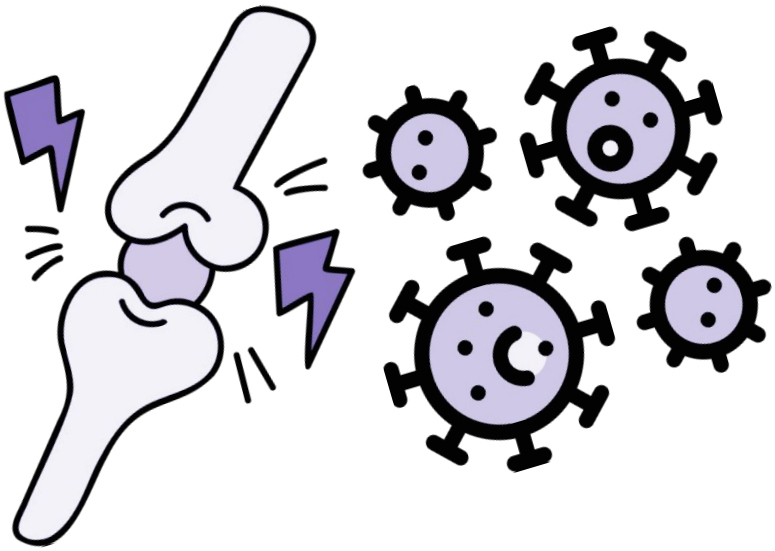
Lecture 41&42

Editing file



Reviewed By

Noura Alturki
Jehad Alorainy

Osteoarthritis & Gout

Lecture content is based on 437 and 438 slides

Objectives:

Osteoarthritis:

- ★ Know the definition of osteoarthritis
- ★ Describe the pathophysiology of osteoarthritis
- ★ Learn the diagnostic work up of osteoarthritis
- ★ Know the differences between osteoarthritis and inflammatory arthritis
- ★ Learn treatment modalities available for management of Osteoarthritis

Gout:

- ★ Describe clinical presentation of gout
- ★ Identify drug & non-drug risk factors for gout
- ★ Compare treatment options for acute gout attacks
- ★ Describe options for control of hyperuricemia / prophylaxis of gout attacks

Color index:

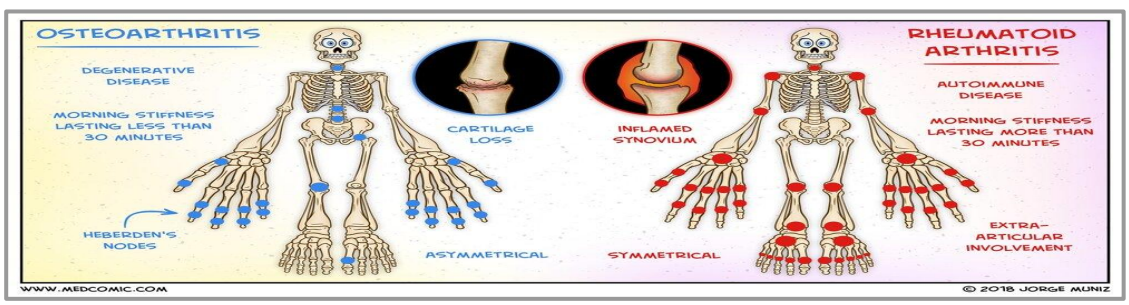
Original text Females slides Males slides
Doctor's notes Textbook Important Golden notes Extra

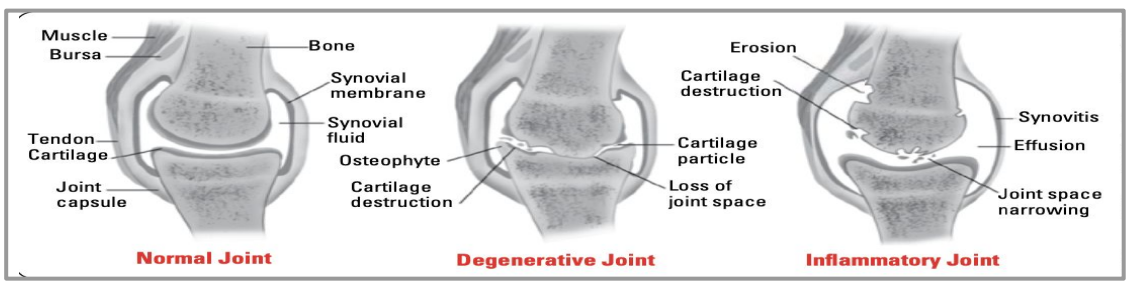
Overview

◀ Osteoarthritis VS Rheumatoid arthritis (obj)

Recall from RA lecture

	Osteoarthritis	Rheumatoid arthritis
Pathogenesis	Mechanical - **wear and tear** destroys articular cartilage **(degenerative joint disorder)**	Chronic, systemic **autoimmune** disease
Predisposing factors	Major risk factor is **age** (common after 60 years); additional risk factors include **obesity** and **joint trauma.**	Associated with **HLA-DR4**, classically arises in women of late childbearing age
Presentation	- Pain and functional restriction - **Early morning stiffness** (lasting **LESS** than 15-20min) - Improves with rest. - targeting the hips, knees, PIP and DIP joints, neck and lumbar spine - But **doesn't involve MCP** - Asymmetric joint involvement - **No systemic symptoms** - Usually the joints are not warm/hot, unless there's coexistent crystal arthritis (either CCPD or Gouty arthritis) - Joint effusion are usually small unless there's coexistent crystal arthritis	- Pain and joint swelling - **Early morning stiffness** (classically lasting **MORE** than 1hr) that gets **better with movement**. - Worsened by rest - Targets small joints of the hands, feet and wrists. And there is large joint involvement - There's spindling of PIPJs and MCP but NOT DIPJs or 1st CMC - Symmetric joint involvement - **Systemic symptoms** - Extra-Articular manifestations - Usually warm/hot - Joint effusion is usually moderate-large
Joint findings	- **Osteophytes** (bone spurs) - Joint space narrowing, Subchondral sclerosis and Cyst formation - **Heberden** and **Bouchard nodes**	- **Pannus** (proliferative granulation tissue) - Erosions, cervical subluxation and ulnar finger deviation - swan neck and boutonniere deformities

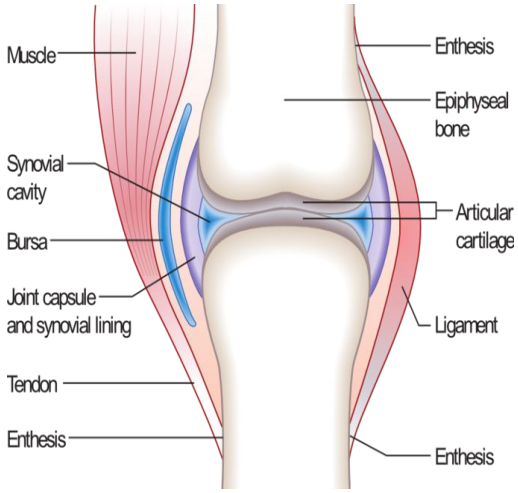




Normal Synovial Joint structure

1 Articular cartilage

- Hyaline cartilage lining the bones within a joint.
- It is **avascular** and derives nourishment from synovial fluid.
- Articular cartilage (chondrocytes) surrounded by extracellular matrix includes proteoglycans and collagen.
- **The cartilage facilitates joint function and protects the underlying subchondral bone by:**
  - Distributing large loads
  - Maintaining low contact stresses
  - Reducing friction at the joint.
- **Defects in articular cartilage and underlying bone are features of osteoarthritis.**

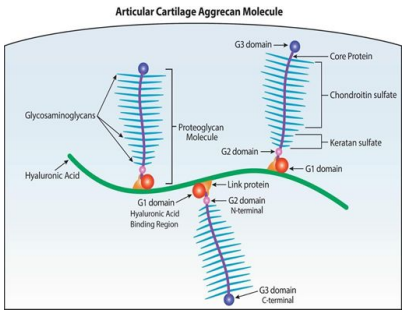


2 Joint capsule and synovial membrane

- The bones of synovial joints are connected by the **joint capsule**, a fibrous structure richly **supplied with blood vessels, nerves and lymphatics** that encases the joint.
- Ligaments are regional thickenings of capsule that act to stabilise joints
- **Synovial membrane** is the inner surface of the joint capsule
  - Comprising an **outer layer** (of blood vessels and loose connective tissue that is rich in type I collagen), and an **inner laye** (consisting of two main cell types. **Type A** synoviocytes are phagocytic cells, **type B synoviocytes** are fibroblast-like cells that **secrete SF**)

3 Synovial fluid

- Viscous liquid that lubricates the joint
- **Formed by synoviocytes:**
  - Synovial cells also manufacture **hyaluronic acid** (HA, also known as hyaluronate)
    - A **glycosaminoglycan** that is the major noncellular component of synovial fluid.



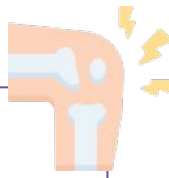
- **Its function:**
  - Synovial fluid supplies **nutrients** to the avascular articular cartilage.
  - Provides the **viscosity** needed to **absorb shock** from **slow** movements
  - Provides **elasticity** required to **absorb shock** from **rapid** movements

4 Subchondral bone (juxta-articular bone)

- The bone that abuts a joint
- Highly **vascular**
- Comprises a light framework of mineralized collagen enclosed in a thin coating of tougher, cortical bone.
- **It withstands pressure poorly if the normal articular hyaline cartilage is worn away, as in osteoarthritis.**

Osteoarthritis

Osteoarthritis



- **Heterogeneous group of conditions resulting in common histopathologic and radiologic changes involving Entire joint structures, including:**
  - The articular cartilage
  - The subchondral bone
  - The synovium

◄ Epidemiology :

- Internationally, osteoarthritis is the **most common articular disease**. Estimates of its frequency vary across different populations.
- 80-90% of individuals **older than 65** years have evidence of radiographic osteoarthritis.
- The prevalence of osteoarthritis is higher among **women** than among men.
- Interethnic differences in the prevalence of osteoarthritis have been noted.

Etiology

- **Heritable metabolic causes:**
  - alkaptonuria, **hemochromatosis**, Wilson disease, cartilage calcification
- **Hemoglobinopathies** :
  - sickle cell disease, thalassemia
- **Neuropathic disorders leading to a Charcot joint:**
  - syringomyelia, tabes dorsalis, and diabetes.
- **Underlying morphologic risk factors:**
  - Congenital hip dislocation and slipped femoral capital
- **Disorders of bone:**[3]
  - Paget disease, avascular necrosis
- **Previous surgical procedures:**
  - meniscectomy[5]
- **Diabetes mellitus**
- haemophilia - recurrent heamarthrosis

Risk factors

- **Age**
- **obesity**[1]
- Trauma
- Genetics[4]
- Gender (women)
- Hypogonadism[2]
- Muscle weakness
- Repetitive use (athletic)
- Infection : Septic arthritis
- Crystal deposition (gout)
- Acromegaly
- Previous inflammatory arthritis (burnt-out rheumatoid arthritis)
- Spondyloarthritis

1- There is a strong association between obesity and OA, **particularly of the hip**. This is thought to be due partly to biomechanical factors due to cytokines released from adipose tissue

2- **Oestrogen appears to play a protective role**: lower rates of OA have been observed in women who use hormone replacement therapy (HRT), and women who receive aromatase inhibitor therapy often experience a flare in symptoms of OA.

3- Osteoporosis reduces the risk of OA

4-The gene that encodes **collagen type II (COL2A1)** is a candidate gene fo**r familial OA** but there is no single gene that associates with all patterns of OA. COL2A1 is associated with **early polyarticular arthritis**

5- the surgical removal of all or part of a torn meniscus.

Osteoarthritis

◀ Pathogenesis

- Consequent structural changes include **surface fibrillation** and **ulceration** with **loss of cartilage** that exposes underlying bone to increased stress, producing **microfractures and cysts** leading to abnormal **sclerotic subchondral bone** and **overgrowths** at the joint margins, called **osteophytes.**
- **Degeneration of articular cartilage**: is the defining feature of OA

01

In early stages: Swelling of the cartilage usually occurs due to chondrocyte hypertrophy

02

The level of **proteoglycans** eventually **drops** very low, the cartilage softens and **lose elasticity** compromising joint surface integrity.

03

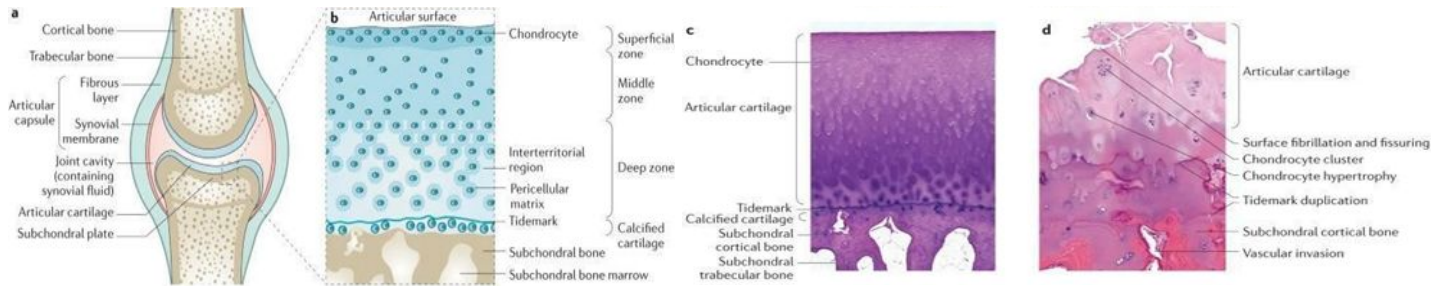
Fissures and **fibrillations** (vertical clefts) develop along on the surface of an osteoarthritic joint

04

Over time , the loss of cartilage results in **loss of joint space** [1] **and articulation of the bones (Advanced OA)**

05

A **greater loss** of joint space occurs at those **areas experiencing the highest loads.**



◀ Bone changes

01

Articulation

Bone denuded of its protective cartilage continues to articulate with the opposing surface

02

Stress

Eventually, the increasing stresses exceed the biomechanical yield strength of the bone

03

Eburnation

The subchondral bone responds with vascular invasion and increased cellularity, becoming thickened and dense (a process known as eburnation) at areas of pressure.

04

Cystic Degeneration

Subchondral bone undergo cystic degeneration

- Osteoarthritic cysts are also referred to as subchondral cysts, pseudocysts, or geodes and may range from 2 to 20 mm in diameter.
- Osteoarthritic cysts in the **acetabulum** are termed **Egger cysts**.

1- It is a degenerative arthritis but occasionally an inflammation can occur due to crystal formation. **Calcium pyrophosphate** and basic calcium phosphate crystals often become deposited in the abnormal cartilage

Osteoarthritis

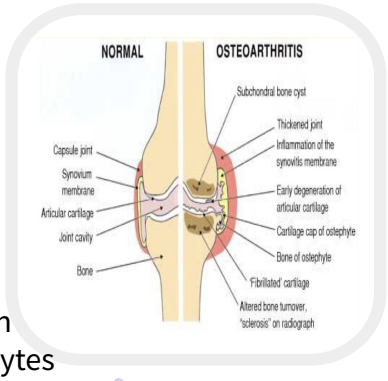
◀ Joint changes

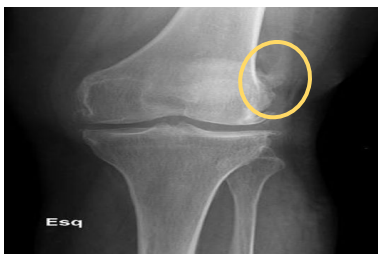
Vascularization of subchondral marrow

Osseous metaplasia of synovial connective tissue

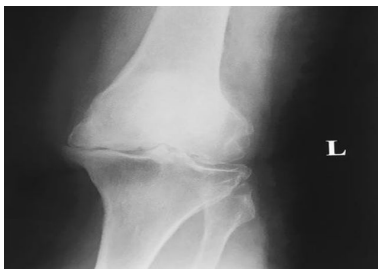
Ossifying cartilaginous protrusions lead to irregular outgrowth of new bone **(osteophytes)**[1].

Fragmentation of these osteophytes or of the articular cartilage itself results in the presence of intra-articular loose bodies **(joint mice).**





Early X-ray showing : Osteophytes, some narrowing and subchondral sclerosis



Advanced OA: The cartilage is lost , femoral epicondyle articulates directly with the tibial epicondyle and severe subchondral sclerosis

◀ other changes

- **Synovium**:
  - Often hyperplastic and may be the site of inflammatory changes
  - **Osteochondral bodies** commonly occur within the synovium, reflecting secondary uptake and growth of damaged cartilage fragments.
- **Capsule**: The outer capsule also thickens and contracts, to retain the stability of the remodelling joint
- **Muscles**: The muscles surrounding affected joints commonly show **wasting**.

◀ Osteoarthritis progression

Stage 1
Breakdown of the cartilage matrix occurs.

Stage 2
Involves the fibrillation and erosion of the cartilage surface

Stage 3
A chronic inflammatory response in the synovium.

Further progression

- The above events alter the joint architecture, compensatory bone overgrowth occurs.
- Joint architecture is changed
- Mechanical and inflammatory stress occurs on the articular surfaces, the disease progresses unchecked.

1-Fibrocartilage is produced at the joint margin, which undergoes endochondral ossification to form osteophytes.

Osteoarthritis

◀ Clinical presentation

★ The main presenting symptoms are **pain** and **functional restriction**

The pain is:

- Insidious onset **over months or years**
- Variable nature over time ('good days, bad days')
- **Worse with movement** and weight-bearing, **relieved by rest**
- **Brief (< 15 mins) morning stiffness**
- Brief (< 5 mins) 'gelling' after rest [1]
- Usually only one or a few joints painful

Clinical signs

- **Restricted movement** [2]
- Palpable, sometimes audible **coarse crepitus** [3]
- Bony swelling around joint margins
- Deformity, usually without instability
- Joint-line or periarticular tenderness
- Muscle weakness and wasting
- Mild or absent synovitis

★ Before labelling any pt to have OA you need to exclude inflammatory causes.
★ large joint effusion and extra articular manifestations suggest an inflammatory cause.

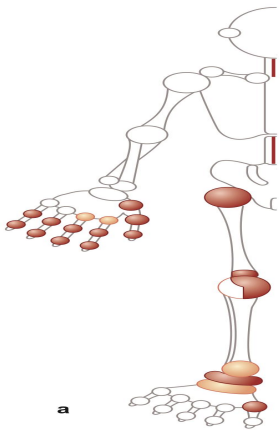
◀ Differential diagnosis

- Crystalline arthropathies (ie, gout and pseudogout)
- Inflammatory arthritis (eg, rheumatoid arthritis)
- Septic arthritis or post infectious arthropathy
- Seronegative spondyloarthropathies (eg, psoriatic arthritis and reactive arthritis)
- Fibromyalgia
- Tendonitis

◀ Involved joints

Weight-bearing joints

- **The knee**
- **The hips**
- Cervical and lumbosacral spine
- Feet



Red circles indicate the more commonly affected sites, and pale ones the less commonly affected sites.

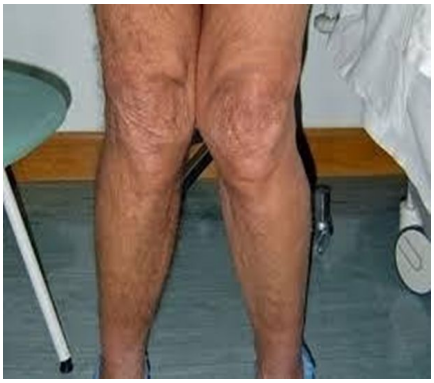
Non-Weight Bearing joints

- The distal interphalangeal (DIP)
- The proximal interphalangeal (PIP) joints.
- the carpometacarpal (CMC) joints.
- The first metatarsophalangeal (MTP) joint of the foot.

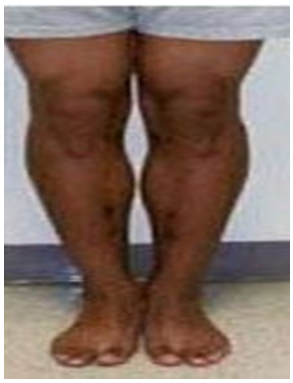
1- Condition that occurs when a joint has been at rest for too long and the synovial fluid becomes thickened , making movement difficult
2- Due to capsular thickening or blocking by osteophyte
3- Due to rough articular surfaces

Osteoarthritis

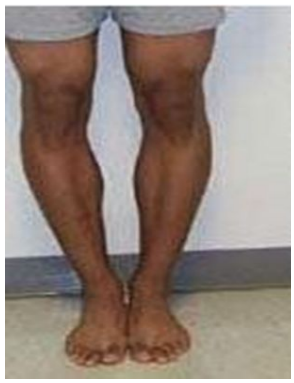
Genu Valgum deformity
indicates secondary OA (RA usually)



Normal

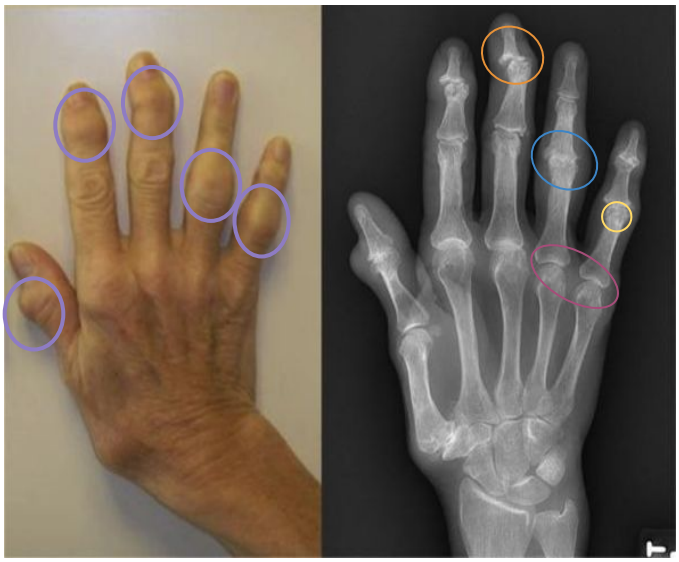


Genu Varum deformity
Primary OA ,The angle is **outward**



Bouchard's nodes
(Bony swelling at the **PIPJ**)
P&B
Heberden's nodes
(Bony swelling at the **DIPJs**)

Both suggests primary OA



Normal space

Subchondral sclerosis and osteophytes

Multiple subchondral cysts

Palmiflexion , can progress leading to dislocation

Types of osteoarthritis

Nodal OA

Characterised by:

- Pain, stiffness and swelling of **one or more PIP and DIP joints,** with DIPs being more often involved than PIPs. Typical pattern of polyarticular involvement of the hand joints.
- The inflammatory phase settles after some months or years, leaving painless bony swellings posterolaterally: **Heberden's nodes (DIPs) and Bouchard's nodes (PIPs)**
- Involvement of the **first CMC joint** is also common causing **squaring of the thumb** base
- Has Good long-term functional outcome for hands
- Predisposition to osteoarthritis at **other joints**, **especially knees → Generalised nodal OA**
- **Female preponderance**, Strong genetic predisposition, Peak onset in late middle age (around female menopause)

Osteoarthritis

Knee OA

- Has a strong relationship with **obesity**
- Mostly **bilateral with symmetrical** involvement
- May be isolated or as part of generalised nodal OA of the hand in elderly women.
- Principally targets the patellofemoral and **medial tibiofemoral compartments** leads to a **varus "bow-legged" deformity**. But eventually spreads to affect the whole of the joint

Hip OA

Two major subgroups:

- **Superior-pole hip OA :**
  - Most common, usually affect men
  - **Unilateral** at presentation.
  - Affect the **upper surface of the femoral head** and adjacent acetabulum.
  - Has poor prognosis.
- **Medial cartilage (central) loss:**
  - Usually affect women, bilateral.
  - Associated with hand involvement (NGOA). Has better prognosis.

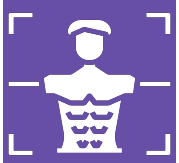
Spine OA

- Cervical (cervical spondylosis) and lumbar spine (lumbar spondylosis) are the most common targeted sites.
- Typical presentation is **pain localised to the low back** region or the neck, **relieved by rest** and worse on movement.
- May be complicated with spinal stenosis or nerve root compression → neurological signs and radiation of pain

Erosive OA

- This term describes an unusual group of patients with hand OA who have a more prolonged symptom phase, more overt inflammation, more disability and worse outcome than those with nodal OA.
- Distinguishing features include preferential targeting of PIP joints, **subchondral erosions on X-rays,** occasional **ankylosis** of affected joints and lack of association with OA elsewhere.

◀ Work up



Laboratory: usually normal with **negative** Antinuclear antibody and Rheumatoid factor

Plain Radiography (X-ray):

- Only **abnormal when the damage is advanced**. They are useful in preoperative assessments.
- **Findings include:** narrowing joint space, Osteophytes, Subchondral sclerosis, and Cyst formation
- For knees, a standing X-ray (stressed) is used to assess cartilage loss and 'skyline' views in flexion for patellofemoral OA.

CT scan, MRI scan, US

MRI: demonstrates meniscal tears, early cartilage injury and subchondral bone marrow changes (osteochondral lesions). MRI of spine should be done **if nerve root compression or spinal stenosis are suspected.**

Bone scintigraphy: to rule out malignancy

Arthrocentesis: In suspicion of **septic arthritis**

WBC :

>100 OA

> 1000 Inflammatory

Osteoarthritis

◀ Treatment

Management targets :

1. **pain**
2. **limitation of joint movement**
3. **weakness of the proximal muscle to the joint.**
4. **depression**

Pharmacotherapy

Doctor's notes:

First choice: Topical therapy

Preferred due to less systemic side effects and it can be added at any step.

Topical NSAIDs are preferred.

Topical capsaicin: very irritating substance , pt should avoid touching the eyes after putting the cream, bc it may lead to conjunctivitis

If the topical therapy is failing, start oral therapy:

First choice : Acetaminophen

- **Solpadeine**: Combination of acetaminophen and low dose codeine.
- Less systemic side effects among oral therapies.

If all of above are failing even with combining oral and topical therapy go to the next step:

Second choice: NSAIDs (ibuprofen, meloxicam)

- Have a lot of side effects. Cox 2 selective NSAIDs have less GI side effects but overall, all of them carry a risk (Some studies also recommend avoiding COX-2 in pts over 60yrs)
- Should be considered in patients **who remain symptomatic**

Third choice : Tramadol

- These aren't usually used, bc at this level (advanced OA) the only solution is arthroplasty, can cause addiction,

Duloxetine : used in depression

Intra-articular corticosteroid injections produce short-term improvement when there is a **painful joint effusion.**

Intervention	Joint		
	Hand	Knee	Hip
Topical nonsteroidal antiinflammatory drugs			
Topical capsaicin			
Oral nonsteroidal antiinflammatory drugs			
Intraarticular glucocorticoid injection			
Ultrasound-guided intraarticular glucocorticoid injection			
Intraarticular glucocorticoid injection compared to other injections			
Acetaminophen			
Duloxetine			
Tramadol			
Non-tramadol opioids			
Colchicine			
Fish oil			
Vitamin D			
Bisphosphonates			
Glucosamine			
Chondroitin sulfate			
Hydroxychloroquine			
Methotrexate			
Intraarticular hyaluronic acid injection	(First carpometacarpal)		
Intraarticular botulinum toxin			
Prolotherapy			
Platelet-rich plasma			
Stem cell injection			
Biologics (tumor necrosis factor inhibitors, interleukin-1 receptor antagonists)			

Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

Osteoarthritis

Non-pharmacological

- **Education**: Education of the individual about the disease and its effects reduces pain, distress and disability and increases compliance with treatment.
- **Lifestyle modification :**
  - **Physical and rehab therapy**[3]
  - Patients with OA are advised to use medical shoes with lateral and medial wedged insoles.
  - In patients with flat feet (also known as pes planus or fallen arches) you need to put the insole on the medial side. Pes planus is a foot condition characterized by the absence or collapsing of the medial longitudinal arch
  - Weight loss[1]

Surgery

- Arthroscopy[2]
- Fusion and joint Lavage
- Osteotomy
- Arthroplasty

Total joint replacement surgery is by far the most common surgical procedure for patients with OA. Surgery should be considered when there is significant impact on the quality of life despite optimal medical therapy and lifestyle advice.

Intervention	Joint		
	Hand	Knee	Hip
Exercise			
Balance training			
Weight loss			
Self-efficacy and self-management programs			
Tai chi			
Yoga			
Cognitive behavioral therapy			
Cane			
Tibiofemoral knee braces		(Tibiofemoral)	
Patellofemoral braces		(Patellofemoral)	
Kinesiotaping	(First carpometacarpal)		
Hand orthosis	(First carpometacarpal)		
Hand orthosis	(Other joints)		
Modified shoes			
Lateral and medial wedged insoles			
Acupuncture			
Thermal interventions			
Paraffin			
Radiofrequency ablation			
Massage therapy			
Manual therapy with/without exercise			
Iontophoresis	(First carpometacarpal)		
Pulsed vibration therapy			
Transcutaneous electrical nerve stimulation			

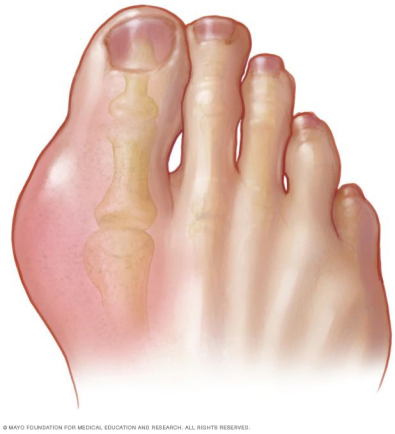
Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

1- Weight loss has a substantial beneficial effect on symptoms if the patient is obese and is probably one of the most effective treatments available for OA of the lower limbs
2- Arthroscopy for knee OA is not beneficial.
3- Local strengthening and aerobic exercises improve local muscle strength (e.g. in OA of the knee you should exercise the quadriceps), improve the mobility of weight-bearing joints and improve general aerobic fitness.

Gout

Gout

- Gout is an inflammatory-arthritis **associated with hyperuricemia** and reaction to intra-articular monosodium urate crystals



◀ Epidemiology

- Gout has become progressively more common over recent years in affluent societies due to the increased prevalence of **obesity and metabolic syndrome**
- **Most common inflammatory arthritis in elderly:**
  - Increasing prevalence
  - Highest 75-85 y.o.
  - **Men** > women, (<65 y.o.)
  - Postmenuposal women due to the Loss of estrogen induced uricosuric effect

◀ Risk Factors

- The risk of developing gout increases with **age** and with **serum uric acid (SUA) levels (**SUA levels are higher in men, increase with age and are positively associated with body weight)
- **Obesity & excessive weight gain** (especially in youth)
- High blood pressure, trauma and surgery

Causes of hyperuricaemia and gout:

Diminished renal excretion
- Increased renal tubular reabsorption (usually genetic)
- **Drugs: Thiazide** and loop diuretics, **Low-dose aspirin<1g/day?** , Cyclosporin, Niacin, Pyrazinamide & ethambutol
- Abnormal kidney function (Renal failure)
- Lead toxicity
- Lactic acidosis
- Moderate to heavy alcohol intake (beer specially)

Generalised OA[1]

Chemotherapy
- **Tumour lysis syndrome** (Due to increased purine turnover)

Increased intake
- **Purine rich foods (Red meat),** nutritional supplements,(Game, Offal , Seafood

Increased production
- Leukemias, lymphomas, and hemoglobin disorders
- Inherited disorders: **Lesch–Nyhan syndrome[2]**
- Psoriasis
- High fructose intake
- Glycogen storage disease

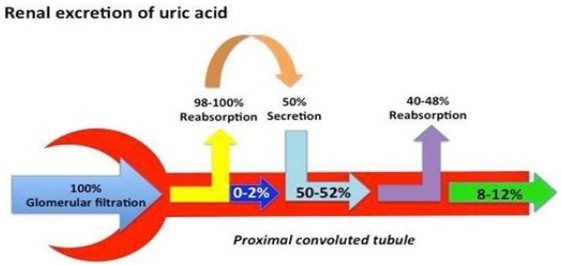
1-The association between OA and gout is thought to be due to a reduction of proteoglycan and other inhibitors of crystal formation in osteoarthritic cartilage, predisposing to crystal formation.
2-Lesch–Nyhan syndrome (HGPRT defciency) is an X-linked recessive form of gout that is also associated with mental retardation, self-mutilation and choreoathetosis. An **inherited cause** should be suspected if other clinical features are present or there is an **early age at onset with a positive family history**

Gout

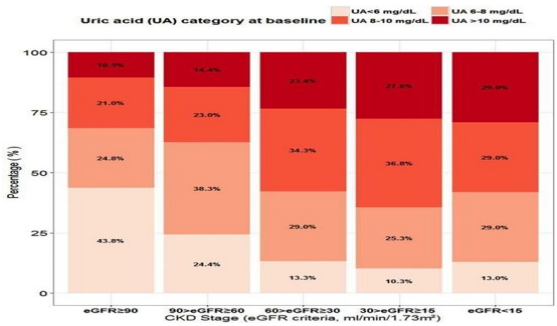
◀ Uric Acid Homeostasis:

- Urate is constantly near its limit of solubility, in a flux balance between production and elimination.
- Uric acid is the final product of endogenous and dietary purine metabolism in humans

- **SUA depends on the balance between** : purine synthesis, ingestion of dietary purines and the elimination of urate by the kidney (66%) and intestine (33%).
- **90% of people with gout have impaired excretion of uric acid** (10% have increased production due to high cell turnover and <1% due to an inborn error of metabolism).
- Renal excretion is coordinated by a group of secretory and reabsorptive **renal tubular urate transport molecules**, some of which are **targets of urate- lowering drugs.**



8-12% will be excreted at the end .



Deteriorating kidney function will eventually lead to higher uric Acid levels

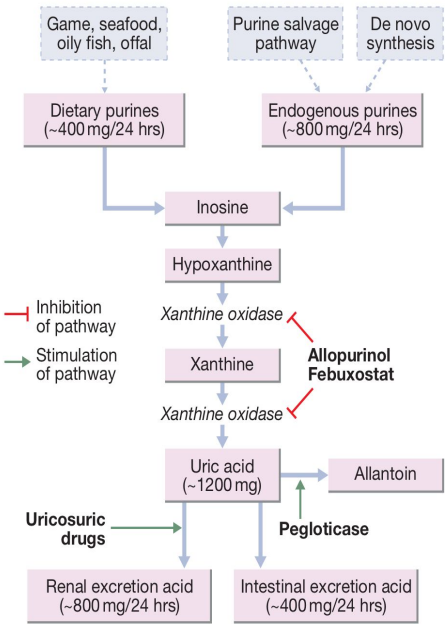
Elimination ⊖↓

Kidney - 10% of filtered load is excreted

- Simultaneous reabsorption and secretion processes.
- Proximal tubule, reabsorb filtered urate anions in exchange for intracellular organic anions such as lactate or ketone bodies.

Production ⊕↑

- Breakdown of purines from nucleic acids
- Hypoxanthine converts to Xanthine which gets turned into uric acid by **Xanthine oxidase.**



1-Although hyperuricaemia is strong risk factor for gout, only a minority of hyperuricaemic individuals actually develop gout.
2- Opsonin molecules include: Antibodies, Complement proteins,Circulating proteins.

Gout

◀ Hyperuricemia

mg/dL	µmol/L	mmol/L	Diagnosis
5 or less	300 or less	.30 or less	Safe
5 – 6	300 – 350	.30 – .35	Good
6 – 7	350 – 400	.35 – .40	Warning
Over 7	Over 400	Over .40	Danger

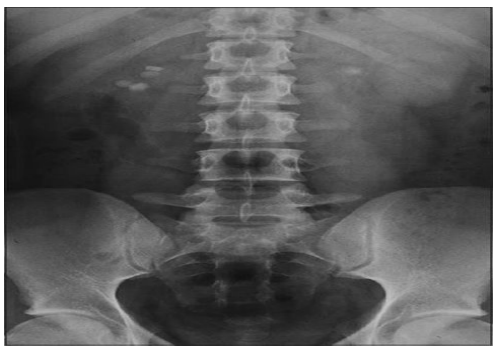
Vital Uric Acid Levels Conversion Chart

- Hyperuricemia in **90% caused by inadequate renal elimination.**
- **For males > 7 mg/dL, Females > 6.8 mg /dL**
- Above serum levels of 6.8 mg/dl (MSU) crystals are forming somewhere in the body. The higher the serum levels over time, the higher the probability of an eventual attack of gout.
- **CRYSTALLIZATION:** dependent on pH, nucleating partners and temperature.
- Urate is **less soluble in synovial fluid and articular cartilage**, especially in peripheral joints, is colder than adjacent tissue for lack of blood supply. Therefore, crystallization is likely to initiate in **small peripheral joints.**

◀ Pathophysiology

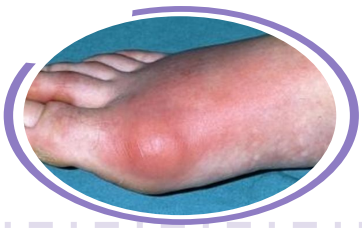
Precipitation of monosodium urate crystals in avascular tissues
- Cartilage, epiphyseal bone, periarticular bone
- Hyperuricemia likely asymptomatic for years[1]

The acute attack - crystals activate plasma proteases
- Can activate factor XII & C5
- Can adsorb opsonins[2] in area, attracting phagocytes!



Can manifest as kidney stones
Mostly radiolucent but sometimes there are deposits of Ca-oxalate and Ca-carbonate making it radio-opaque.
Diagnosed with US

◀ Clinical Features



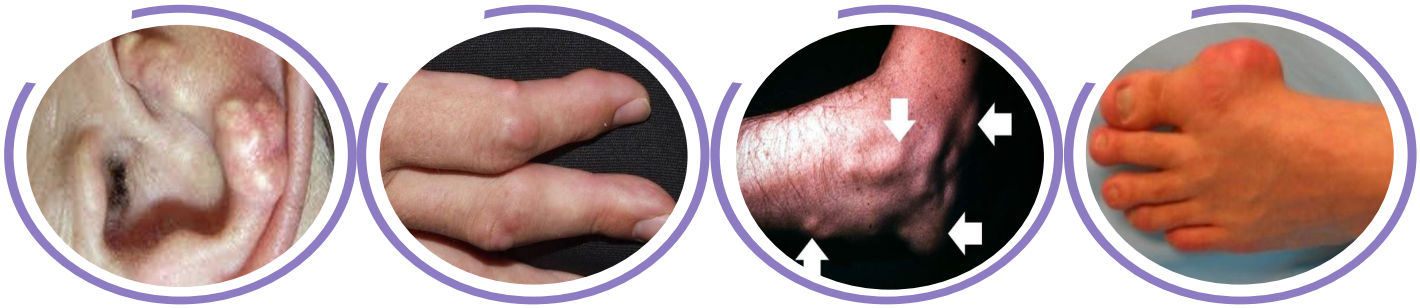
Acute monoarthritis

- If a pt presented to you with acute monoarthritis, **how can you differentiate between gout and septic arthritis by history and physical examination?**
  - Chills and rigors are in favor of septic.
  - Unlike septic arthritis, gout arthritis usually start as cellulitis, inflammation of the skin and the soft tissue, erythema of skin, induration and edema

The classical presentation is with an acute monoarthritis, which affects **the first MTP joint of the big toe** in over 50% of cases. Other common sites are the **ankle**, **midfoot**, **knee**, **small joints of hands**, **wrist** and **elbow**. The axial skeleton and large proximal joints are rarely involved. Typical features include:

- **Rapid and sudden onset**
- **Severe pain**. often described as the 'worst pain ever'
- **Extreme tenderness**. patient is unable to wear a sock or to let bedding rest on the joint
- **Marked swelling** with overlying red, shiny skin
- **Self-limiting** over 5–14 days, with complete resolution
- There may be accompanying fever, malaise and even delirium, especially if a large joint such as the knee is involved.
- As the attack subsides, pruritus and desquamation of overlying skin are common giving the impression of cellulitis
- The attack may be **precipitated** by dietary or **alcoholic excess**, by **dehydration** or by **starting a diuretic**.

Gout



Chronic tophaceous gout

- Patients with uncontrolled hyperuricemia who suffer multiple attacks of acute gout may also progress to chronic gout.
- There is **chronic pain and joint damage**, and occasionally severe deformity and functional impairment
- **Characterised with Tophi:** irregular firm **white nodules** produced when crystals are deposited in the soft tissue. These have a predilection for the **extensor surfaces** of **fingers**, **hands**, **forearm**, **elbows** (difficult to differentiate from RA nodules), **Achilles tendons** and sometimes the **helix of the ear**.
- Tophi can **ulcerate**, **discharging white gritty material and become infected.**
- In patients with chronic tophaceous gout who are on **diuretic therapy**, the hyperuricaemia may be complicated by renal stone formation and, if severe, **renal impairment** due to the development of interstitial nephritis as a result of urate deposition in the kidney.
- Whenever possible, **stop the diuretics or change to less urate-retaining ones, such as bumetanide**

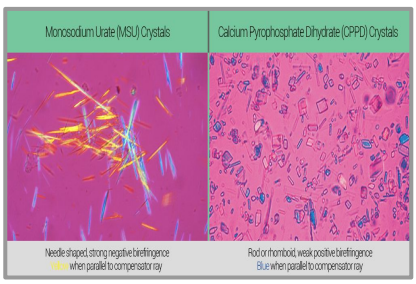
Diagnosis

Biochemical screen: including renal function, **uric acid**, glucose and lipid profile, should be performed because of the association with metabolic syndrome.

1. Acute gout is characterised by an elevated ESR and CRP and with a neutrophilia, all of which return to normal as the attack subsides.
2. Hyperuricaemia is usually present in gout but **levels may be normal during an attack** because serum urate falls during inflammation.

The clinical picture is often diagnostic, as is the **rapid response to NSAIDs or colchicine.**

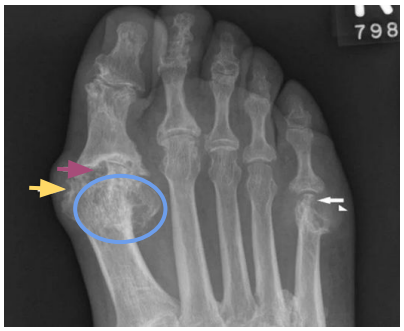
Joint aspiration (Synovial fluid analysis: Cell count, polarized microscopy and culture):
1- To exclude septic arthritis
2- To confirm the diagnosis , Joint fluid microscopy is the most specific and diagnostic test but is technically difficult.
Uric acid crystals are often intra-cellular and appear **needle-shaped** and yellow (**negatively birefringent**) When examined with a polarizing filter and red compensator filter, they are yellow when aligned parallel to the slow axis of the red compensator but turn blue when aligned across the direction of polarization (i.e. they exhibit negative birefringence).
CPPD crystals appear rhomboid shaped and blue (weakly positively birefringent)



X-ray:

1. **Normal** in **acute** gout
2. Well-demarcated **erosions** may be seen in patients with **chronic** or tophaceous gout

In Gouty arthritis the bone density is usually preserved unless in advanced stages.
1- Punched out intra-articular erosions
2- Periarticular erosions
3- Hypertrophy of the distal metatarsal bone with subchondral cysts.



Gout

◄ Principles of Management

★ Patient presenting with acute **monoarthritis: Give Antibiotics** on presentation and do not discontinue the Antibiotic even if the crystals were seen. You only stop the antibiotic when the culture comes back negative, there might be coexistence of septic arthritis and crystal induced arthritis.

★ Antibiotics are always given first in cases of acute monoarthritis because septic arthritis is the most dangerous, as it may lead to septicemia, septic shock and death eventually unlike gout which usually resolves by itself within 2wks even without treatment, but we usually give anti-inflammatory meds to abort the attack quickly

★ Can high WBC exclude gout? NO, gout pts may also present with high WBC

1 **Terminate acute attacks**
NSAIDs - Colchicine - Corticosteroids

2 **Prevent recurrence & reverse complications**
Eliminate urate crystals from joints & tissues

3 **Address co-morbid conditions**
Obesity, Hypertriglyceridemia, Hypertension, Diabetes mellitus, Excessive alcohol

1. Terminate acute attacks[1]

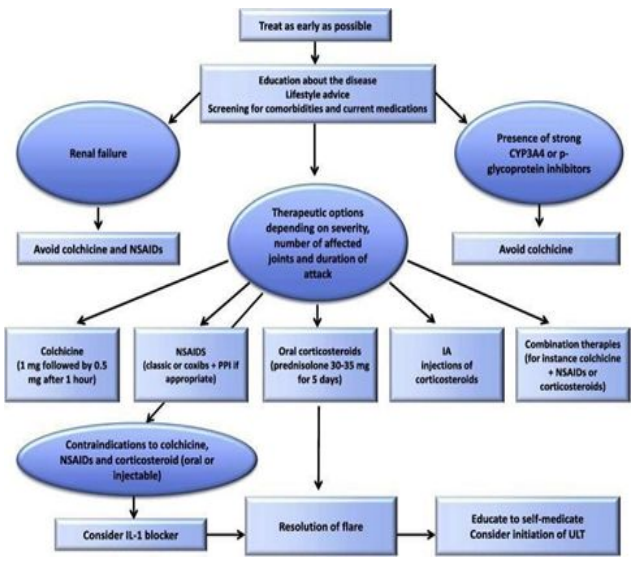
Directed at WBC inflammatory response

The first dose should be taken at the first indication of an attack. After 24–48 hours, reduced doses are given for a further week.

Options:

NSAIDS **Colchicine** **Corticosteroids**

- Choice depends on:
  - **co-morbidities & history**
  - **More importantly** - rapidity of treatment selection!
    - Keep agent close at all times; start as soon as possible as needed
    - Especially with poor renal function, slower response = increased drug exposure over course of a flare.



Doctor's notes:

In renal impairment:

- **Steroids**: preferred, either intra-articular or systemic.
- **Colchicine:** if needed, can be used in mild renal impairment (Cr clearance >70)
- **NSAIDs:** should be avoided
- Cr clearance < 50: Colchicine and NSAIDs are contraindicated.

Joint involvement:

- **Monoarthritis:**
  Intra-articular steroid injection is preferred
  NSAIDs and colchicine also can be used.
  Recall: Intra-articular steroids are contraindicated in septic arthritis
- **Polyarthritis:**
  NSAIDs or Colchicine

1-IL-1β inhibitor canakinumabis effective but extremely expensive and so seldom given.

- **Local ice packs** can also be used for symptomatic relief
- **Joint aspiration** can give pain relief, particularly if a large joint is affected, and may be combined with an **intra-articular glucocorticoid injection**

Gout

1.NSAIDS

a. Fast onset of action (within 1 hour)
b. Effective even after a few days of symptoms onset prefered over Colchicine if the pt presented after 24hrs of onset of symptoms

Choose based on: toxicity, Cost, Convenience

- CrCL
  - Avoid in **CKD**
- Risk of ADRs
  - (Nausea, vomiting, diarrhea, GI bleed, fluid retention, acute renal failure, etc)
- Cost & availability
  - Rx vs Over the counter
- For elderly: Choose shorter half-life (t ½)
  - Ibuprofen (2-4 hrs); **diclofenac (2 hrs);** indomethacin (4.5 hrs);
  - **Avoid in CHF, CKD, peripheral edema, PUD/GERD**
- N.B. increased risk of GI bleed with concurrent ASA, even 81 mg!
  - Consider adding a PPI

2.Colchicine

- Slower onset (around 6-8 hours)
- **Weak effect after 24-36 hours after symptoms onset**
- Most specific agent in use, Used for centuries.
- **OVERALL EFFECT:**
- **Decreases leukocyte motility**
  - - Binds to tubulin and inhibits microtubule formation, arresting neutrophil motility
  - Decreases phagocytosis in joints
  - Decreases lactic acid production
  - Interruption of inflammatory process
- PO or IV
  - Avoid IV - **Potentially fatal** if mis-dosed
  - Risk of **Arrhythmia**
- **Alternative regimens**
  - 1 mg loading dose, then 0.5 mg q 2-6 hrs
  - OR 0.5 - 1 mg TID
  - OR 1.2 mg initially, then 0.6 mg BID
- Most effective w/i first 12 hrs of attack
- Dose low! Try TID dosing first
- **Narrow therapeutic index (neurotoxicity, myotoxicity and GI upset)**
- **D/C if GI distress develops e.g. diarrhea or colicky abdominal pain**

3.Corticosteroids

- **Reserved for:**
  - Intolerant of NSAIDs or colchicine
  - Comorbidities that prohibit use of other meds
- Good alternative for **elderly w/ poor renal function**
  - Few trials - choice is empiric
  - Eg. Prednisone 20-60 mg/day PO
  - Are low doses less effective?
  - Noted flares in transplant patients on 7.5-15 mg/day
- **Methylprednisolone** 125 mg/day IV or IM q 1-4 days prn
  - Use smallest gauge needle (esp if on Warfarin).

2. Prevent recurrence & reverse complications

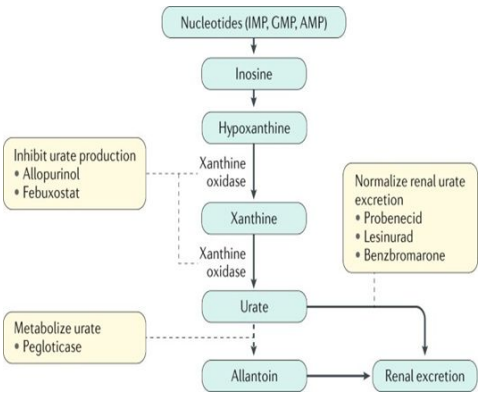
Recommendations: Urate Lowering Therapy

- **EULAR:**
  - "with recurrent attacks, arthropathy, tophi or radiographic changes"
- **US Panel:**
  - "if tophaceous deposits, erosive changes on X-ray, or ≥2 attacks per year"
- **Others:**
  - "After first attack" → Disease declared, high rate of recurrence
  - "Based on frequency of attacks" → Since second attack may not occur for years

- **Must eliminate excess body urate**
  - Else tophi may continue to enlarge
  - Destructive, chronic mononuclear cell inflammatory responses that destroys cartilage and bone, resulting in chronic arthritis
- High likelihood of recurrence
  - 62% w/i 1 yr
  - 78% w/i 2 yrs
  - 90% w/i 5 yrs

- **Recommended urate levels <360 umol/L**
  - Normal range 140-340 (Dynacare)
- At > 360 umol/L, fluids are supersaturated and crystal can **precipitate**
- At < 360 umol/L, deposits dissolve, mobilize and are **eliminated**

- **Recall**: Lowering urate can precipitate a flare!
- Acute flares of gout often follow initiation of urate-lowering therapy. The patient should be warned about this and **told to continue therapy**, even if an attack occurs. The risk of flares can be reduced by prophylaxis with oral colchicine or an NSAID for the first few months. Giving prophylaxis to the prophylaxis ..
  - Increased risk w/ more rapid & severe changes
  - ~25% of patients
- **Start 2-3 weeks after flare resolved**
  - Uricosuric agents- increase excretion
    - **Probenecid**
    - **Sulfinpyrazone**
  - Xanthine Oxidase Inh.- decrease production
    - **Allopurinol** - agent of choice
    - **Febuxostat** - new agent (ULORIC ™)
  - **Pegloticase**

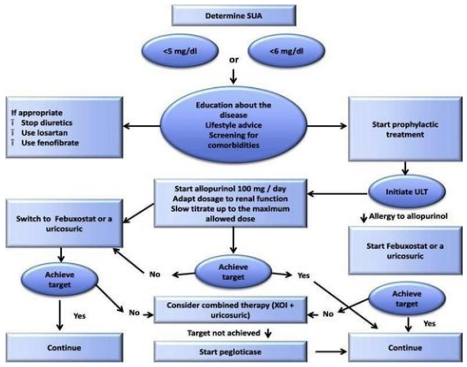


Allopurinol:
- First choice

Febuxostat:
- there's a concern about sudden cardiac death

Pegloticase or Rasburicase:
- used in tumor lysis syndrome due to chemotherapy

Urate drugs:
- have weaker action



Gout

Xanthine oxidase inhibitors

Allopurinol

1. The drug of **first choice**
2. Treatment is not started within 1 month after an acute attack and NSAIDs or colchicine are given for 4 weeks before and after starting allopurinol

Start Allopurinol at **low dose** and titrate up **to avoid precipitating event**

GOAL: lowest dose to target urate < 360 umol/L

N.B Dose adjust for renal function

- Dosing according to CrCL may not attain control

ADRs: (well tolerated)

- **Common:**
  - GI upset,
  - Rash, esp if on Amox/Amp or Cyclophosphamide)
- **Rare:**
  - Blood dyscrasias
  - Jaundice
  - TEN
  - Hypersensitivity Syndrome (including rash)
- **If mild rash occurs, hold and re-challenge**

Febuxostat (ULORIC ™)

- A non-purine, selective xanthine oxidase inh.
- **More potent than allopurinol**

Efficacy vs Allopurinol:

- **Lower** frequency of gout **flares**
  - N.B. Higher frequency of flare with initiation at higher doses! commonly provokes acute attacks when therapy is initiated
- Improved serum urate lowering effect
- Limiting RCTs - need more evidence in:
  - Renal dysfunction, concominant use of urate raising drugs (eg. ASA, thiazides), comparison against non-fixed doses of Allopurinol
- undergoes **hepatic metabolism** and no dose adjustment is required for renal impairment
- **CrCL > 30 mL/min - no dose adjustment**
- **CrCL < 30 mL/min - unstudied - avoid**

Side effects:

- Rash (1% to 2%)
- Liver function abnormalities (5% to 7%)
  - F/U LFTs in 2 & 4 months after starting tx
- Arthralgia (1%)

Treat the same as allopurinol

- Start **prophylaxis before** urate lowering therapy
  - Eg. Daily, low dose NSAID or colchicine 2-3 weeks before allopurinol
  - Eg. Indomethacin 25 mg bid
- Continue 3-6 months and/or [urate] < 360 umol/L

Note Bene (N.B.)

- Acute flare prevented but crystal deposition in tissue continues!
- Hence no warning signs of continues cartilage and bone damage and deposition in organs, especially kidneys!
- **Remember**: Colchicine is NOT uricosuric

Gout

Uricosuric Agents

Probenecid	Sulfinpyrazone

• 500 mg to 3g/day divided bid-tid
• Start: 250 mg BID
  ○ Increase by 500 mg q4wk
• May decrease by 500mg q6mo if stable >6 mo till urate starts to rise
• ADRS: GI upset, rash
	• Up to 800 mg/day divided bid
	• Start: 100mg BID
	  ○ Increase q1wk
	• May decrease to 200 mg/d once urate controlled
	• ADRs: GI upset, rash

Pegloticase

A biological treatment (a conjugated uricase enzyme)

a. It is indicated for the treatment of **tophaceous gout resistant to standard therapy** (Standard therapy is allopurinol and/or uricosuric agents) and is administered as an intravenous infusion every 2 weeks for up to 6 months. It is highly effective at controlling hyperuricaemia and can cause regression of tophi.
b. Used preventatively in people undergoing chemotherapy for **malignancies (tumour lysis syndrome)**
c. **The main adverse effects:**
   i. Infusion reactions (which can be treated with antihistamines or glucocorticoids)
   ii. Flares of gout
   iii. Development of antibodies to pegloticase.

Medication	Route	Usual Dose	Generic Availability	Estimated Cost for 30-Day Supply ($)[a]
Chronic gout				
allopurinol (various products)	Oral	300-600 mg/day	Yes	18-36
febuxostat (Uloric)	Oral	40-80 mg/day	No	186
probenecid (various)	Oral	1-2 g/day (in 2 divided doses)	Yes	50-100
Treatment-refractory gout				
pegloticase (Krystexxa)	Intravenous	8 mg every 2 wk	No	5520

[a]Based on average wholesale price.

Summary of Gout Prevention:

- High likelihood of recurrence
- Eliminate excess body urate to prevent chronic destructive changes
  - Colchicine is **not** uricosuric!
  - No prophylaxis without urate lowering therapy!
- Manage risk factors
  - Drugs, diet, comorbidities
- Allopurinol - drug of choice
  - Start low, go slow
  - May have to push dose to attain

3. Address co-morbid conditions

- Obesity
- Hypertriglyceridemia
- Hypertension[1]& Diabetes mellitus
- Excessive alcohol

Obesity & Hypertriglyceridemia

- Weight loss independently lowers urate levels
- Decreased alcohol consumption, regular exercise and weight reduction will lower TGs
  - Fibrates
    - Especially fenofibrate - mild uricosuric effect

Diet restrictions

- Highly restrictive diet is not necessary.
- Total diet restriction only lowers urate levels by ~52.9 umol/L (1 mh/dL)
  - Very unpalatable
  - Poor compliance
- Purine sources matter
  - Increase with meat & seafood
  - Decrease with dairy
    - Daily consumption lowers urate levels
  - Oatmeal and purine rich vegetables do not increase risk of gout
    - Peas, mushrooms, lentils, spinach, cauliflower

Our slides

Dietary sources

Avoid if Possible:-
Organ Meats – liver, kidney, heart, sweetbreads, tripe, brain and tongue
Limit:-
Beef. Chicken.camel. Seafood sardines , Tuna , Lamb..lard or pork pig, mushrooms[fungi]
vegetable:-
high purine content include cauliflower, spinach, Chickpeas, Soy beans, Peanut, high fructose corn syrup, sweetened soda (high in fructose which increases the production of UA , also in the long term it will affect kidney function decreasing UA secretion).

EXTRA

Pseudogout (pyrophosphate arthropathy)

Definition:

- Calcium pyrophosphate deposits in hyaline and fibrocartilage produce the radiological appearance of chondrocalcinosis. Shedding of crystals into a joint precipitates acute synovitis which resembles gout, except that it is more common in elderly women and usually affects the knee or wrist. The attacks are often very painful. In young people it may be associated with haemochromatosis, hyperparathyroidism, Wilson's disease or alkaptonuria.

Diagnosis:

- The diagnosis is made on joint fluid microscopy demonstrating small brick-shaped pyrophosphate crystals which are positively birefringent under polarized light (compare uric acid) or deduced from the presence of chondrocalcinosis on X-ray.

Treatment: Joint aspiration and NSAIDs or Colchicine.

1. If possible, substitute the antihypertensive drugs that increase uric acid (e.g. thiazides, β-blockers and ACEI) with losartan which has uricosuric effect

Summary

	Osteoarthritis	Gout
Pathogenesis	Mechanical - **wear and tear** destroys articular cartilage **(degenerative joint disorder)** Gradual degeneration of the articular cartilage of the joint , which lead to the formation of **osteophytes**	an inflammatory reaction to monosodium urate crystals. (Most common inflammatory arthritis in elderly)

Predisposing factors	• Age
	• obesity
	• Heredity
	• Gender (women)
	• Trauma to joints
	• Hypogonadism
	• Muscle weakness
	• Infection (septic arthritis)
	• Previous inflammatory arthritis
	• Repetitive use (specially in athletics)
		• Age
		• Obesity
		• Purine rich foods
		• Drugs
		  ○ **Thiazides**
		  ○ **Low dose ASA**
		  ○ Niacin
		  ○ Cyclosporin
		  ○ Pyrazinamide & ethambutol
		• Moderate to heavy alcohol intake
		• High blood pressure
		• Abnormal kidney function
		• Leukemias, lymphomas, and hemoglobin disorders
		• Trauma & Surgery

Presentation	- Pain & functional restriction - **Early morning stiffness** (lasting LESS than 30 min) - Not involve MCP - Asymmetric joint involvement - No systemic symptoms	- Sudden onset of severe pain with extreme tenderness & swelling - Commonly affects the the **first MTP joint of the big toe (podagra)**
Investigations	All labs are normal X-ray : narrowing of the joint space, osteophytes , subchondral sclerosis and cyst formation	• Biochemical screening : RFT , uric acid and lipid profile • Joint aspiration and synovial fluid analysis (cell count & polarized microscopy) : to exclude septic arthritis & confirm gout diagnosis - joint fluid microscopy will show uric acid crystals as needle shaped (negatively birefringent) • X-ray : normal in acute gout , well demarcated erosions in chronic gout
Treatment	Management targets : - pain - Limitations of joint movement - Weakness of muscles proximal to joints affected - Depression Treatment: Lifestyle modification (weight reduction & rehab) Pharmacotherapy : - First **topical NSAIDs** - Oral therapy if topical is failing: 1st choice is **acetaminophen**, 2nd is **NSAIDs** (ibuprofen, meloxicam), 3rd is tramadol	- **Antibiotics** (until culture comes back negative) - Terminate acute attacks (**NSAIDs** , **Colchicine** , **Corticosteroids**) - Prevent recurrence & reverse complications by urate lowering therapy : use xanthine oxidase inhibitors , 1st choice is **Allopurinol** ,2nd is febuxostat - Lifestyle modification (weight reduction , diet restriction , manage DM & HTN)

Lecture Quiz

Q1: A 75-year-old woman presents to accident and emergency complaining of pain in her knees. She mentions that this has been troubling her for several months. Pain is generally worse in the evenings and after walking. On examination, there are palpable bony swellings on the distal interphalangeal joints of the fingers on both hands. In addition, there is reduced range of movement and crepitus in the knees. What is the most likely diagnosis?

A- Rheumatoid arthritis
B- osteoarthritis
C- reactive arthritis
D- polymyalgia rheumatica
E- gout

Q2: A 79-year-old woman presents to her GP with pain in the left knee. This is particularly bad in the evenings and is stopping her from sleeping. The GP explains that her discomfort is most likely due to osteoarthritis and arranges for her to have an x-ray of the knee. Which of the following descriptions are most likely to describe the x-ray?

A- Reduced joint space, subchondral sclerosis, bone cysts and osteophytes
B- Increased joint space, subchondral sclerosis, bone cysts and osteophytes
C- Reduced joint space, soft tissue swelling and peri-articular osteopenia
D- Increased joint space, soft tissue swelling and peri-articular osteopenia
E- normal x-ray

Q3: A 70-year-old woman presents to accident and emergency with sudden onset pain and swelling in the right knee. Her past medical history includes hypertension and hypercholesterolaemia. She is currently taking aspirin, ramipril and simvastatin. On examination, she is apyrexial and the right knee is swollen. There is reduced range of movement in the knee due to swelling and pain. X-ray of the right knee shows chondrocalcinosis. What is the most likely diagnosis?

A- gout
B- psuedo-gout
C- septic arthritis
D- reactive arthritis
E- osteoarthritis

Q4: A 53-year-old man, who works as a chef, presents to accident and emergency with sudden onset severe pain, tenderness and swelling of the first metatarsophalangeal joint. The pain is making it difficult for him to mobilize. He has had two previous similar episodes. Blood tests reveal a raised serum urate level. The most likely diagnosis is:

A- gout
B- psuedo-gout
C- septic arthritis
D- reactive arthritis
E- osteoarthritis

Q5: A 59-year-old man presents to his GP with sudden onset severe pain, tenderness and swelling of the first metatarsophalangeal joint. He is known to suffer from acute gout and has had several previous similar episodes. What is the most appropriate treatment?

A- Allopurinol
B- NSAIDs
C- Conservative measures including reduced alcohol intake and weight loss
D- Intra-articular steroid injection
E- methotrexate

Answers: Q1:B | Q2:A | Q3:B | Q4:A | Q5:B

Answers Explanation File!

THANKS!!

This lecture was done by:

- Ghadah Alsadhan
- Razan alzohaifi
- Amirah Aldakhilallah
- Deana Awartani

Quiz and summary maker:

- Sarah Alhelal

Note taker:

- Jude Alkhalifah
- Mashal AbaAlkhail

Females co-leaders:
Raghad AlKhashan
Amirah Aldakhilallah

Males co-leaders:
Mashal AbaAlkhail
Nawaf Albhijan

Send us your feedback:
We are all ears!