MSS

pathology

LEC no. 6 V2

Writer: -Zahra' Al-Haddad
-Shahd Alahmad

Corrector: Reenas Khresat

Doctor: Tariq Aladily

MUSCULOSKELETAL PATHOLOGY-6 JOINT DISEASES

Professor Tariq Aladily

Department of Pathology

The University of Jordan

tnaladily@ju.edu.jo

NOTE: Anything in this color and between brackets **(like this)** -->
Is what the Dr said in the lec
Deal ?

OSTEOARTHRITIS

- The most common joint disorder
- Important cause of physical disability in individuals over the age of 65. So, it's a disease of the elderly (who complain of joint diseases).
- Classification: degenerative joint disease, results from cartilage degeneration. Causes disintegration of joint structure, which happens specifically in the cartilage.
- Inflammation(minimal) can be present as a minor and secondary process, occurs after degeneration.
- Clinically, we have two settings: **1) Primary OA** (95%): most common, insidious onset, no initiating factor, oligoarticular, old age
- **2) Secondary OA** (5%): of cases, young age. Either due to history of trauma or systemic disease like: DM, hemochromatosis, marked obesity, subchondral osteonecrosis(detachment of cartilage, interruption to normal architecture), one or many joints.
- Gender has some influence; knees and hands are more commonly affected in women, whereas spine and hips are more commonly affected in men.

Remember:
the joint consists of many components. Like bone, synovium, synovial fluid, tendons and cartilage.

✦**Insidious onset:** onset isn't sharp, it takes longer time until it appears.
✦**Oligoarticular:**(characteristic) affects only a single or very few joints, not systemic.

Hemochromatosis: accumulation of iron in the tissues, joints. Physical damage.

PATHOGENESIS

* Mechanical stresses and aging causes damage to chondrocytes

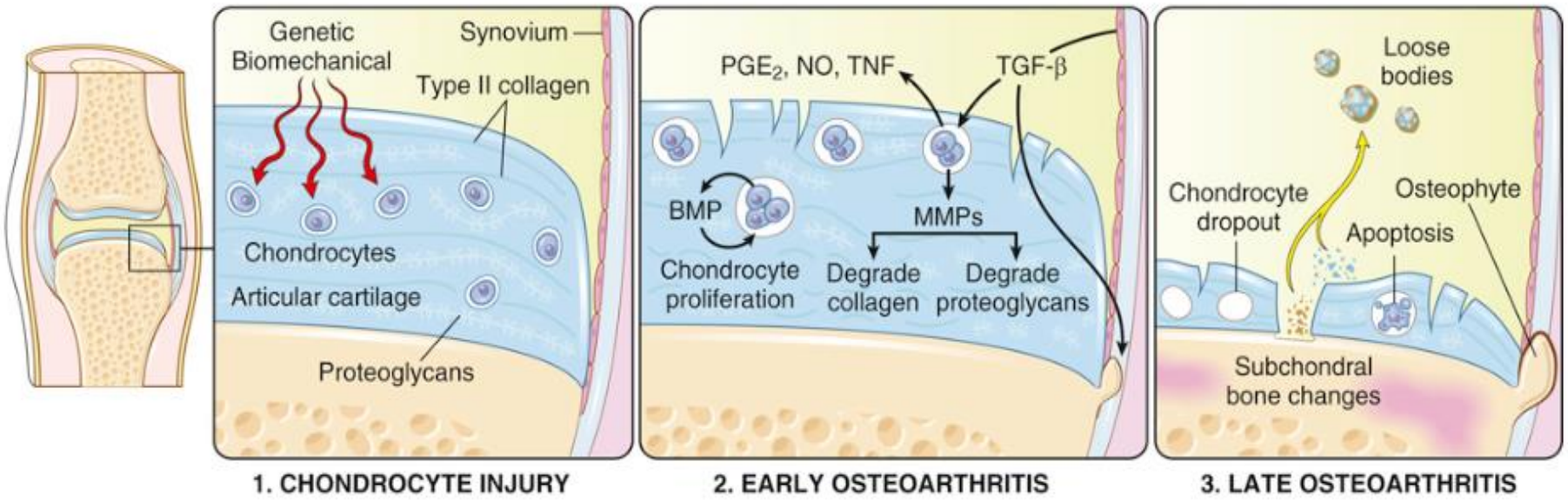
- Polymorphism in genes encoding components of the matrix and signaling molecules (repair after chondrocyte damage)
- After injury, chondrocytes proliferate (they try to repair and compensate for the damage) and secrete metalloproteinases, that degrade collagen-II (normally appears as horizontal lines in cartilage)
- Cartilage becomes more soft and watery, less dense than the normal one. So, the concentration of proteoglycans decreases (dilution).
- Superficial cartilage becomes soft, shows clefts and cracks
- Cytokines, secreted from chondrocytes, synovial cells and macrophages (**TGF-β**), **nitric oxide (NO)**, **IL-1, IL6**, **prostaglandins** induce production of metalloproteinases and further damage cartilage.
- TGF-β & bone morphogenic proteins induce **bone** growth and formation of ***osteophytes*** (bone spurs, projections at the peripheral part of the joint).

Dissecting proteins

Normally, collagen-II appears as dark blue horizontal lines in cartilage. So, when collagen gets degraded, cartilage becomes more soft and watery.

Remember: we have inflammation but it's minor NOT prominent.

These figures illustrate the pathogenesis of OA



- Schematic view of osteoarthritis (OA). OA is thought to be initiated by chondrocyte injury (1) in a genetically predisposed patient leading to changes in the extracellular matrix. (2) Although chondrocytes may proliferate and attempt to repair damaged matrix, continued degradation exceeds repair in early OA. (3) Late OA is evidenced by loss of both matrix and chondrocytes with subchondral bone damage. BMP, Bone morphogenetic protein; MMPs, matrix metalloproteinases; NO, nitric oxide; PGE2, prostaglandin E2; TGF-β, transforming growth factor β; TNF, tumor necrosis factor.

1. Along with biochemical stress, together causing chondrocyte damage and change in matrix. You can see the collagen-II as blue horizontal lines within cartilage. So, when we lose it, the conc. of proteoglycans will decrease.

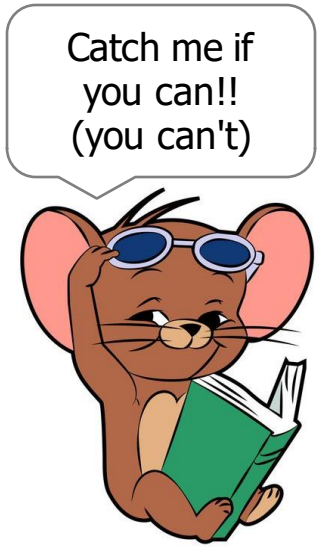
2. In the middle figure, there's proliferation of chondrocytes, you can see 2 or 3 cells inside the spaces. Then, cracks or clefts will start to form in the superficial part of the cartilage. And in this stage, cytokines will be secreted.

(Look at the 3rd pic on the previous slide, then read)

3.figure on the right, advanced changes: [1]marked loss of cartilage (thickness is much diminished), [2]exposure of subchondral bone أهم شغلة(physically exposed to the other part of the joint), [3]loose bodies which are fragmented cartilage, they move freely in the joint space. At the periphery you can see [4]bone projection, it's called osteophyte which formed due to secretion of bone morphogenic proteins and TGF.

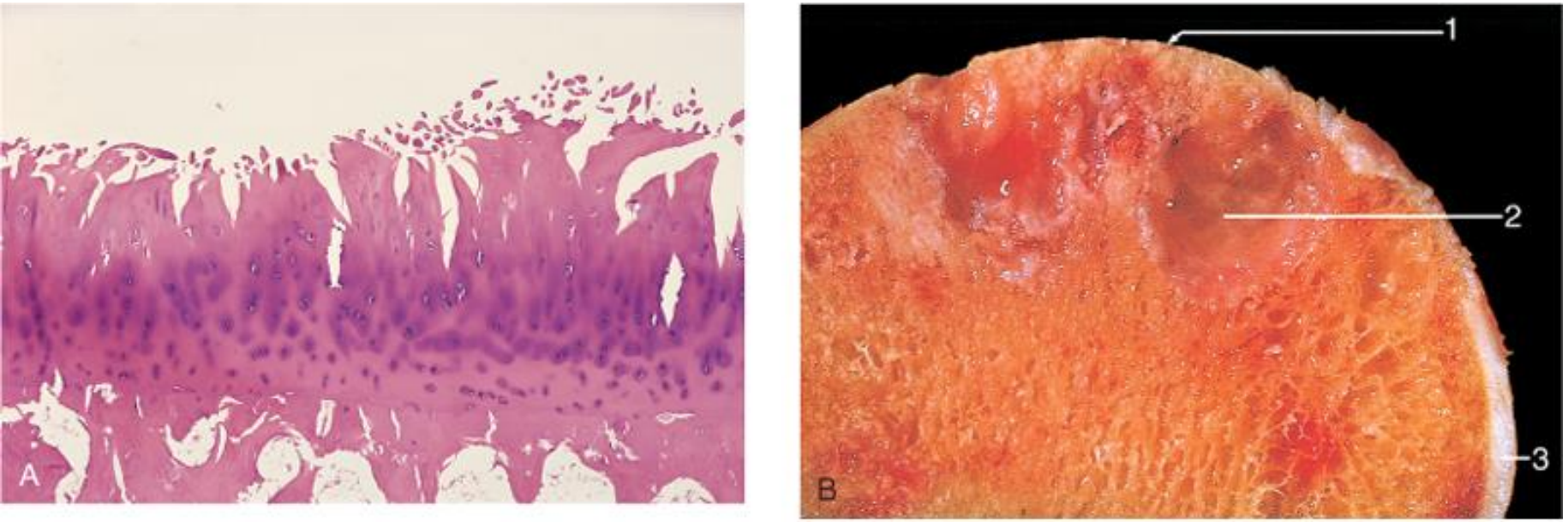
MORPHOLOGY

- Advanced stage of OA: full thickness cracking of the matrix, amount of cartilage is much less than before.
- Detached fragments of cartilage move freely in joint space ***(joint mice)***, move easily, you cannot catch. Them it can be felt by physical examination, patient can feel something moving in the joint.
- Loss of chondrocytes
- Subchondral bone becomes exposed, Bone is exposed to the joint and to the other fragment of joint. Like in the knee, femur and tibia can touch each other easily. friction between bones change their appearance as polished ivory العاج(*bone eburnation*). Bone is more white and shiny as a result of the friction between the 2 exposed bones
- Small fractures develop in exposed bones, allowing synovial fluid to accumulate deep in gaps in the bone and form a fibrous cyst in subchondral bone, filled with fluid. Seen in morphologic examination.
- Mushroom-shaped **osteophytes** (bony outgrowths) develop at the margins of the articular surface. Causing disfigurement, decreased movement, pain due to the pressure on surrounding nerves.



EXTRA: Imagine Jerry running in the patient's joint as you examine it.

These figures show advanced stage of OA. On the left, microscopic examination, you can see the long vertical cracks in cartilage. Fragmentation on superficial part.



On the right side. Bone is exposed.
(3) is a white line that shows residual cartilage.
On the rest of the bone, you can't see this cartilage, it totally disappeared, exposing the bone.
(1) is the white part of the bone, secondary to physical friction with the other bone (eburnation) – more shiny and white than the normal.
(2) subchondral cyst due to the movement of synovial fluid within the bone.

- Osteoarthritis. (A) Histologic demonstration of the characteristic fibrillation of the articular cartilage. (B) Eburnated articular surface exposing subchondral bone (1), subchondral cyst (2), and residual articular cartilage (3).

CLINICAL FEATURES

- Insidious onset, takes a long time until the symptoms appear.
- Patients, in their 50s and 60s
- Characteristic symptoms include deep, [1]aching pain (consistent and annoying, not sharp) exacerbated by use (worst pain at the end of the day), [2]morning stiffness, [3]crepitus (noise during movement of the joint بيطقطقyou can hear and feel the noise), and [4]limited range of movement (due to alteration of joint's anatomy)
- Vertebral involvement: osteophytes cause nerve impingement and neuropathy. They exert pressure on the nerve leading to sensory or motor impairment.
- ***Heberden nodes*** in the fingers, representing prominent osteophytes at the distal interphalangeal joints, are characteristic in women.

⁂**Treatment:** they only take non-steroidal anti-inflammatory drugs OR in severe cases, they undergo joint replacement (prosthetic joint).

- (if left untreated) with time, significant joint deformity can occur, but unlike rheumatoid arthritis, fusion does not take place.

In the joints of the digits, osteophytes form and appear prominently, and we call them ***Heberden nodes.***

RHEUMATOID ARTHRITIS

- Chronic autoimmune arthritis (non-suppurative, not infectious, not degenerative)
- Characteristic: severe inflammation, leading to joint destruction and joint fusion (ankylosis)

Joint disappears, totally destroyed. Joint space is no longer present, as the two bones exposed to each other fuse together.

- Symmetric arthritis, affecting mainly small joints(digits, wrist).
- Inflammaton can also occur outside the joint: ***extraarticular inflammation*** may affect skin, lung, blood vessels, heart
- More common in women (since it's an autoimmune disease), peaks in 30-50 years.
- Chronic, so, Insidious onset (builds up slowly)
- Joint pain and stiffness is more prominent in the morning or following inactivity (in contrast with OA)

Ankylosis: two bone fusion.

A lot of joints involved in this inflammation and they are symmetrical in the body.

PATHOGENESIS

- CD4+ T-cells become autoreactive against normal joint antigens
- Secreted ***TNF** **(the most important mediator in this disease, causes cartilage destruction)**, ***IL-1**, ***IL-6** from macrophages lead to secretion of proteases that destroy cartilage
- ***IL-17** recruits neutrophils and monocytes
- ***RANKL** is expressed on activated T-cells, stimulating osteoclasts which lead to bone resorption
- Activated B-lymphocytes and plasma cells secrete two main antigens important in the disease:
- **1)** anti-citrullinated peptide antibody (ACPA): which targets normal structures like fibrinogen, collagen-II, vinculin & α-enolase. present in 70% of patients.
- **2)** Rheumatoid factor: IgM or IgA autoantibodies that target Fc fragment of normal serum IgG, present in 80% of patients

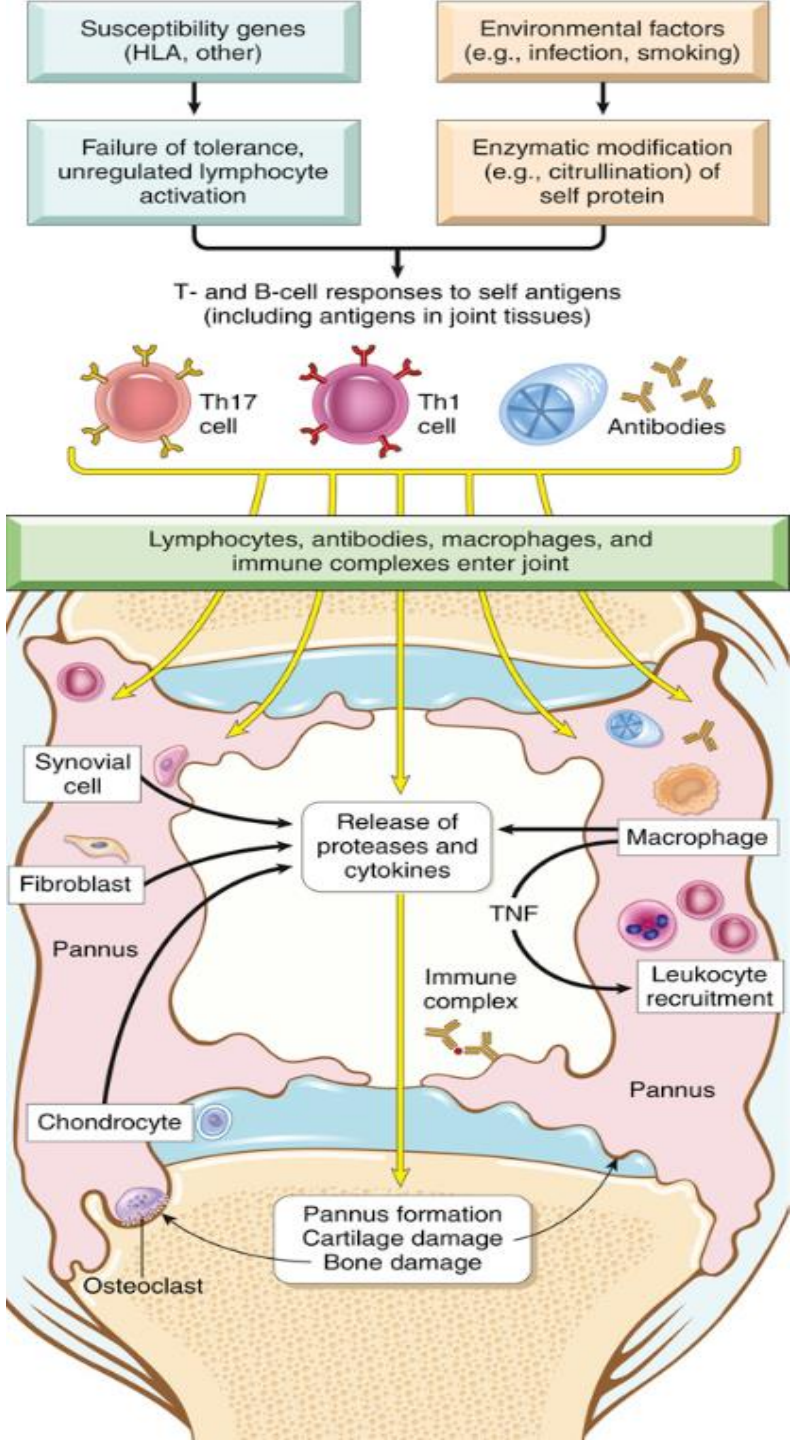
Both of these antibodies are crucial in the pathogenesis & diagnosis of the disease

- Genetic susceptibility (affects women more than others): more common in people with HLA-DR4 (human leukocyte antigen, theory says that it causes exaggerated inflammation).
- Environmental factors: smoking & local infection promote citrullination of proteins, triggering immune response

When CD4+ cells get activated, they activate all other inflammatory cells. So they activate macrophages in the synovium. Which secret TNF, IL-1, IL-6.

IgM and IgA here are abnormal autoantibodies, they bind normal antibodies in serum. Leading to deposition of the complexes of these antibodies

Citrullination: abnormal process, affecting peptides in the tissue if they have arginine (post-translation alteration of these peptides). Arg-->Citrulline, which is identified as foreign, abnormal protein and it'll be attacked by inflammatory cells .



- Major processes involved in the pathogenesis of rheumatoid arthritis. HLA, Human leukocyte antigen; TNF, tumor necrosis factor

Because of inflammation and cytokine production, proteases get activated and destroy the cartilage (blue), which causes proliferation of the synovium (purple, looks like a frame, appears very thick in rheumatoid arthritis) when it's thickened we call it *pannus,* which is very thick synovium due to infiltration by inflammatory cells, also by proliferation of fibroblast as a result of cytokines and presence of immune complexes (rheumatoid factors).

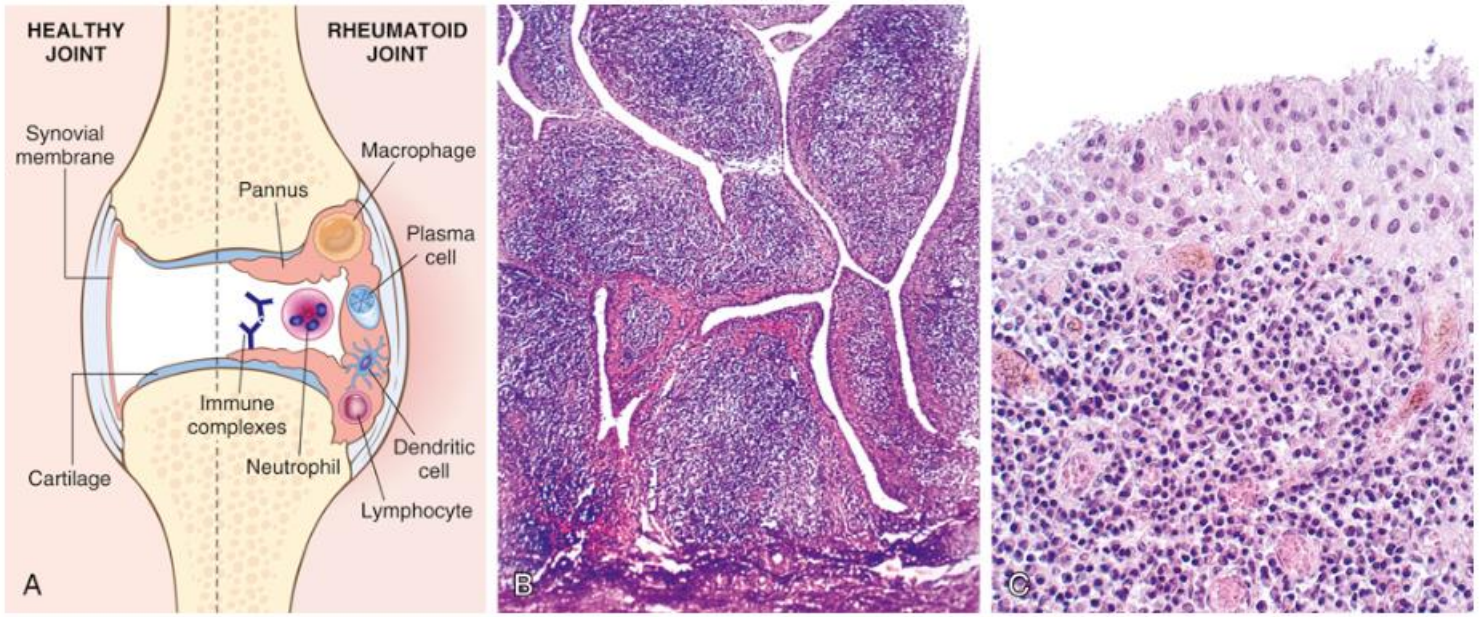
The joint then becomes filled with pannus, the space decreases. Also remember the occurrence of bone resorption due to RANK-L secretion.

MORPHOLOGY

- Synovium is markedly thickened (pannus). again, WHY?secondary to synovial cell hyperplasia, inflammatory cells infiltration, fibroblast proliferation.
- Microscopically, we see: granulation tissue: Neutrophils (because of cartilage damage), new blood vessel formation (angiogenesis), fibrin.
- Cartilage damage
- Prominent osteoclasts in bone trabeculae, subchondral cyst.
- With time, pannus fills the joint space, make a bridge between bones, then ossifies, causing ankylosis and lose of the joint space.

Like in OA

A B C



★ Fig A: most prominent is cartilage damage with pannus formation.

★ Fig B: you can see how the pannus looks like, full of lymphocytes (blue in color).

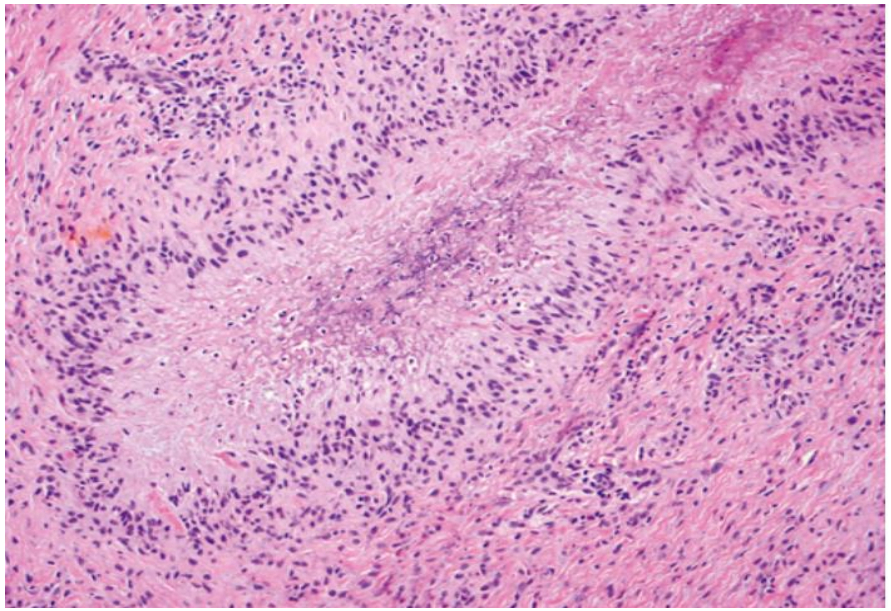
★ Fig C: higher magnification, these blue cells are T & B lymphocytes along with plasma cells. Upper part: larger, synovial cells causing synovial hyperplasia (since they are more than one layer) + lymphocyte infiltration. Lastly, fibroblast proliferation deep in the pannus.

- Rheumatoid arthritis. (A) Schematic view of the joint lesion. (B) Low magnification shows marked synovial hypertrophy with formation of villi and a dense lymphocytic infiltrate. (C) At higher magnification, numerous plasma cells are seen beneath the hyperplastic synovium

RHEUMATOID NODULE

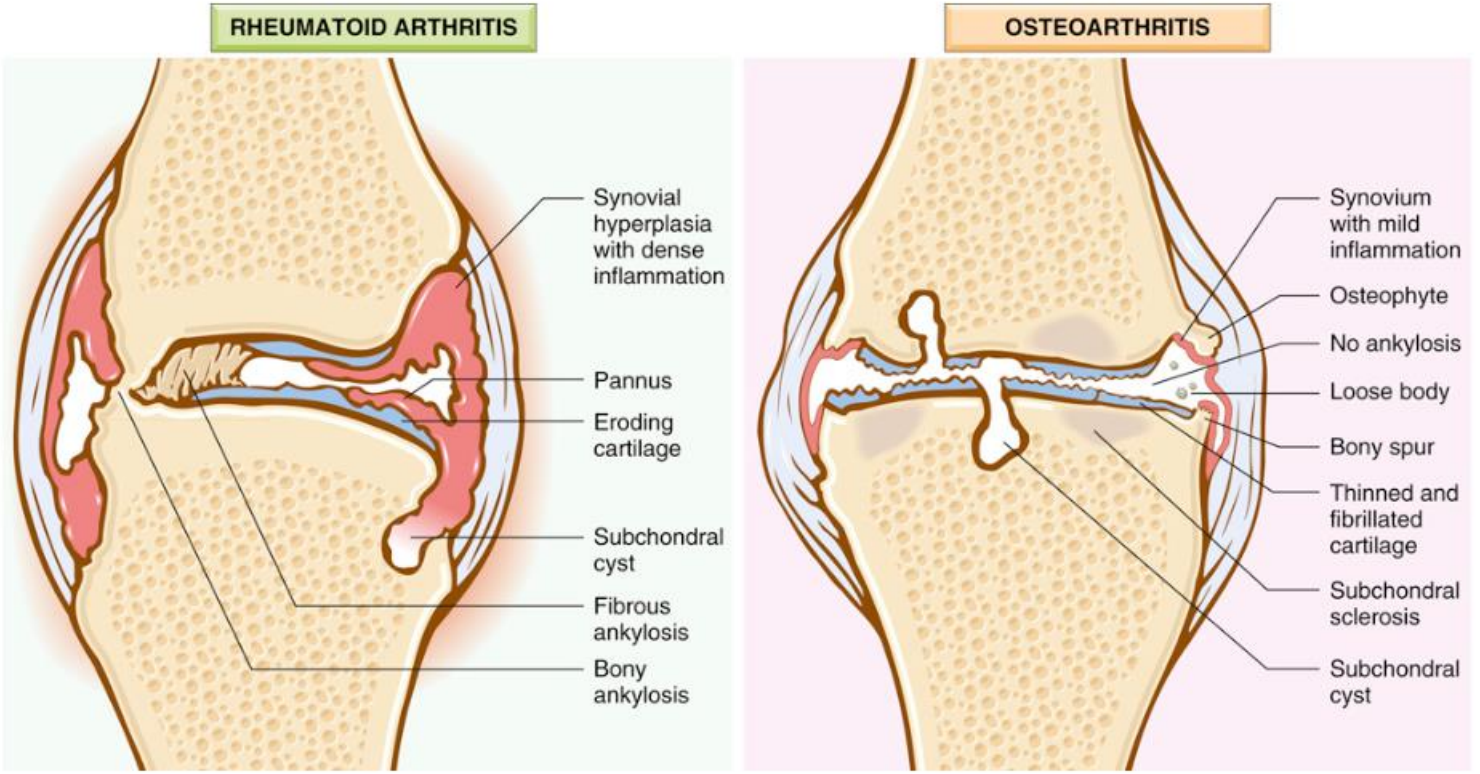
Extraarticular involvement: inflammation in many tissues of the body, which sometimes takes the form of a mass, causing a big nodule which the patient can feel in the subcutaneous area. We call it rheumatoid nodule. It can be palpated.

- A subcutaneous firm mass appears in forearm(most likely), occiput, lower back or lung
- Microscopically shows central necrosis rimmed by palisaded histiocytes



Center: necrotic acellular area, full of debris, appears purple.
Surrounding: palisade, which looks like a wall.
Together they are called ***rheumatoid nodule.***

- Comparison of the morphologic features of rheumatoid arthritis and osteoarthritis.



- Pannus formation, which can connect the two bones together
- Ossification, bridging (ankylosis) DOESN'T occur in OA.
- Subchondral cyst & cartilage damage.
- NO osteophyte.

- Cartilage damage/loss
- Bone eburnation, appears shiny
- Subchondral cyst
- Osteophytes at the edges of bone.

Comparative Features of Osteoarthritis and Rheumatoid Arthritis

	Osteoarthritis	Rheumatoid Arthritis
Primary pathogenic abnormality	Mechanical injury to articular cartilage	Autoimmunity
Role of inflammation	May be secondary; inflammatory mediators exacerbate cartilage damage	Primary: cartilage destruction is caused by T cells and antibodies reactive with joint antigens
Joints involved	Primarily weight bearing (knees, hips)	Often begins with small joints of fingers; progression leads to involvement of multiple joints
Pathology	Cartilage degeneration and fragmentation, bone spurs, subchondral cysts; minimal inflammation	Inflammatory pannus invading and destroying cartilage; severe chronic inflammation; joint fusion (ankylosis)
Serum antibodies	None	Various, including ACPA, rheumatoid factor
Involvement of other organs	No	Yes (lungs, heart, other organs)

(they're celebrating because you're halfway through this, bravo!!)

Pus formation due to the inflammation

SUPPURATIVE ARTHRITIS

it has another name which is septic arthritis
In this condition, bacteria came from distant place, until it reaches the joint by blood

- Bacterial infection of joints
- Usually hematogenous route(Major route), but can be by direct implantation (trauma, drug abuse) or extension from adjacent infection (osteomyelitis)
- Staph aureus is the most common bacteria in children and adults
- Group B-strep , **E- Coli** and Neisseria gonorrhea in neonates (through maternal genital tract)
- Pseudomonas and Gram-negative in immune suppression or drug abuse
- Complement factors deficiency: gonoccoal polyarthritis

part of immune deficiency, which is the complement system

CLINICAL FEATURES

- Rapid onset of joint pain, warmth, swelling, limited motion, leukocytosis and fever. (Acute disease)
- Most cases involve a single joint
- Joint fluid aspiration shows purulent fluid (we take it from synovial fluid then make culturing to know what bacteria type)

LYME ARTHRITIS

- Caused by Borrelia burgdorferi, transmitted by Ixodes deer ticks
- Common in USA
- Initial infection of skin, called erythema migrans (early localized stage), then skin, cranial nerves, heart and meninges (early disseminated stage), then chronic arthritis and visceral infection (late disseminated stage).
- 60-80% of untreated patients develop arthritis, which drops to less than 10% if treated early
- Arthritis is most common in knee joints(but it can appear in any joint), migratory, lasts weeks to months
- Histology: Thick synovium (synovial hyperplasia, chronic inflammation, fibrin deposition) + thick-wall arteries (onion-skin)multiple layers , may resemble rheumatoid arthritis

so remember that " Lyme arthritis of lyme disease " happens in the **late** disseminated stage

the patient has to take antibiotics as early as possible,
if the disease developed to arthritis the treatment become much more difficult

arteries give multiple layers of collagen so it appears onion-shape

Migratory = means inflammation start for example in the right knee, it lasts week or months then it subsides , then it start appearing in different joint

CRYSTAL-INDUCED ARTHRITIS

- Endogenous: monosodium urate (which causes gout) or calcium pyrophosphate dehydrate (which causes pseudogout)
- Exogenous: joint prosthesis
- All crystals induce inflammation and destroy joint cartilage

Crystal causes physical effect it acts as a foreign body in the cartilage of the joints so it induces inflammation and arthritis, it has many sources :

GOUT

- Transient attacks of severe acute arthritis(most important clinically, acute phase then the pain subsides then repeated again and again) , induced by monosodium urate crystals deposition in and around joints
- Patients have hyperuricemia secondary to overproduction (enzymatic deficiency) or reduced excretion (more common, unknown pathway) or both
- 90% of cases are primary (the patient does not have another disease which developed to gout)
- 10% of cases are secondary to renal failure, chemotherapy causing tumor lysis syndrome (because when they receive chemotherapy , malignant cells lysis so the purines get out from these cells and they are metabolized to be uric acidespecially leukemia)
- Only 10% of patients with hyperuricemia develops gout, usually after a long time (20-30 years) . (but patients with gout always have hyperuricemia)
- Old age, genetic predisposition, alcohol consumption, obesity, thiazide (it inhibits excretion of uric acid in the urine) are risk factors (

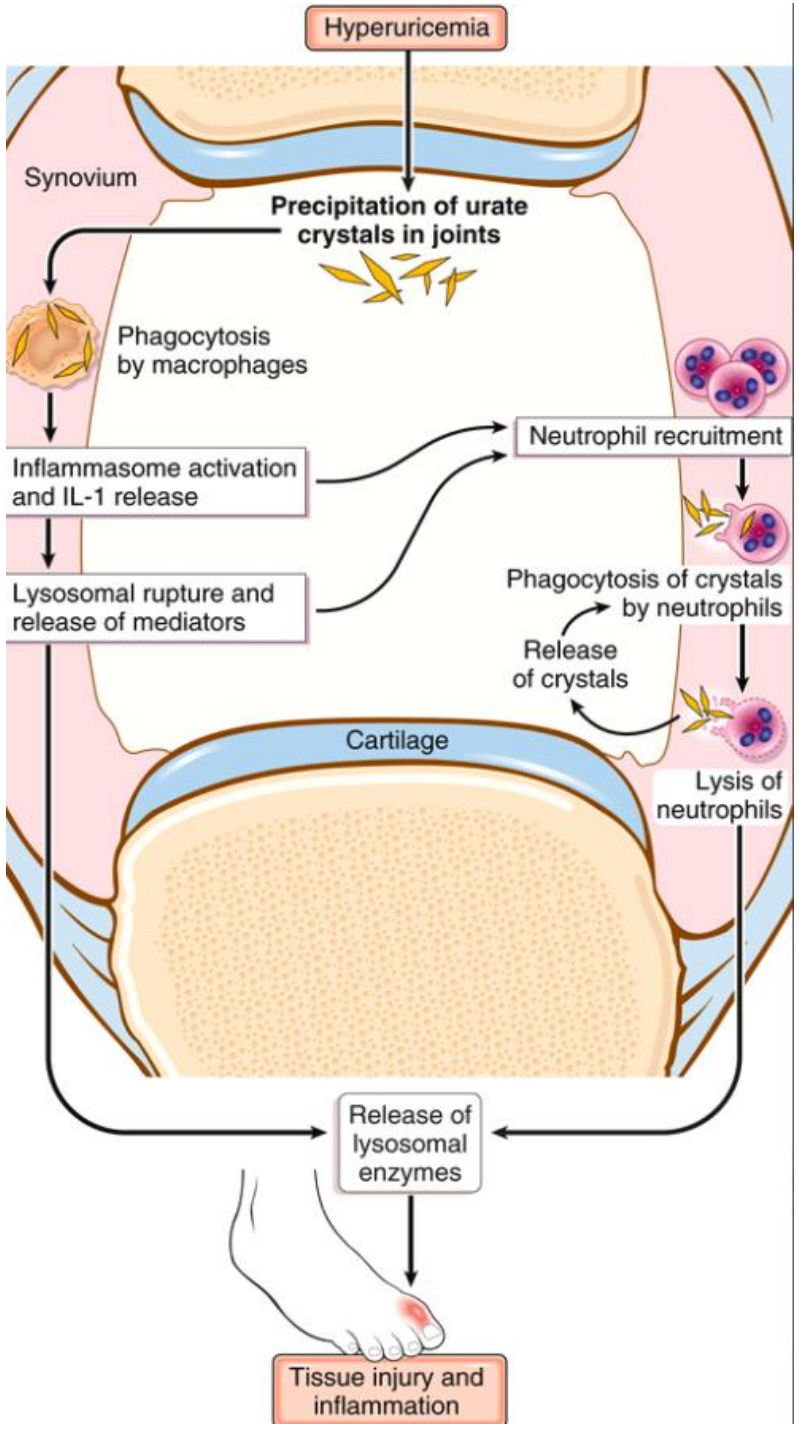
PATHOGENESIS

- Macrophages in synovium phagocytose urate crystals, causing activation of cytosolic inflammasome, which activates caspase-1, which leads to production of IL-1, which stimulates neutrophilic infiltration in the joint.
- Neutrophils release cytokines, free radicals, proteases, causing tissue damage
- Ingested crystals may damage phagosomes leading to leakage of lysosomal enzymes, causing further damage (because lysozymes in normal conditions attack bacteria and waste, but here their content will leak out)
- The disease shows acute onset, which subsides spontaneously within days or weeks, but recur later on
- Repeated attacks result in formation of tophi (large aggregates of crystals and inflammatory cells) in joint and adjacent soft tissue ear, nose

They can be seen by physical examination

PATHOGENESIS

- Urate crystals are phagocytosed by macrophages and stimulate the production of various inflammatory mediators that elicit the inflammation characteristic of gout. Note that IL-1, one of the major proinflammatory cytokines, in turn stimulates the production of chemokines and other cytokines from a variety of tissue cells
- (As U can see in the pic, the most common site of gout is the big toe -->)

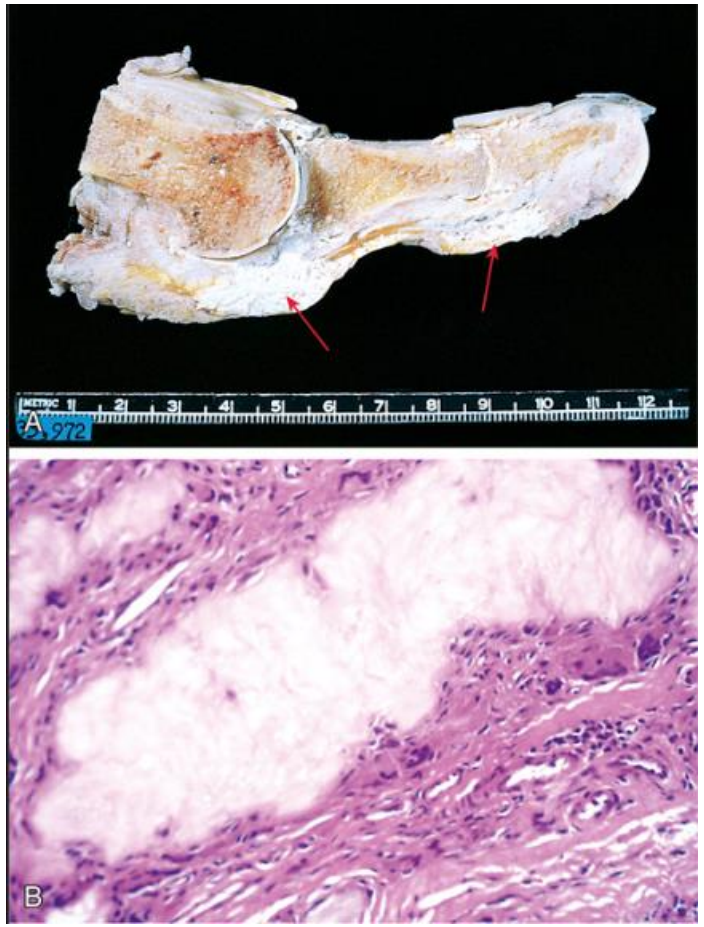


MORPHOLOGY

- Acute gout arthritis: intense inflammation (neutrophils) in synovium and synovial fluid
- Urate crystals appear in the cytoplasm of neutrophils
- They look long, needle shaped, negatively birefringent (they reflect light in certain way) in polarized microscope (another thing is that some of them give yellow color) , sharp-like needles structures.

MORPHOLOGY

- Chronic tophaceous arthritis: (white, chalky material) مثل الطباشير
- Chalky deposits in synovium, causes pannus and cartilage damage
- out. (A) Amputated great toe with a tophi (arrows) involving the joint and soft tissues. (B) Gouty tophus—an aggregate of dissolved urate crystals is surrounded by reactive fibroblasts, mononuclear inflammatory cells, and giant cells



CLINICAL FEATURES

- Asymptomatic hyperuricemia begins around puberty in men and after menopause in women
- Acute arthritis(remember that suppurative arthritis is acute as well): sharp onset and joint (severe)symptoms, 50% affect big toe, usually monoarticular, resolves spontaneously

الدكتور نبّه على اهميتها

- Repeated attacks become more progressive, polyarticular
- Chronic tophaceous gout: loss of join space

PSEUDOGOUT

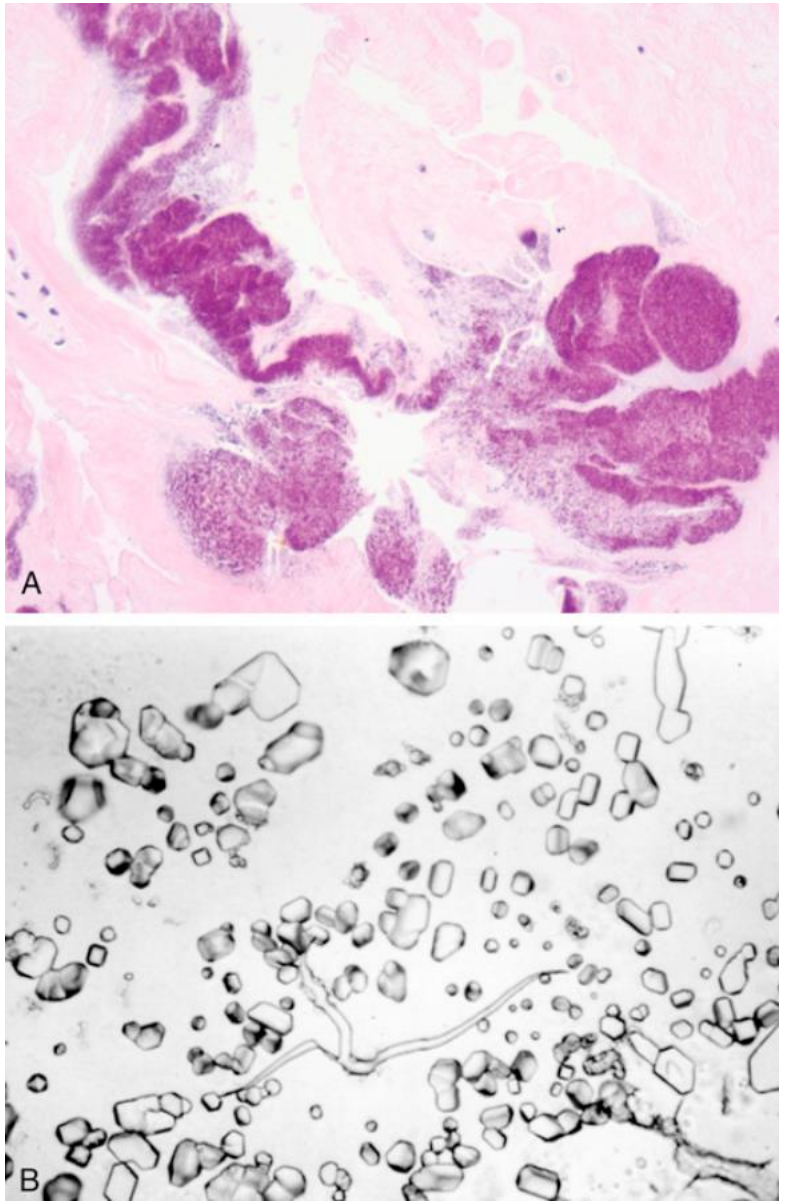
- Calcium pyrophosphate crystals (these crystals enlarge with time and seed into the joint)
- Most patients are older than 50 years
- Sporadic or hereditary (autosomal dominant), mutation in pyrophosphate transport channel
- Crystal formation occurs in joint cartilage, when they enlarge, they rupture and seed the joint
- Crystals appear oval or rhomboid, blue or purple in color in hematoxylin and eosin stain (H&E staining), appear positive birefringent in polarized microscope
- Inflammation is minimal, compared to gout (less serious than gout)

- **Tip to memorize**
- **Pseudogout = positive birefringent**

MORPHOLOGY

- Pseudogout. (A) Deposits are present in cartilage and consist of amorphous basophilic material. (purpule to blue)
- (B) Smear preparation of calcium pyrophosphate crystals

(oval or rhomboid, in opposite to gout which was needle-shaped)



مهم الفرق بين ⚠️
Gout VS Psuedogout

*After 2 slides, U'll see **additional** slide which compares between :)

CLINICAL FEATURES

- **Knee joint is the most common site**
- Variable presentation, may be acute, subacute or chronic
- Can be monoarticular or polyarticular
- Significant joint destruction in 50% of cases (as it has no treatment)

Feature	Gout	Pseudogout
Causative Crystals	Monosodium urate	Calcium pyrophosphate dehydrate
Common Age of Onset	Old age	Mostly older than 50 years
Risk Factors	Genetic predisposition, alcohol consumption, obesity, thiazide diuretics	Hereditary (autosomal dominant mutation in pyrophosphate transport channel), age
Crystal Appearance ❗ ❗	Needle-shaped, negatively birefringent under polarized light	Rhomboid or rod-like, positively birefringent under polarized light
Typical Joint(s) Affected	Often affects the big toe, but can be polyarticular in chronic cases	Knee joint is the most commonly affected
Pathogenesis	Overproduction or underexcretion of uric acid leads to crystal deposition	Crystal formation in joint cartilage, possibly due to abnormal pyrophosphate metabolism
Clinical Presentation	Acute attacks of severe pain, swelling, and redness, resolving spontaneously but may become chronic	Can be acute, subacute, or chronic with variable presentation; significant joint destruction in 50% of cases
Inflammation	High, with intense inflammation during acute attacks	Generally less intense compared to gout

. TEST BANK (ADDITIONAL QUESTIONS FOR THIS LEC.)

What is the primary mechanism of damage in osteoarthritis (OA)?

A) Inflammatory cell infiltration leading to joint destruction

B) Autoimmune destruction of synovial membranes

C) Degeneration of cartilage due to mechanical stress and aging

D) Deposition of monosodium urate crystals in the joint

Which of the following is NOT a characteristic feature of rheumatoid arthritis (RA)?

A) Symmetric arthritis mainly affecting small joints

B) Presence of rheumatoid factor in 80% of patients

C) Formation of osteophytes at the margins of the articular surface

D) Chronic autoimmune (non-suppurative) inflammation leading to joint fusion

What is the most common cause of suppurative arthritis in children and adults?

A) Staphylococcus aureus B) Neisseria gonorrhoeae

C) Pseudomonas aeruginosa D) Group B Streptococcus

which cytokine is primarily implicated in the pathogenesis of osteoclastogenesis leading to bone resorption in rheumatoid arthritis?

A) Interleukin-1 (IL-1)

B) Tumor Necrosis Factor-alpha (TNF-α)

C) (RANKL) D) Interferon-gamma (IFN-γ)

Which statement correctly describes the genetic susceptibility in rheumatoid arthritis (RA)?

A) Most RA patients have a mutation in the gene encoding for urate oxidase.

B) The presence of HLA-DR4 allele is associated with an increased risk of RA.

C) Autosomal dominant inheritance of a pyrophosphate transport channel mutation is a risk factor.

D) Genetic predisposition is mainly due to mutations in the collagen-II gene.

Which statement about Lyme arthritis is true?

A) It is caused by the direct implantation of bacteria into the joint.

B) It is most commonly associated with infection by Staphylococcus aureus.

C) It develops in 60-80% of untreated patients, mainly affecting the knee joints.

D) It is characterized by the formation of tophi within the joint space.

Gout is characterized by the deposition of which type of crystals in and around joints?

A) Calcium pyrophosphate dehydrate

B) Monosodium urate

C) Cholesterol

D) A+B

اللهم اغفر للمسلمين
والمسلمات، والمؤمنين والمؤمنات،
الأحياء منهم والأموات

- **Answers : C C A C B C B**

- **V2**
- **Answers of the Test Bank were corrected ✔**