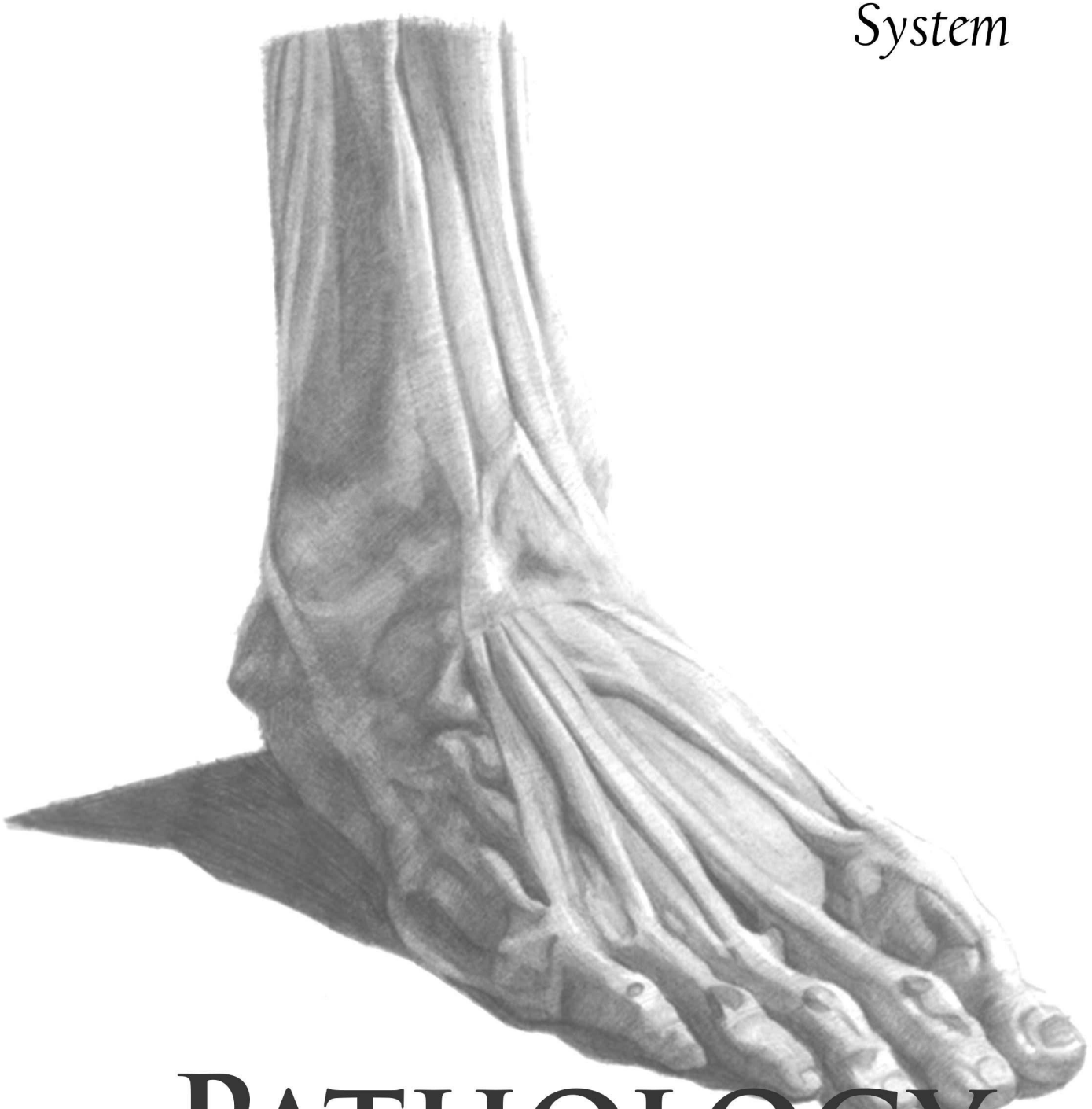
Medical Committee
The University of Jordan

The Skin and
MUSCULOSKELETAL
System



PATHOLOGY

SLIDES ☐
SHEET ■
LECTURE # 4

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JOINT DISEASES

Today we are going to talk about four joint diseases:
osteoarthritis
gout
psedogout
lyme disease

1- Osteoarthritis :

there is an inflammation of the joints however it is at degenerative bone

> **Note:** diseases in pathology (in general):
> 1-inflammation
> 2-infectious
> 3-degenerative
> 4- tumors
>
> any disease can be in one bone or a combination

- **Degenerative bone (degeneration) :** premature death of cells which cause the disease and this is the free mechanism of the disease of osteoarthritis
- We have component of inflammation but it is a degenerative disease
- It is most common joint disorder and most common joint disease
- Elderly people who complain from joints pain ⟶ means they have osteoarthritis
- It is important cause of physical disability in individuals predominantly in elderly older than 65
- Again: it is a degenerative disease, and inflammation takes place in articular cartilage so the name is not accurate about what is happening. means inflammation happened but in minor component
- It is degenerative and the main region is in the cartilage not the bone itself

- Bone changes are secondary , so the main region begins in the cartilage , then the bone is affected

- So , remember these shiny words :
  degenerative disease , inflammation can be present , main pathology in cartilage , bone is secondary affected

- We have two clinical settings :

1- primary :

- primary means : there is no initiation factor or something obvious
- it is the most common
- the disease manifest as a joint disease mainly , there is nothing prior to effect
- it is chronic disease (insidious onset), it builds up slowly and progressively
- it is oligoarticular : not in the all joints , in specific areas , so few joints are affected

2- secondary :

- less common , only 5% of osteoarthritis patients are affected
- we have obvious disease that causes damage in the joints , most commonly is **trauma** especially in sports and athletics (significant trauma in joints) so they will have degeneration and inflammation.
  diabetes mellitus is a common cause of secondary osteoarthritis
  hemocrumatosis means recurrent bleeding , the bleeding itself causes physical damage in the joints
  severe obesity also can cause osteoarthritis
- this type appears early in life , because the initiation factors " mentioned above" can occur early in life
- it affects one or few joints

Note : we said "oligoarticular" about osteoarthritis to differentiate between it and rheumatologic diseases (we will not talk about it , we will take it in medicine in clinical years enshallah :D)
the most common joint disease is : osteoarthritis , but rheumatoid diseases are very numerous such as : rheumatoid arthritis and systemic lupus and others

Back to osteoarthritis:
there is some influence of the gender:

- **in men :** the most common joints are : hip and lower spine
- **in women :** the most common joints are small joints specially the hand

- **Pathogenesis of the osteoarthritis :**
- the disease mainly in joint cartilage , cartilage's normal function is to prevent friction between the bones in the joint and damage , also it spreads the load according to the weight and the pressure which spreads upon the bone beneath it , so it is preventive and protective from damage.

- cartilage has two physiological characteristics:
  1- **it is elastic** (flexible): this is because the presence of proteoglycan
  2- **it is tense** : you can't break or torn it , this is because the presence of type II collagen.

- what happens in osteoarthritis is damage in cartilage (to be specific at the chondrocytes) , chondrocytes synthesize these components , so when there is deficient in cartilage cells "chondrocytes" the synthesis of proteoglycan will decrease , so the cartilage matrix will be deficient (we have cartilage but its characteristics are not good : it can be easily torn , it can't maintain and protect the bone).

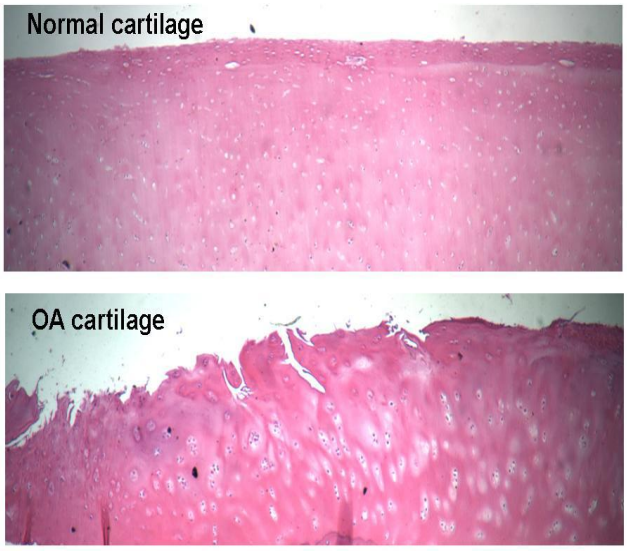
- **<u>about chondrocyte degeneration</u>:** as we said the primary has no obvious initiation factor but because of **aging,** the power of replication and function well will decrease , also with aging the chance of trauma increases so the cartilage cells die early
  Also , **genetic factors** affect osteoarthritis , the family history of osteoarthritis , so some families tend to have osteoarthritis more than other families. which means the genetic factor makes these chondrocytes die early
- In degenerating cartilage , chondrocytes can't synthesis proteoglycan well , so the matrix will have more water and less proteoglycan.
  secondary, when the cells die , we will have replication in the deep chondrocytes
  so the first morphology sign in osteoarthritis : increased proliferation of the chondrocytes in the deeper layers to compensate the died cells in the superficial layers then the disease becomes more progressive.
- **<u>the morphology:</u>**
- The earliest sign is replication and hyperplasia of the chondrocytes in the superficial layers.
- The cartilage matrix itself will have more water and less proteoglycan , this is abnormal and can't maintain the function , so with the movement the cartilage will break and torn causing cracks (شقوق) within it , because the cartilage is not normal.

- To keep the morphology of osteoarthritis in your mind remember these 2 points :

  1- proliferation of chondrocytes

  2- big cracks in the cartilage matrix

Histology of Human Normal and Osteoarthritic Cartilage



- **Changes in the bone :**
- After having these cracks , the cartilage has damaged ,broken and eventually gone , so the bone beneath it becomes exposed to each other , and this causes secondary changes in the bone itself , we called it **sub-chondral bone** (means : under the cartilage) , firstly , physical irritation takes place , the bone becomes damaged and then it will proliferate (any tissue will have proliferation after physical irritation)
  because of friction , the bone with time becomes active so it will synthesize its matrix and the bone will become like ivory (عاج) , this is called **Bone eburnation**, the shape of the bone changes , it (ivory) is mainly matrix , solid , shiny , no cellular components.
  Within the normal bone we have the matrix and the hematopoietic cells (the bone marrow) , but ivory is mainly the matrix so the bone becomes like ivory (sclerotic and thickened bone and shiny).
- Because of the damage and cracks we will have small fractures of the bones and pieces of cartilage and bone that move within the joints which called **joint mice** like a mouse , you can feel few pieces that move within the joint itself (joint mice is composed of small fractured bones and pieces of cartilage)
- **Osteophyte** :(نتوء) it is like polyp due to repetitive damage, some parts will be prominent more than other parts, these parts called osteophytes . osteophytes can be seen by x-ray as small protrusions (they make the diagnose of osteoarthritis much easier) . sometimes , osteophytes can cause physical damage , it becomes bigger on the expense of the surrounding tissue , especially if a nerve found beside it , it causes symptoms and damage to the nerve.

- **To sum up :**
- **The changes in the cartilage :**

  1- hyperplasia (replication)

  2- cracks
- **The changes in the bone:**

  1-bone eburnation

  2-joint mice

  3-osteophyte

- **The synovium :**
- When the underdying area is exposed , no cartilage , bone is damaged , the synovium goes downwards in the direction of bone matrix. This is not something normal , irritation and proliferation happen , the synoviom moves down in the exposed areas in the bone and it proliferates in big amounts forming an abnormal tissue called pannus

  pannus : it is a proliferation of synovium in an abnormal sites , it causes physical damage , and sometimes it takes a form of a **cyst**. (pannu+cyst).
- The microscopic changes : longitudinal cracks and fragmentation (small pieces)
- Grossly : at peripheral we have white areas which is the cartilage , we said that the cartilage is the main focus of damage in osteoarthritis , in the entire bone there is no cartilage anymore , and this is advanced stage . we see a rim of cartilage so the bone becomes exposed and the shape of the bone is pale and this is bone eburnation. We have empty areas and these are the cysts formed by synovium

- **Clinical features :**

- Don't forget : the primary osteoarthritis is most common , disease of elderly , it is insidious onset disease (it's a chronic disease).
- **Symptoms are related to pain**, pain is deep , significant in the bone, exacerbated by physical stress and damage
- **Morning stiffness**
- **Crepitus** : noise upon movement , you can here this voice!
- **Limitation of movement** : because of the damage , the cartilage function is not normal (limited movement)
- In advanced disease , the patients will have **deformity**
- In osteophyte , which is a bony growth , they can cause damage to the surrounding tissue like nerves. Nerves become irritated and causes more pain (radicular pain : it is the pain secondary to nerve irritation or damage due to the physical damage to the surrounding tissue)
  osteophytes might press the nerve causing symptoms , and the nerve damage causes **muscle spasm** (muscles are affected when the nerve is damaged) , the spasm is followed by **muscle atrophy** after a while and **neurological deficits.**
- Clinically **: Heberden nodes** :
  they are osteophytes in the fingers , at the distal interphalangeal joints in the hand , you can pulpate it and see it , sometimes it causes deformity . this occurs only in osteoarthritis.
- **Joint deformity** : the joint has deformity , destruction , you don't have the normal fingers, they are very deformed and not oriented
  Note : joint fusion " Ankylosis " is the ultimate damage in the joint , both bones are fused together .
  joint fusion doesn't occur in osteoarthritis but it occurs in other diseases like : rheumatoid arthritis

- **Osteoarthritis ..... NO joint fusion**
- **Rhematoid arthritis ....joint fusion**

- **Gout : (النقرس)**
- Metabolic disease: accumulation in certain material in the blood which causes disease and damage
- In gout disease the substance which accumulate is : uric acid
- Uric acid is an end product of purine metabolism. (purine is one of the nucleotides in DNA material)
- It is an acute attacks (unlike osteoarthritis that is insidious and builds up progressively), this one (gout) has sharp attacks , single severe attack continues for a while , then it becomes less , then back severe again and so on . this is a recurrent episodes of acute arthritis.
- Sometimes accompanied by physical crystalline formation
- Uric acid causes arthritis , sometimes it causes masses in soft tissue and physical damage
- **Tophi (plural of tophus)** : a collection of uric acid that causes a mass.
- Uric acid is called monosodium urate , it have sodium and uric acid together (later on we will talk about another disease related to uric acid but it has calcium not sodium)
- There is monosodium urate crystals
- Uric acid is always high level in blood of those patients

- **Important Note :**patients with gout they always have increased uric acid in the serum BUT a patient has increased serum uric acid doesn't mean he will have gout
- **In other words :** gout always associated with high serum uric acid , BUT high serum uric doesn't necessarily mean gout

- so there are other factors that cause the disease which are not known yet

- **Gout is divided into:**

1-primary:

- We don't have obvious factor before the disease develop
- More common and frequent (90% of the cases)
- The basic cause is not known or the patient has enzyme deficiency early in life (the enzyme is related to uric acid metabolism "hyperuricemia")
- Patients have increased uric acid either by :
  #increased production of uric acid (abnormality in metabolism of uric acid)
  #decreased excretion in the kidneys
  *we won't go throw pathways details , it is biochemistry and pharmacology stuff *

2- secondary:

- Less common (10% of patients)
- Caused by an obvious diseases :
  # leukemia and cancer : the patients have a huge amount of abnormal cells , these cells when they die by giving chemotherapy , they lyse and release what inside them (usually DNA) , so DNA increased in the body , so uric acid increases causing gout
  # chronic renal failure: usually uric acid gets out with urine , so in renal failure it increases and accumulates in the body due to decreased its excretion causing gout

Table 20–3 Classification of Gout

Clinical Category	Metabolic Defect
Primary Gout (90% of cases)	
Enzyme defects—unknown (85% to 90% of cases)	Overproduction of uric acid Normal excretion (majority) Increased excretion (minority) Underexcretion of uric acid with normal production
Known enzyme defects—e.g., partial HGPRT deficiency (rare)	Overproduction of uric acid
Secondary Gout (10% of cases)	
Associated with increased nucleic acid turnover—e.g., leukemias	Overproduction of uric acid with increased urinary excretion
Chronic renal disease	Reduced excretion of uric acid with normal production
Inborn errors of metabolism	Overproduction of uric acid with increased urinary excretion, e.g., complete HGPRT deficiency (Lesch-Nyhan syndrome)

HGPRT, hypoxanthine guanine phosphoribosyl transferase.

- **To sum up :**
- Gout is **metabolic disease**
- It has re**current acute attack**
- The material which increases is : **monosodium urate**
- This material increases in the joint causing arthritis
- It can form a mass in soft tissues **(Tophi) in the sub tissue**
- **Primary gout :** no obvious factors , or inborn enzymatic deficiency

- **Secondary gout :** an obvious disease : cancer specially leukemia or renal failure (decreased uric acid execration).

- **Clinically : (how patients manifest with gout disease) :**

1- Acute arthritis :

- acute attack
- gout has the severest pain in rheumatologic disease
- The main target in gout is synovium (NOT chondrocyte as in osteoarthritis)
- Under the microscope: we see neutrophils sheets extending into the synovium and destroying it.
- We got inflammation because of accumulation of uric acid in synovium when neutrophils come and destroy it.

2- Chronic tophaceous arthritis :

- Repetition and recurrent episodes of acute arthritis
- Synovium is thickened
- Repetitive damage , causing secondary hyperplasia , so the synovium becomes hyperplastic and fibrosis due to recurrent inflammation and presence of recurrent inflammatory cells so they form (pannus)

pannus : is big tissue of synovium , an abnormal big tissue , due to recurrent and persistent hyperplasia.

- Pannus can destroy (causing physical damage to) the cartilage and the bone below it , causing bone erosion.
- It can result in bone fusion "ankylosis"

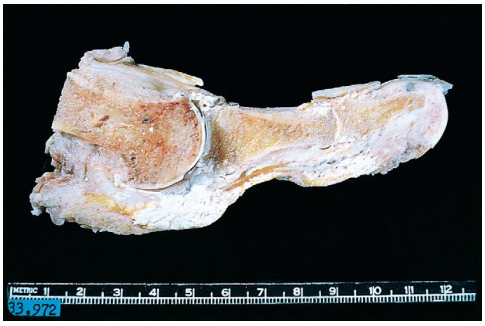
3- Tophi

- It is different than arthritis
- They can develop in the joint itself and in the soft tissue
- Remember : we said (tophus) is a mass by uric acid , which accumulate with inflammatory cells to form a big mass
  so tophi is : large aggregates of uric acid surrounded by tense inflammatory reaction , usually chronic cells such as : lymphocytes , plasma cells , macrophages and the foreign body multi nucleated giant cells
- Tophi can appear in joints , ligaments , tendons , sub-tissues , also in cartilage in earlobes , nose , and sometimes even in the finger to the skin

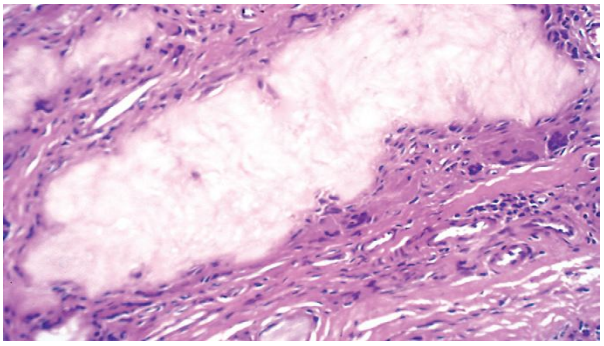
Kidney (gout nephropathy) :

- Kidney is a sensitive organ , so it has a portion of the disease
- Uric crystals will condensate in the medulla (NOT in the cortex) , cortex still has more fluid , but in the medulla any material is concentrated there , so it causes damage to the medulla of the kidney.
- Tophi can appear in the medulla or precipitation (smaller than tophi) and uric acid crystals
  the crystals of uric acid is radiolucent (شفافة) , in x-ray it appears in black color
- Any crystal can cause obstruction of the urine flow and secondary inflammation (pyelonephritis)

- **Grossly :** an amputated great toe with gout , you can a whit collection of material (which is tophus or uric acid) it is in the soft tissue and can present in the joint itself . Big toe is the favorite site of gout, causing severe pain there.



- **Under the microscope:** this is the tophus, we have an amorphous material , white in color , surrounded by dense inflammation, fibrosis and multinucleated giant cells.



- **Crystals themselves activate two cells :**

  # **neutrophils :** they are small , when they swallow the crystals by phagocytosis , the crystals are like needles they cause bursting and lysis of neutrophils releasing their contents , the most important contents are lysozymes (lysosomal enzymes) , causing tissue damage and destruction to the joint.

  # **macrophages (monocytes) :** they are big , swallow the crystals , and release the cytokines (IL1 , IL6 , TNF) when they are released they cause secondary release of proteases enzymes which cause damage and destruction to the tissue , so it causes inflammation

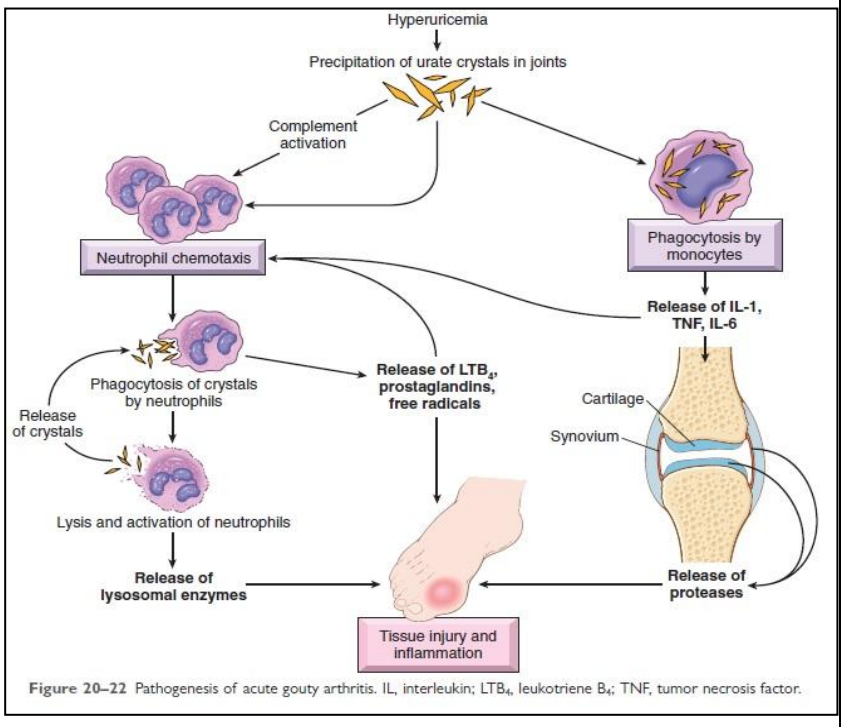


Figure 20–22 Pathogenesis of acute gouty arthritis. IL, interleukin; LTB_4, leukotriene B_4; TNF, tumor necrosis factor.

- **Pseudogout (chondrocalcinosis):**

- Less common than gout but more aggressive
- psedogout also known as **chondrocalcinosis**
- Calcium crystals are the main material in this disease
- It is secondary to precipitation of calcium pyropophosphate crystals in the joint (NOT monosodium urate)
- These crystals have calcium , so they are radiopaque, and this is how we differentiate between gout and pseudogout in x-ray
- A disease for elderly.
- It lasts for longer time
  (in gout : sharp attack, severe pain but it resolves ..... in pseudogout : encoded sub-acute , it takes days to weeks until it resolves)
- Crystals activates inflammatory cells which cause tissue damage
- The most common site is the knee (unlike gout, its common site is the big toe)
- 50% of patients will reach the case of significant joint damage
- There is no treatment (BUT in Gout we have some drugs that blocks the uric acid production)

- Lets compare between Gout and Psedogout : Calcium pyrophosphate

	Gout	Psedogout
The material	Monosodium uric acid	Calcium pyrophosphate
appearance	radiolucent	radiodense or radiopaque
Common site	Big toe	knee
treatment	We have some drugs	No treatment

- **Infectious arthritis :**

- Caused by bacteria
- Mainly hematogenous (comes from blood) , or it can spread from osteomyelitis which spreads to the bone and joints causing damage (Remember : we talked about osteomyelitis in the previous lecture)
- Clinically : we call it **(septic arthritis)** , it has very rapid , sharp , acute attacks with severe pain and systemic symptoms like : **fever** , **glycocytosis** , **rapid destruction in the joint structure** and it causes **permanent disability**
- Bacteria is always aggressive so it causes severe destruction if not treated
- In general , most common bacteria ⟶ S. aureus
- In lower age of 2 years , most common bacteria ⟶ Haemophilus influenza
- In teenagers (in west), most common bacteria is Gonococcus (it's one of the sexual transmitted diseases, it also causes infection in joints)
- In sickle cell patients , most common bacteria ⟶ Salmonella (it causes infectious arthritis in joints)

- **Lyme diseae :**

- It is prevalent in the west specially US , it is not common in our region
- It is caused by bacteria of spirochetes called Borrelia burgdorferi
- This bacteria is transmitted by ticks (البق) which lives on the deers (غزلان) , so this disease (bacteria) is transmitted by tick bite from deers to humans (lyme disease results from a tick bite)
- As you know the most common example on spirochetes is syphilis which was a disastrous disease before antibiotics discovery , because it spreads to the entire body (it is systemic) , and lasts for long time in the body killing it !
- This bacteria is same as syphilis , causing systemic disease

- **We have 3 clinical stages (NOT settings) , this means it starts from one and then moves to another :**
- **Stage 1 :**
- It is localized at the place of the bite
- It causes skin rash known as (erythema chronicum migrans) " migrans means moving from one place to another "
- It causes fever
- It causes enlargement of lymph nodes (for example : enlargement of lymph nodes in axillary in the upper arm) due to reaction of the bacteria
- It takes days then it resolves alone (body stabilizes this infection)

- **Stage 2 :**
- It happened after a while , when systemic or vesiral involvement starts
- It is the disseminated stage in lyme disease , bacteria goes to viscera so any organ can be affected but we focus on joints here
- **Migratory joint inflammation is a charactarestic of lyme disease** , it happens in large joints such as : sholder , knee and hip joints
- Migratory means: it starts by severe inflammation then subsides then it starts to move to a new joint (this is the characteristic of lyme disease) . this starts in stage 2 causing **migratory arthritis joint**
- This stage if not treated with antibiotics , the body con control it but the bacteria still dormant in the body then it goes to stage 3

- **Stage 3 :**
- It occurs 2-3 years after the infection
- It is mainly arthritic (predominant in joints) , less in viscera. joints will have inflammation and destruction
- Arthritis in lyme disease starts at stage 2 but it becomes predominant at stage 3 when patients will have chronic arthritis

*** Returning back to the the disease :***

- Lyme arthritis will occur in 60-80% of lyme patients
- The bacteria infects the synovium causing damage and destruction to it
- Under the microscope :
  We see **chronic papillary synovitis , synovium hyperplasia** (papillary growth not pannus) , if we do special stain (**silver stain**) so we can see **the microorganism** , however it can be seen in 25% in the cases only . Also **fibrin** and **chronic inflammatory cells** can be seen
- After papillary ⟶ chronic pannus develops (Remember : pannus is a solid tissue from the synovium) causes damage and deformity to the bone
- Again : arthritis happened in 80% of lyme patients
- Permanent deformity (end stage (3) if not treated (only in 10% , but it still can occurs)

- **Make sure that you know about lyme disease** :
- The bacteria
- The way of transmition
- The stages
- Clinical characteristics " the most important one is : migratory joint disease "
- The appearance under the microscope " papillary synovial hyperplasia , then pannus formation " and the stain used " silver stain"

- Muscle diseases will be discussed in CNS enshalla , not in this system ☺

And this is the end ,,,

Done by : Ola Atif

"و تحسب أنك جرم صغير ... و فيك انطوى العالم الأكبر "