joint diseases

By: Shefaa’ qa’qa’
Osteoarthritis

• degenerative joint disease
• characterized by degeneration of cartilage that results in structural and functional failure of synovial joints.
• It is the most common type of joint disease.
Although the term osteoarthritis implies an inflammatory disease, it is considered to be an intrinsic disease of cartilage in which chondrocytes respond to biochemical and mechanical stresses resulting in breakdown of the matrix.
• **idiopathic or primary osteoarthritis:**
  - m.c
  - appears insidiously, without apparent initiating cause, as an *aging* phenomenon (wear and tear).
  - The disease is usually oligoarticular (affects few joints) but may be generalized.
• **secondary osteoarthritis:**
  - 5% of cases
  - Appears in younger individuals with some predisposing condition, such as joint deformity, a previous joint injury, or an underlying systemic disease such as diabetes, ochronosis, hemochromatosis, or marked obesity that places joints at risk.
• Pathogenesis:
- The lesions of osteoarthritis (OA) stem from degeneration of the articular cartilage and its disordered repair.
- The changes to chondrocytes can be divided into three phases:
  
  (1) **chondrocyte injury**, related to genetic and biochemical factors.
  
  (2) early OA, in which **chondrocytes proliferate** and secrete inflammatory mediators, collagens, proteoglycans, and proteases, which act together to remodel the cartilaginous matrix and initiate secondary inflammatory changes in the synovium and subchondral bone.
  
  (3) late OA, in which repetitive injury and chronic inflammation lead to **chondrocyte drop out**, marked loss of cartilage, and extensive subchondral bone changes.
Virtually every extracellular component of articular cartilage is affected in OA. Collagen type II is degraded by matrix metalloproteinases.

Although chondrocytes continuously synthesize and secrete proteoglycans during disease progression, degradation ultimately exceeds synthesis, and the composition of proteoglycans changes.

Inflammatory cells are sparse, but cytokines and diffusible factors associated with other inflammatory conditions, particularly TGF-β (which induces matrix metalloproteinases), TNF, prostaglandins and nitric oxide, have been implicated in osteoarthritis.
MORPHOLOGY:
- The normally horizontally arranged collagen type II fibers in the superficial zone are cleaved, yielding fissures and clefts at the articular surface.
- The dislodged pieces of cartilage and subchondral bone tumble into the joint, forming loose bodies (joint mice).
- The exposed subchondral bone plate becomes the new articular surface, and friction with the opposing surface smooths and burnishes the exposed bone, giving it the appearance of polished ivory (bone eburnation). Sclerosis of bone.
- Small fractures through the articulating bone are common, and the fracture gaps allow synovial fluid to be forced into the subchondral regions (cysts).
- Mushroom-shaped osteophytes (bony outgrowths) develop at the margins of the articular surface.
- The synovium is usually only mildly congested and fibrotic, and may have scattered chronic inflammatory cells.
• Clinical Course:
  - Osteoarthritis is an insidious disease. Patients with primary disease are usually asymptomatic until they are in their 50s.
  - Characteristic symptoms include deep, achy pain that **worsens with use**, morning stiffness, crepitus, and limitation of range of movement.
  - Impingement on spinal foramina by osteophytes results in cervical and lumbar nerve root compression and radicular pain, muscle spasms, muscle atrophy, and neurologic deficits.
• Typically, only one or a few joints are involved.
• The joints commonly involved include the hips, knees, lower lumbar and cervical vertebrae, proximal and distal interphalangeal joints of the fingers, first carpometacarpal joints, and first tarsometatarsal joints.
• **Heberden nodes**, prominent osteophytes at the distal interphalangeal joints.
• The wrists, elbows, and shoulders are usually spared.
• With time, joint deformity can occur, but unlike rheumatoid arthritis, fusion does not take place.

• There are still no satisfactory means of preventing primary osteoarthritis, and there are no effective methods of halting its progression. Therapy includes management of pain, activity modification and, for severe cases, arthroplasty.
Rheumatoid Arthritis

• Rheumatoid arthritis (RA) is a chronic inflammatory disorder of autoimmune origin that may affect many tissues and organs but principally attacks the joints, producing a nonsuppurative proliferative and inflammatory synovitis.

• The disease peaks in the second to fourth decades and is three times more common in women than men.
• Pathogenesis:
As in other autoimmune diseases, genetic predisposition and environmental factors contribute to the development, progression, and chronicity of the disease.

The pathologic changes are mediated by antibodies against self-antigens and cytokine-mediated inflammation, predominantly secreted by CD4+ T-cells.
CD4+ T helper (TH) cells may initiate the autoimmune response in RA by reacting with an arthritogenic agent, perhaps microbial or a self-antigen. The T cells produce cytokines that stimulate other inflammatory cells to effect tissue injury. Although a large number of cytokines can be isolated from inflamed joints, the most important ones include:

- IFN-γ from TH1 cells activates macrophages and resident synovial cells.
- IL-17 from TH17 cells recruits neutrophils and monocytes.
- TNF and IL-1 from macrophages stimulates resident synovial cells to secrete proteases that destroy hyaline cartilage.
- RANKL expressed on activated T cells stimulates bone resorption.

Of these, TNF has been most firmly implicated in the pathogenesis of RA and TNF antagonists have proved to be remarkable effective therapies for the disease.
The synovium of RA contains germinal centers with secondary follicles and abundant plasma cells which produce antibodies, some of which are against self-antigens:

- **anti-CCP** (citrullinated peptides) **antibodies**.
- **rheumatoid factor** (serum IgM or IgA autoantibodies that bind to the Fc portions of their own IgG). They are not uniformly present in all patients with RA (80%) and can be found in patients without the disease.

These autoantibodies are deposit in joints as **immune complexes**.
• The environmental arthritogen whose antigens initiate RA by activating T or B cells remains uncertain.

• CCPs are produced during inflammation, so insults such as infection and smoking may promote citrullination of self-proteins, creating new epitopes that trigger autoimmune reactions. The robust immune reaction to these autoantigens suggests that they may be important arthritogenic agents.
• It is estimated that 50% of the risk of developing RA is related to inherited genetic susceptibility. Specific **HLA-DRB1** alleles are linked to rheumatoid arthritis. PTPN22 gene is also implicated.
Figure 26-42 Major processes involved in the pathogenesis of rheumatoid arthritis.
MORPHOLOGY:
- RA typically manifests as a symmetric arthritis principally affecting the small joints of the hand and feet.
- synovial cell hyperplasia.
- dense inflammatory infiltrates (frequently forming lymphoid follicles) of CD4+ helper T cells, B cells, plasma cells, dendritic cells, and macrophages.
- **pannus**: a mass of edematous synovium, inflammatory cells, granulation tissue, and fibroblasts that grows over the articular cartilage and causes its erosion. In time, after the cartilage has been destroyed, the pannus bridges the apposing bones to form a **fibrous ankylosis**, which eventually ossifies and results in fusion of the bones, called **bony ankylosis**.
Rheumatoid subcutaneous nodules are the most common cutaneous lesions. They occur in approximately 25% of affected individuals, usually those with severe disease, and arise in regions of the skin that are subjected to pressure (elbows). Rheumatoid nodules are firm, nontender, and round to oval. Less commonly they form in the lungs, spleen, pericardium, myocardium, heart valves, aorta, and other viscera.

Microscopically: central zone of fibrinoid necrosis surrounded by a prominent rim activated macrophages and numerous lymphocytes and plasma cells.

vasculitis
• Clinical Course:
- In about half of patients, RA may begin slowly and insidiously with malaise, fatigue, and generalized musculoskeletal pain,
- After several weeks to months the joints become involved. The pattern of joint involvement varies, but it is generally **symmetrical** and the **small joints** are affected before the larger ones. Symptoms usually develop in the hands (metacarpophalangeal and **proximal interphalangeal joints**) and feet, followed by the wrists, ankles, elbows, and knees.
- The lumbosacral region and hips are usually spared.
• Involved joints are swollen, warm, painful, and particularly stiff when rising in the morning or following inactivity.
• The typical patient has progressive joint enlargement, decreased range of motion evolving to complete ankylosis, with the greatest damage occurring in the first 4 or 5 years.
• Approximately 20% of affected individuals enjoy periods of partial or complete remission, but the symptoms inevitably return and involve previously unaffected joints.
• A minority of individuals (10%) have an acute onset over several days with severe symptoms and polyarticular involvement.
• Inflammation in the tendons, ligaments, and occasionally the adjacent skeletal muscle frequently accompanies the arthritis and produces the characteristic **radial deviation of the wrist, ulnar deviation of the fingers and flexion-hyperextension of the fingers** (swan-neck deformity, boutonnière deformity).

• The end result is a joint that has no stability and minimal or no range of motion.

• Large synovial cysts, like the **Baker cyst** in the posterior knee, may develop as the increased intra-articular pressure causes herniation of the synovium.
• The presence of multisystem involvement must be distinguished from other forms of chronic arthritis (lupus, scleroderma, Lyme disease).

• The treatment of rheumatoid arthritis is aimed at relieving the pain and inflammation, and slowing or arresting the relentless joint destruction.

• Therapies include corticosteroids, synthetic and biologic disease-modifying drugs such as methotrexate, and, most notably, antagonists of TNF.
Crystal-Induced Arthritis

• **Endogenous crystals** shown to be pathogenic include monosodium urate (gout), calcium pyrophosphate dehydrate (pseudogout), and basic calcium phosphate.

• **Exogenous crystals**, such as corticosteroid ester crystals and talcum, silicone, polyethylene, and methyl methacrylate are used in **prosthetic joints**, and their debris that accumulates with long use and wear may result in local arthritis and failure of the prosthesis.
Gout

- Gout is marked by transient attacks of acute arthritis initiated by crystallization of monosodium urate within and around joints.
- Gout can be divided into primary and secondary forms, both sharing the common feature of hyperuricemia.
  - **primary form:** (90% of cases), gout is the major manifestation of the disease and the cause is usually unknown.
  - **Secondary gout:** (10% of cases), uric acid is increased because of a known underlying disease that usually dominates the clinical picture.
• Uric acid is the end product of **purine catabolism**. The synthesis of purine nucleotides, in turn, involves two interlinked pathways. In the de novo pathway, purine nucleotides are synthesized from nonpurine precursors, and in salvage pathways they are synthesized from free purine bases from dietary intake and catabolism of purine nucleotides.

• Hyperuricemia can result from either overproduction or reduced excretion (kidney).
• The vast majority of primary gout is caused by increased uric acid biosynthesis for unknown reasons (enzymatic defects).

• Secondary gout can also be caused by increased production (e.g., rapid cell lysis during chemotherapy for leukemia) or decreased excretion (chronic renal disease).
• The inflammation in gout is triggered by precipitation of monosodium urate (MSU) crystals into the joints, which result in the production of cytokines that recruit leukocytes.

• The solubility of MSU in a joint is modulated by temperature and the chemical composition of the fluid. Synovial fluid is inherently a poorer solvent for monosodium urate than plasma. The lower temperature of the peripheral joints also favors precipitation. Crystallization is dependent on the presence of nucleating agents such as insoluble collagen fibers, chondroitin sulfate, proteoglycans and cartilage fragments.
Hyperuricemia does not necessarily lead to gouty arthritis. Many factors contribute to the conversion of asymptomatic hyperuricemia into primary gout, including the following:

- Age of the individual and duration of the hyperuricemia. Gout usually appears after 20 to 30 years of hyperuricemia.
- Genetic predisposition. In addition to the well-defined X-linked abnormalities of HGPRT, primary gout follows multifactorial inheritance and runs in families. Polymorphisms in genes involved in urate transport and homeostasis (URAT1 and GLUT9) are also associated with gout.
- Heavy alcohol consumption
- Obesity
- Drugs (e.g., thiazides) that reduce excretion of urate
- Lead toxicity (so-called saturnine gout)
The distinctive morphologic changes in gout are:

1. Acute arthritis (dense neutrophilic infiltrate. When the episode of crystallization abates and the crystals are resolubilized, the acute attack remits).
2. Chronic tophaceous arthritis (repetitive acute attacks. Pannus formation that destroys the underlying cartilage and lead to juxtaarticular bone erosions. In severe cases, fibrous or bony ankylosis ensues, resulting in loss of joint function).
3. Tophi in various sites
4. Gouty nephropathy (MSU crystals or tophi in the renal medullary interstitium or tubules------ uric acid nephrolithiasis and pyelonephritis)

- **MSU crystals** are arranged in small clusters in the synovium. They are long, slender, and needle-shaped.
- **Tophi** are the pathognomonic hallmark of gout. They are formed by large aggregations of urate crystals surrounded by an intense inflammatory reaction of foreign body giant cells.
Clinical Course:
- Gout is more common in men and after the age of 30.
- Four clinical stages are recognized:

1. **Asymptomatic hyperuricemia**, appears around puberty in males and after menopause in females.

2. **Acute arthritis**, presents after several years as sudden onset of excruciating joint pain associated with localized hyperemia. Most first attacks are monoarticular; **50% occur in the first metatarsophalangeal joint** (joints involved commonly: ankles, heels, knees, wrists, fingers, and elbows). Untreated, acute gouty arthritis may last for hours to weeks, but gradually there is complete resolution.

3. **Asymptomatic intercritical period**: symptom free interval between acute attacks.

4. **Chronic tophaceous gout**, develops on average about 12 years after the initial acute attack and the appearance of chronic tophaceous arthritis.
Renal manifestations sometimes appear in the form of renal colic associated with the passage of gravel and stones and may proceed to chronic gouty nephropathy. About 20% of those with chronic gout die of renal failure.

Numerous drugs are available to abort or prevent acute attacks of arthritis and mobilize tophaceous deposits. Their use is important, because many aspects of the disease are related to the duration and severity of the hyperuricemia. Generally, gout does not materially shorten the life span, but it may impair the quality of life.
Calcium Pyrophosphate Crystal Deposition Disease (Pseudo-Gout)

- The sexes and races are equally affected.
- Usually occurs in individuals older than 50 years of age.
- CPPD is divided into sporadic (idiopathic), hereditary, and secondary types.
- The secondary form is associated with various disorders, including previous joint damage, hyperparathyroidism, hemochromatosis, hypomagnesemia, hypothyroidism, ochronosis, and diabetes.
- Calcium Pyrophosphate Crystal are rhomboid, 0.5 to 5 μm in greatest dimension.
- the knees, followed by the wrists, elbows, shoulders, and ankles, are most commonly affected.
• **Seronegative spondyloarthropathies:**
  are a heterogeneous group of likely autoimmune arthritides that preferentially involve the sacroiliac and vertebral joints, are associated with HLA-B27 and absence of rheumatoid factor.

Ankylosing Spondylitis
Reactive Arthritis
Enteritis Associated Arthritis
Psoriatic Arthritis
• **Infectious Arthritis:**
  - Suppurative Arthritis
  - Mycobacterial Arthritis
  - Lyme Arthritis
  - Viral Arthritis