration in the quality of life. [77]

Physical examination

A physical examination should be done to confirm and characterize joint involvement and to exclude pain and functional syndromes arising from other causes, especially periarticluar structures and inflammatory arthritis. A normal examination does not rule out the diagnosis of osteoarthritis, however, especially disease of early nature or of modest severity.

Joint enlargement results from joint effusion or bony swelling or both, which are mainly observed in advanced disease. Bony swelling is easily recognized in superficial joints, such as the finger joints or knees. A synovial effusion may be seen during osteoarthritis flares, but also can occur during chronic phases as a persistent feature. It is most easily detected in knees by the evidence of patellar shock (tap) or by the elicitation of a fluid thrill (wave test).[78]

Joints are usually tender during active motion testing and under pressure. Limited passive movement can be the first and only physical sign of symptomatic osteoarthritis. Bursitis, tendinitis, muscle spasm, and, especially for the knee, a torn meniscus, can cause the same pain syndrome and must be sought carefully during examination. Crepitus, an audible or palpable sensation of crunching or crackling, is commonly felt on passive or active mobilization of an osteoarthritis joint. This sensation is due to the irregularity of the opposing cartilage surfaces or intra-articular debris. [78]

Joint deformities reflect advanced disease with joint destruction involving the cartilage and surrounding bone and soft tissue, the articular capsule, and the ligaments. This destruction contributes to misalignment, joint instability, and limb (usually manifest as leg) shortening. Misalignment also is a cause of compartmental knee osteoarthritis (e.g., varus angulation of the knee responsible for medial tibiofemoral damage and valgus angulation for lateral tibiofemoral damage).[79]

The physical examination should include examination of the legs with the patient standing (i.e., to facilitate detection of varus or valgus malalignment). The knees are farther apart than the feet in the frontal plane in cases of varus alignment, whereas the knees are closer together than the feet in cases of valgus alignment. Varus and valgus alignments are responsible for medial and lateral tibiofemoral osteoarthritis.[80] Both can affect the range of motion and accelerate joint space narrowing; they may enhance the development of osteoarthritis. The presence of anterior laxity also should be evaluated because a decrease in anteroposterior laxity is associated with decreased joint space. [81]

A joint can lock if loose bodies or fragments of cartilage get into the joint space. This occurrence is rare, but care should be taken to distinguish between the stiffness experienced after prolonged immobilization of a limb and true mechanical locking, which

suggests a meniscus lesion.Musculature and joint laxity should be evaluated because periarticular muscle spasms may occur. The circumference of the quadriceps should be measured and compared with that of the opposite side—this may be particularly informative in asymmetric disease. A weak quadriceps femoris is a known disability factor in knee osteoarthritis. This weakness can more convincingly explain the knee "giving way" than the often suggested ligament instability. A lax joint is defined by the excess displacement or rotation of the tibia with respect to the femur in the varus-valgus direction. Joint laxity increases functional disability owing to weak muscles.[82]

Imaging OA

The diagnosis of OA is often obvious after an interview and physical examination. In straightforward presentations, radiological investigation is often not necessary to confirm the diagnosis of hand or forefoot OA. However, some regions and clinical scenarios require a radiological examination in order to exclude other diseases including avascular osteonecrosis, Paget's disease, inflammatory arthropathies and stress fractures. Less commonly involved locations such as the ankle, shoulder or elbow also require radiological examination. Radiographic assessment is not only helpful to diagnose OA, but also useful to establish the severity of joint damage, to monitor disease activity, progression and any response to therapy, and to look for complications of the disorder or the treatment. [83]

Standard radiographs are the most common investigations, depending on the region involved. Weight-bearing X-rays are mandatory for knee and hip OA. However, standard radiograph cannot always diagnose early OA. The radiographic hallmarks of the most common form of OA, also called as "hypertrophic OA", includes localized joint space narrowing, subchondral bone sclerosis, osteophytes formation and bone cysts. Subchondral bone sclerosis and joint-space narrowing are classically seen in more advanced OA. However, clinical symptoms and radiograph findings are poorly correlated, many joints with radiographic evidence of OA remain asymptomatic and, conversely, the joints of many patients with severe symptoms can appear only marginally affected on X-ray. [84]

Demineralization is not a classical feature of OA and its presence strongly suggests an inflammatory arthropathy. Joint space narrowing is not only related to a decreased volume of articular cartilage, but also to meniscal cartilage lesions and cartilage extrusion.[85]. Although standard X-rays are useful for monitoring the evolution of OA, the optimal frequency of radiographs that can best inform practice is not well defined. Gross deformity, subluxation, and loose bodies may occur in advanced cases. "Atrophic" OA, is a rare form of OA, characterized by an absence of osteophytes and sclerosis; it usually involves the hip and especially rapidly destructive hip. Ankylosis in OA is uncommon, with the exception of erosive hand OA.[86]

All the tissues involved in OA, including cartilage lesions, fluid effusion, subchondral bone marrow edema, low grade synovitis and meniscus or ligament lesions can be seen by magnetic resonance imaging (MRI) . MRI can be useful for excluding tumour and avascular osteonecrosis. Cartilage thickness could precociously detected by MRI [87]. The pain, progression and even development of knee OA seem to be associated with the bone marrow edema seen on MRI, but this remains controversial [88-90].

Development of knee OA can be predicted by the presence of a such bone marrow edema in the absence of knee pain [91]. Bone marrow edema is a MRI observation but autopsy examinations have shown that necrosis, fibrosis, and abnormal remodelled trabecula are the most common features . The presence of bone resorption is also clearly recognized as part of OA progression. [92]

Synovitis can also be viewed by MRI and is associated with histopathological inflammation seen by arthroscopy, with the severity of radiographic knee OA and with pain [93,94] . The meniscus tears seen by MRI are common in middle-aged and older adults, with or without knee pain. Thus, although MRI accurately detects meniscus or ligament damage, which are known to be associated with increased OA progression, this finding is usual at the age of osteoarthritic patients and thus does not influence therapeutic management and should not lead to aggressive procedures [95]. MRI is now being used to assess the quantity and function of cartilage, synovium and bone. However, the routine use of MRI has no clinical application in daily practice.

Ultrasound is useful for detecting joint effusions, including a minimal effusion undetectable upon clinical examination, changes in cartilage such as fibrillation of cartilage or cleft formation, synovitis and osteophytes.[96] Popliteal cysts can also be visualized by ultrasound, and potential complications including compression of adjacent vascular structures can be diagnosed. Many studies are presently evaluating the advantages of this procedure in terms of early diagnosis, evaluation of pain symptoms, severity and prognosis. [97]

Ultrasonography has been extensively studied in knee OA to detect inflammatory flares (i.e., synovitis or effusion), popliteal cysts and could serve for assessment of treatment efficacy [98]. Ultrasonography can be used to perform aspirations and injections within the joint and peri-articular tissue.

However, ultrasound imaging is limited by its inability to visualize the whole cartilage surface, by artefacts caused by the position of the probe and finally by inter- and intra-observer variations. Thus, this imaging procedure needs standardization before use in daily clinical practice, except for specific situation (i.e., popliteal cysts, guided aspiration or injection).

The knee joint is easily accessible to clinical examination. However, very small effusions or synovitic proliferations which are missed clinically can often be demonstrated by US. Small amounts of effusion can be detected in the suprapatellar longitudinal and transverse scans in neutral position when pressure is exerted on the suprapatellar and parapatellar pouch by tightening of the quadriceps muscle..[99]

An important indication for musculoskeletal US is the examination of pathological processes of the popliteal region. Popliteal cysts (Baker's cysts) are fluid accumulation in the bursa of the gastrocnemius or semimembranosus muscles. Frequently those cysts communicate with the joint space. To confirm the diagnosis of a popliteal cyst this comma shaped extension has to be visualised sonographically in the posterior transverse scan between the medial head of gastrocnemius and semimembranosus tendon. Popliteal cysts can extend far into thigh and calf muscles and US allows precise definition of their shape and size. A rupture of a popliteal cyst, which may clinically mimic a deep vein thrombosis, is easily identified by US..[100]

Loose joint bodies in the knee can be detected sonographically in the suprapatellar pouch and in the infrapatellar and popliteal regions. However, the failure to detect a loose body in the knee or any other joint can never rule out its presence..[101]

US detectable pathology

1. Suprapatellar and parapatellar pouch:

- Synovial proliferation
- Synovial folds
- Effusion

2. Quadriceps tendon:

- Tear (partial or complete)

3. Femoropatellar joint:

- Irregular contours
- Bony lesions (erosions, osteophytes)

4. Patellar ligament:

- Tear (partial/complete)

5. Deep infrapatellar bursa:

- Bursitis

6. Tuberosity of tibia:

- Irregular bony contour (Mb. Osgood-Schlatter)
- Infrapatellar bursitis

7. Ligaments:

- Tear/lesion

8. Meniscus (lateral/medial):

- Lesion
- Cyst

9. Popliteal fossa:

- Popliteal cyst (volume, echogenicity signs of leakage)

- Compression of vessels

Arthroscopy visualizes cartilage, synovial membranes, osteophytes, and meniscal lesions. Note that this approach, like MRI, may detect findings of dubious significance such as meniscal lesions which are frequent in patients over 60, but rarely the cause of pain. On the other hand, dissection of the meniscus could be highly deleterious by accelerating the progression of OA. This procedure is less used since the use of MRI became more common. [102-104]

Criteria for defining osteoarthritis

The groups of patients with osteoarthritis who participate in clinical trials should be as homogeneous as possible, and need to fulfill a set of criteria that includes the clinical and radiologic items proposed by the American College of Rheumatology (ACR) (Table-I). Osteoarthritis also should be classified as primary or secondary, specifying the cause of the secondary osteoarthritis. International guidelines proposed by the Osteoarthritis Research Society International suggest that secondary osteoarthritis should be excluded. [95]

The sensitivity and specificity of the ACR hip criteria are estimated to be 91% and 89%, whereas the sensitivity and specificity of ACR knee criteria are estimated to be 91% and 86%. The osteoarthritic changes seen on x-ray have not been found to add to the ACR diagnostic criteria for hand osteoarthritis; the sensitivity is 92%, and the specificity is 98%. The ACR criteria are very specific. These criteria are useful for differentiating patients with osteoarthritis from patients with inflammatory disorders because the sensitivity is less impressive, but not for differentiating patients with early osteoarthritis from healthy controls. Their use in population-based research is less clearly defined, and the prevalence of osteoarthritis is underestimated compared with a definition based on radiographic criteria. [96]

Table I: American College of Rheumatology Criteria for Osteoarthritis

		Osteoarthritis if the Items Are Present
Hand	**Clinical** 1. Hand pain, aching, or stiffness for most days or prior months 2. Hard tissue enlargement of ≥2 of 10 selected joints[*] 3. Metacarpophalangeal joint swelling in ≥2 joints 4. Hard tissue enlargement of ≥2 distal interphalangeal joints 5. Deformity of ≥2 of 10 selected hand joints[*]	1, 2, 3, 4 or 1, 2, 3, 5
Hip	**Clinical and Radiographic** 1. Hip pain for most days or prior monts	1, 2, 3 or 1, 2, 4 or 1, 3, 4

		Osteoarthritis if the Items Are Present
	2. ESR of <20 mm at the first hour 3. Femoral or acetabular osteophytes on radiographs 4. Hip joint space narrowing on radiographs	
Knee	**Clinical** 1. Knee pain for most days or prior months 2. Crepitus on active joint motion 3. Morning stiffness lasting ≤30 min 4. Age ≥38 yr. 5. Bony enlargement of knee on examination	1, 2, 3, 4 or 1, 2, 5 or 1, 4, 5
	Clinical and Radiographic 1. Knee pain for most days or prior months 2. Osteophytes at joint m rgins on radiographs 3. Syno ial fluid typical of osteoarthritis (laboratory) 4. Age ≥40 years 5. Crepitus on active joint motion 6. Morning stiffness lasting ≤30 min	1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6

Biomarkers

Molecular markers in OA have been the object of growing attention due to their potential usefulness in formulating early diagnosis, in assessing disease activity and severity and in evaluating drug effects. In this respect, biochemical markers or biomarkers are ideal, as they are non-invasive and inexpensive measures.[107] The Osteoarthritis Biomarkers Network, a consortium of five National Institutes of Health-designated sites, has recently proposed a classification scheme of biomarkers for OA. Five categories of biomarkers (captured in the acronym BIPED) were proposed to aid the study of all aspects of OA, from basic science research to clinical trials: burden of disease, investigative, prognostic, efficacy of intervention, and diagnostic. [108] It may be concluded, however, that although a great number of substances are continually proposed, only a few can be considered true OA "disease markers". [109-111]

Until now no biomarkers appear to have been able to assist in OA disease diagnosis in the pre-radiological stages, but with the recent introduction of highly sensitive (hs) immunoassays, a growing number of studies have suggested that CRP may be a marker of

OA activity and severity. [112,113] It would seem that higher CRP levels may predict worse disease outcomes over the next 4 years.

It has been observed that serum hsCRP levels are higher in patients with erosive hand osteoarthritis (EHOA) than in non-EHOA patients. [114] This probably reflects disease activity rather than subtype, since hsCRP levels correlate with clinical activity scores.

As MMPs are particularly involved in cartilage degradation, their levels or activities have been investigated in an attempt to obtain information concerning OA severity or progression. The most abundant MMP both in serum and SF is MMP-3 [115]. It has been hypothesised that pro-matrix MMP-3 acts as a marker for post-traumatic cartilage degradation. [116,117]

The molecular markers most useful in identifying cartilage synthesis or degradation originate from different articular sources such as cartilage, bone and synovial tissue . Serum hyaluronan (HA), a marker of synovial proliferation and hyperactivity, appears to reflect OA progression. Other interesting biochemical markers are serum keratin sulphate (KS), COMP, and urinary C-terminal crosslinking telopeptides of collagen types I and II (uCTX-II). COMP concentrations in synovial lavage fluids as well as in serum are an early indicator of radiographic progression at follow-up [118]. It has also been seen that COMP is the most sensitive test for identifying subjects affected with the genetic form of premature OA.[119,120]

Molecular markers are molecules, or fragments of connective tissue matrices which are released into biological fluids during tissue biosynthesis and turnover and which can be measured by immunoassays. [121] Several molecular markers of bone, cartilage, and synovium have been described and their changes have been investigated in patients with OA. Because the loss of articular cartilage, the hallmark of OA, is believed to result mainly from increased degradation and because type II collagen is the most abundant protein of cartilage matrix, the assessment of type II collagen breakdown is an attractive approach for the investigation of OA.[122]

The CTX-II epitope is a part of the non-helical carboxyterminal crosslinked telopeptide and consists of six amino-acids attached to a cross-link (X). It is released during the degradation of type II collagen. It is mainly concentrated in calcified articular cartilage at the junction with sub-chondral bone. [123,124]

The type II collagen molecule has been investigated as a potential source of biomarkers in osteoarthritis. This is because type II collagen is the most abundant protein component of cartilage and it is relatively specific for hyaline cartilage. Furthermore, damage to the type II collagen meshwork is a critical event in the pathology of osteoarthritis, in part because of the very slow rate of collagen turnover within cartilage.[125]

Recently, the BIPEDclassification was created to provide a common language related to osteoarthritis biomarkers for both clinical and research applications. Briefly, the markers were grouped into five categories, namely burden of disease, investigative, prognostic,

efficacy of intervention, and diagnostic (hence the acronym 'BIPED'). Herein, we propose an update to the BIPED classification of the type II collagen biomarkers.[126] (Table II)

Table 1I : Summary of the type II collagen biomarkers responding to the criteria of the BIPED classification

BIPED classification	Definition	Type II collagen biomarkers	References
Diagnostic	Differentiates disease from nondisease	Urinary CTX-II, serum Coll2-1 and Coll2-1NO2, serum C1,2C, serum C2C, urinary TIINE, urinary Helix-II, serum and synovial fluid CPII, serum PIIANP	(127-133)
Burden of disease	Biomarker associated with extent or severity of osteoarthritis	Urinary CTX-II, serum Coll2-1, urinary TIINE, serum C2C	(134-136)
Prognostic	Predicts onset or progression	Urinary CTX-II, Coll2-1 and Coll2-1NO2; combined serum PIIANP and urinary CTX-II; serum C1,2C:C2C, C2C: CPII and C1,2C: CPII ratios; synovial fluid CPII	(137-144)
Efficacy of intervention	Indicative or predictive of treatment efficacy	Urinary CTX-II, serum C2C	(145-150)
Investigative	Biomarker not yet meeting criteria for another category	Coll2-2, Coll2-2NO2, Col2-1/4N1, Col2-1/4N2, AH12, AH8, AH9	(151-153)

BIPED: Burden ofdisease, investigative, prognostic, efficacy of intervention, and diagnostic
CPII: Carboxyl propeptide of type II procollagen
CTX: Carboxyl-terminal cross-linked telopeptide of type II collagen
JSN: Joint space narrowing
JSW: Joint space width
MMP: Matrix metalloproteinase
PIIANP: Procollagen type IIA N-propeptide
TIINE: Collagen type II neoepitope

Diagnostic biomarkers

Diagnostic markers can classify individuals as being either diseased or nondiseased. Many studies have reported that urinary CTX-II concentrations were higher in patients with osteoarthritis and those with rheumatoid arthritis than in age-matched and sex-matched control individuals.[154-156]

Burden of disease biomarkers

These markers are used to assess the severity or extent of disease among patients with osteoarthritis. This can be thought of as severity within a particular joint or as severity in terms of number of joints involved or speed of progression over a period of time. The most investigated biomarker in terms of burden of disease assessment is urinary CTX-II. A positive association was found between urinary CTX-II levels and the number of joints (including knee, hand, hip, and cervical and lumbar facet joints and discs) with radiographic signs of osteoarthritis, based on Kellgren and Lawrence score. Subsequently, it was shown that radiographic osteoarthritis scores of hip, knee, hand, and facet joints contributed independently to urinary CTX-II levels, whereas spinal disc degeneration did not.[157,158]

Prognostic biomarkers

Prognostic markers can predict progression of osteoarthritis among patients with existing disease or future onset of osteoarthritis among those without osteoarthritis

Efficacy of intervention biomarkers

Changes in joint space width (JSW) are small compared with the precision error of radiography, and therefore at least 1–3 years are required to assess accurately progression of joint damage or any reduction with treatment. To develop effective disease- modifying osteoarthritis drugs, there is an urgent need for new tools, such as biomarkers, with improved sensitivity. According to the US National Institutes of Health biomarkers network definition, a marker of efficacy of intervention provides information about the efficacy of treatment among patients with osteoarthritis or those at high risk for developing osteoarthritis.[159,160]

Management

The management of OA can be divided into non pharmacologic interventions (Table III) [161-163], pharmacologic interventions[164,165] (Table IV), and surgical options. Pharmacologic interventions can be further subdivided into symptomatic therapy and potential structure- or disease-modifying therapy.

Table III : Non pharmacological management of OA

Nonpharmacologic recommendations for the management of knee OA
We strongly recommend that patients with knee OA should do the following:
Participate in cardiovascular (aerobic) and/or resistance land-based exercise
Participate in aquatic exercise
Lose weight (for persons who are overweight)
We conditionally recommend that patients with knee OA should do the following:
Participate in self-management programs
Receive manual therapy in combination with supervised exercise
Receive psychosocial interventions
Use medially directed patellar taping
Wear medially wedged insoles if they have lateral compartment OA
Wear laterally wedged subtalar strapped insoles if they have medial compartment OA
Be instructed in the use of thermal agents
Receive walking aids, as needed
Participate in tai chi programs
Be treated with traditional Chinese acupuncture*
Be instructed in the use of transcutaneous electrical stimulation*
We have no recommendations regarding the following:
Participation in balance exercises, either alone or in combination with strengthening exercises
Wearing laterally wedged insoles
Receiving manual therapy alone
Wearing knee braces
Using laterally directed patellar taping
* These modalities are conditionally recommended only when the patient with knee osteoarthritis (OA) has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure.

Table IV : Pharmacological management of OA

Pharmacologic recommendations for the initial management of knee OA*
We conditionally recommend that patients with knee OA should use one of the following: Acetaminophen Oral NSAIDs Topical NSAIDs Tramadol Intraarticular corticosteroid injections
We conditionally recommend that patients with knee OA should not use the following: Chondroitin sulfate Glucosamine Topical capsaicin
We have no recommendations regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics

* No strong recommendations were made for the initial pharmacologic management of knee osteoarthritis (OA). For patients who have an inadequate response to initial pharmacologic management, please see the Results for alternative strategies. NSAIDs = nonsteroidal antiinflammatory drugs.

Systemic Agents

Non-narcotic Analgesics

Acetaminophen (paracetamol) has often been touted as the initial systemic intervention for the management of OA. This is mainly due to its favorable side effect profile but also to a perception of its equivalent efficacy to NSAIDs.[166]

Nonsteroidal Anti-inflammatory Drugs

NSAIDs are widely used for the management of OA. They include ibuprofen, naproxen, diclofenac, and others. NSAIDs are usually analgesic at lower doses but have both analgesic and anti-inflammatory effects at their higher recommended doses. They are prescribed either in fixed doses or "as needed" and are quite effective as symptom modifiers; however, they have no structure- or disease-modifying effects. NSAIDs should be used in the smallest dose that provides satisfactory symptom relief, because GI toxicity has been linked to dosage. Adverse GI events have also been linked to patient age, previous history of peptic ulcers or bleeding, and the presence of comorbid conditions such as heart disease.[167]

Narcotic Analgesics

Although several options exist for the management of pain in OA, some patients obtain suboptimal pain relief. If a patient has failed to respond to other nonpharmacologic and pharmacologic modalities and has no additional identifiable causes of pain (such as fibromyalgia), a narcotic analgesic should be considered.[168]

Intra-articular Agents

Corticosteroids

Although there is no role for systemic corticosteroids in OA, local intra-articular corticoid preparations have a long history in the management of OA. Corticosteroids have been shown to downregulate the expression of adhesion molecules. This, in turn, can reduce cellular infiltration into the joint and subsequent inflammation. Corticosteroid injections slow macrophage-like cell infiltration of the synovium in OA. The dose of steroid injected is determined by the volume of the joint being injected, with larger joints such as the knee receiving higher doses. The risk of joint infection is very low if proper technique is employed. Post-injection flares due to corticosteroid crystal synovitis can occur.[169]

Surgical intervention

Surgical interventions in OA usually consist of osteotomies or joint replacements. Osteotomies can be effective pain-relieving interventions and can delay the need for joint replacement surgery in selected patients. These tend to be younger subjects with OA.

Joint replacement surgery (joint arthroplasty) is effective in providing pain relief and restoring function in many patients with OA. Hip and knee joint replacements are most common. Indications for surgery include pain that is refractory to the previously discussed interventions and significant impairment of the patient's daily life.[170]

Other potential rationales for surgical intervention in OA include removal of loose bodies, stabilization of joints, redistribution of joint forces (e.g., osteotomy), and relief of neural impingement (e.g., spinal stenosis, herniated disk). The value of arthroscopic debridement or lavage in OA has been questioned.[171]