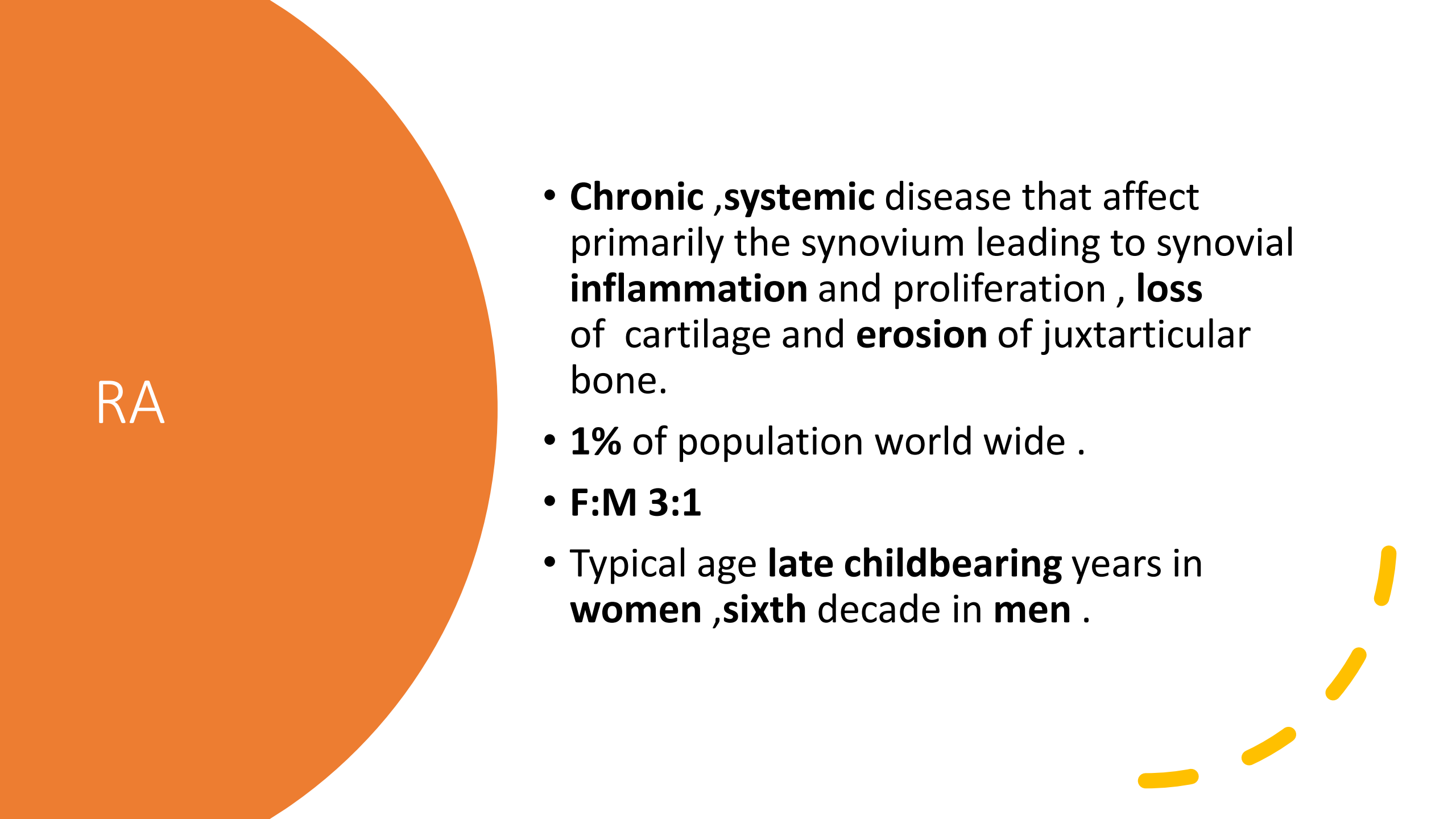




Rheumatoid Arthritis



RA

- **Chronic ,systemic** disease that affect primarily the synovium leading to synovial **inflammation** and proliferation , **loss** of cartilage and **erosion** of juxtaarticular bone.
- **1%** of population world wide .
- **F:M 3:1**
- Typical age **late childbearing** years in **women ,sixth** decade in **men** .

Cause :

- **Genetic** predisposition , strongest association is with alleles **HLADRB1**.
- It encodes the Beta chain of HLA-DR directly involves in the presentation of antigen to T cells
- Shared epitope encoding **HLADRB1** confers the risk only for RA associated with antibodies to **citruillinated** protein epitopes(present in 70% of all patients with RA)
- **Citrullination** is a post translational modification of protein in which argnine residues are converted to citrulline-at sites of inflammation

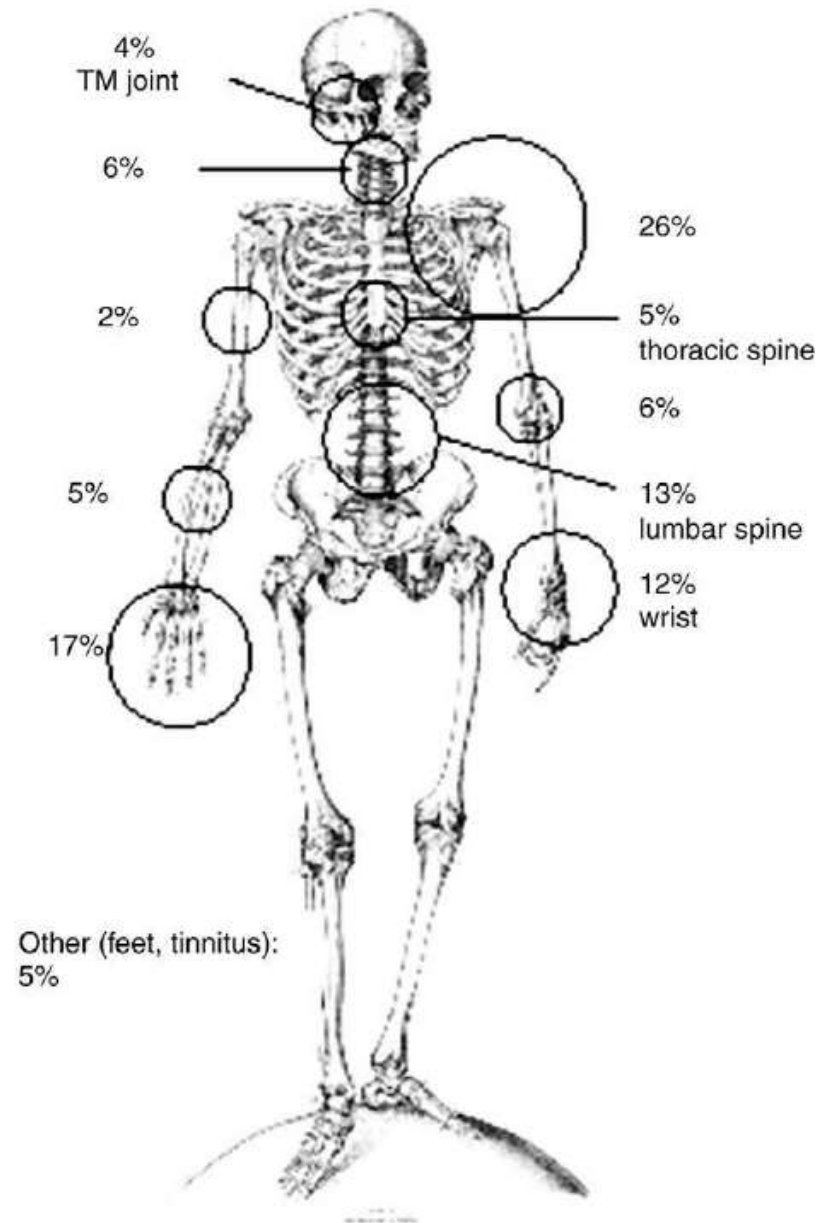
- Smoking and Periodontitis are linked to increased citrullination in the lungs and periodontal tissues.

Clinical findings :

- **Onset:**
- **insidious** onset of pain , stiffness , swelling in multiple joints over weeks to months.
- Or ptns may have **fulminant** presentation .
- Many may have **persistent** mono or **oligoarthritis** before manifesting the more typical pattern of polyarticular involvement .
- **Palindromic** rheumatism (episodic self limited attacks of polyarthritis)may evolve into RA .
- Rarely **extraarticular** features before e.g. scleritis .

- **Systemic manifestation** ; fatigue , fever (low grade), wt loss .

Distribution of joints

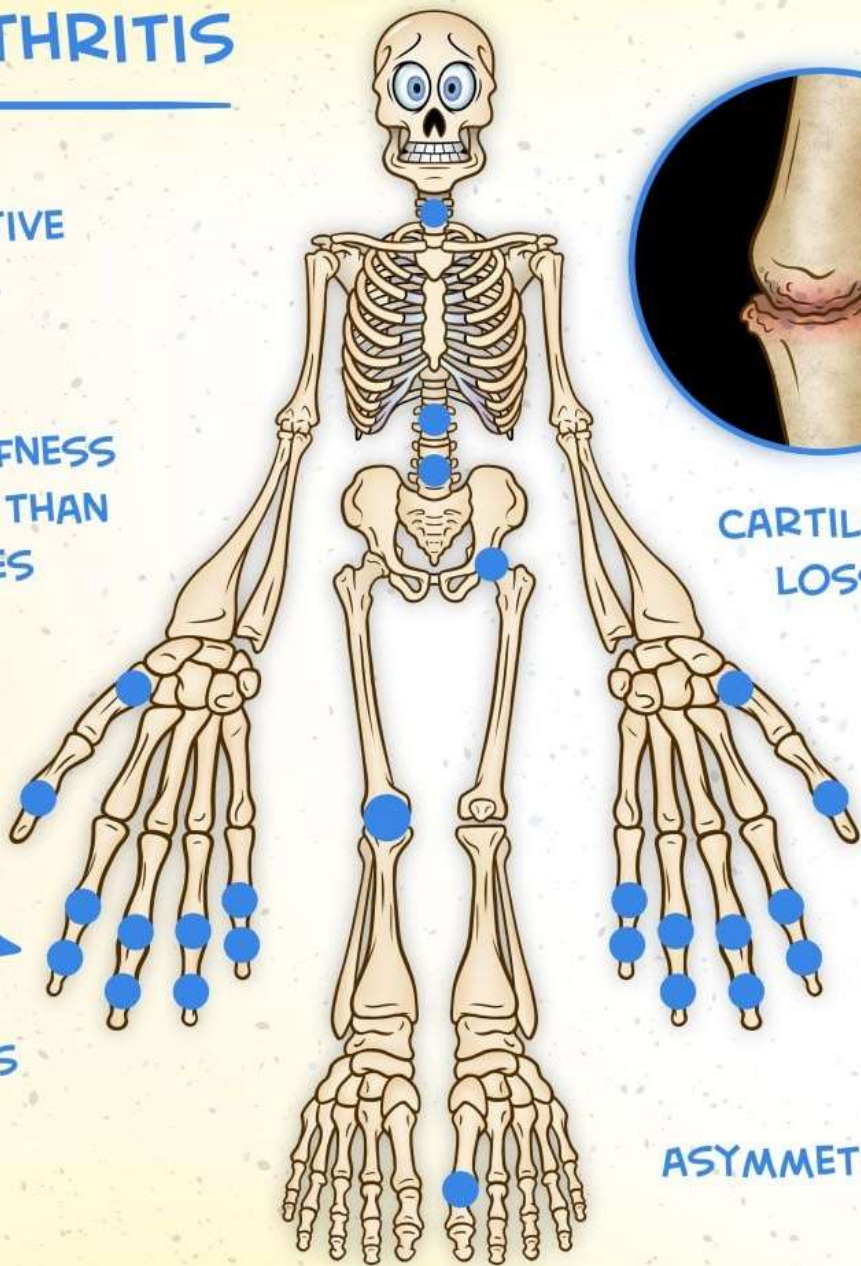


OSTEOARTHRITIS

DEGENERATIVE
DISEASE

MORNING STIFFNESS
LASTING LESS THAN
30 MINUTES

HEBERDEN'S
NODES



CARTILAGE
LOSS

ASYMMETRICAL



INFLAMED
SYNOVIUM

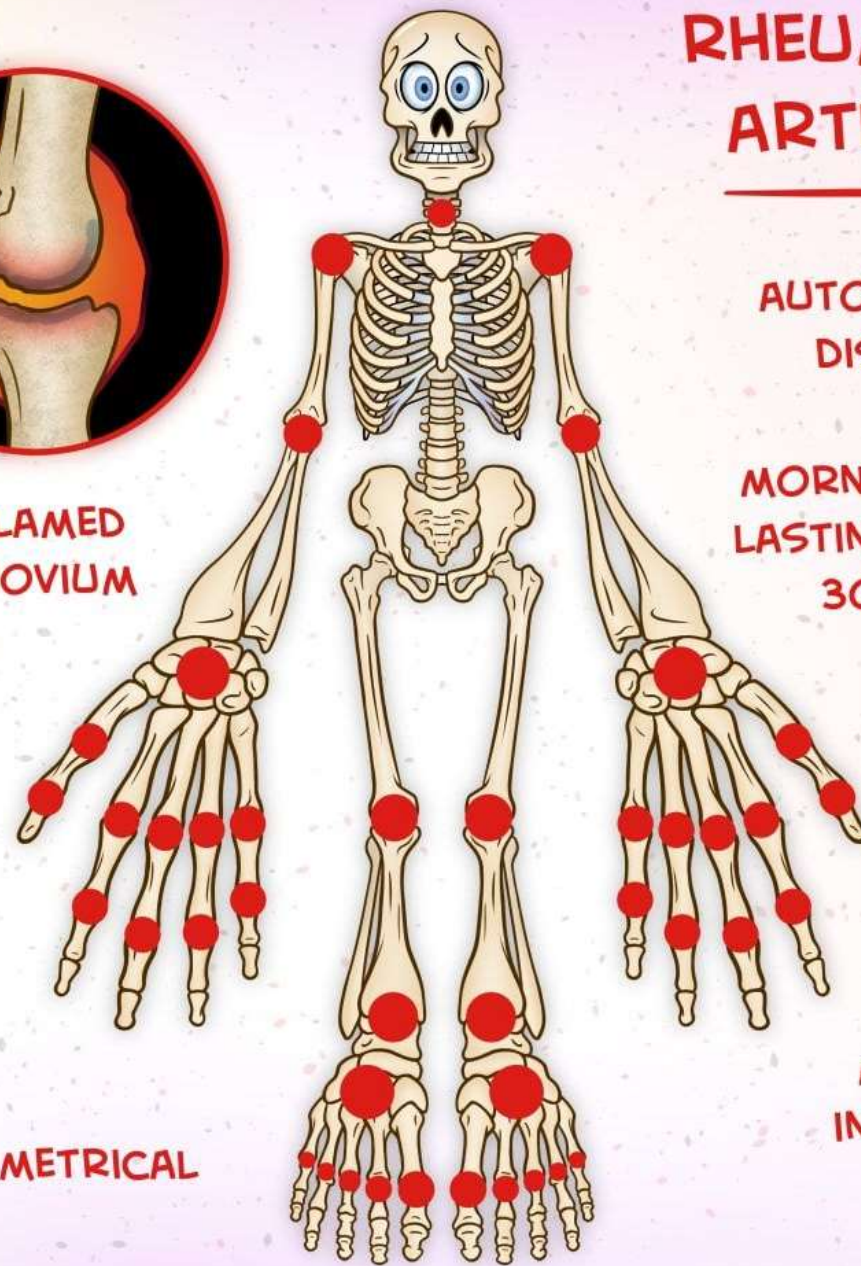
SYMMETRICAL

RHEUMATOID ARTHRITIS

AUTOIMMUNE
DISEASE

MORNING STIFFNESS
LASTING MORE THAN
30 MINUTES

EXTRA-
ARTICULAR
INVOLVEMENT





Mornning
stiffness:

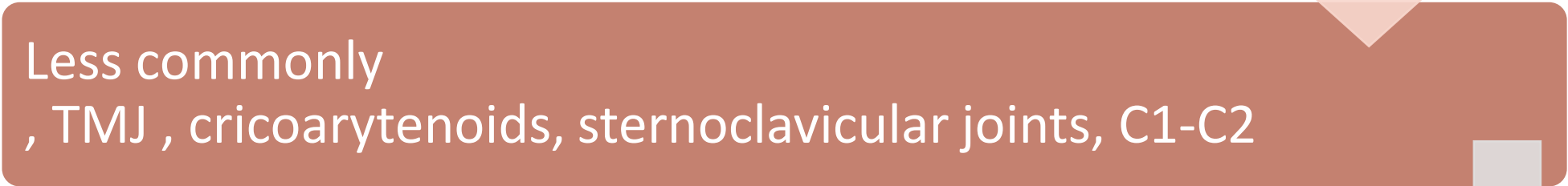
- Hallmark of inflammatory arthritis and is a prominent feature of RA .
- 

Articular Manifestation :

MCP, PIPS, MTP, Wrists, Knees, elbows, ankles, hips and shoulders.

An orange rectangular box with rounded corners. A light orange arrow points downwards from the bottom right corner of the box.

Less commonly
, TMJ , cricoarytenoids, sternoclavicular joints, C1-C2

A brown rectangular box with rounded corners. A light brown arrow points downwards from the bottom right corner of the box.

Never involved DIP.

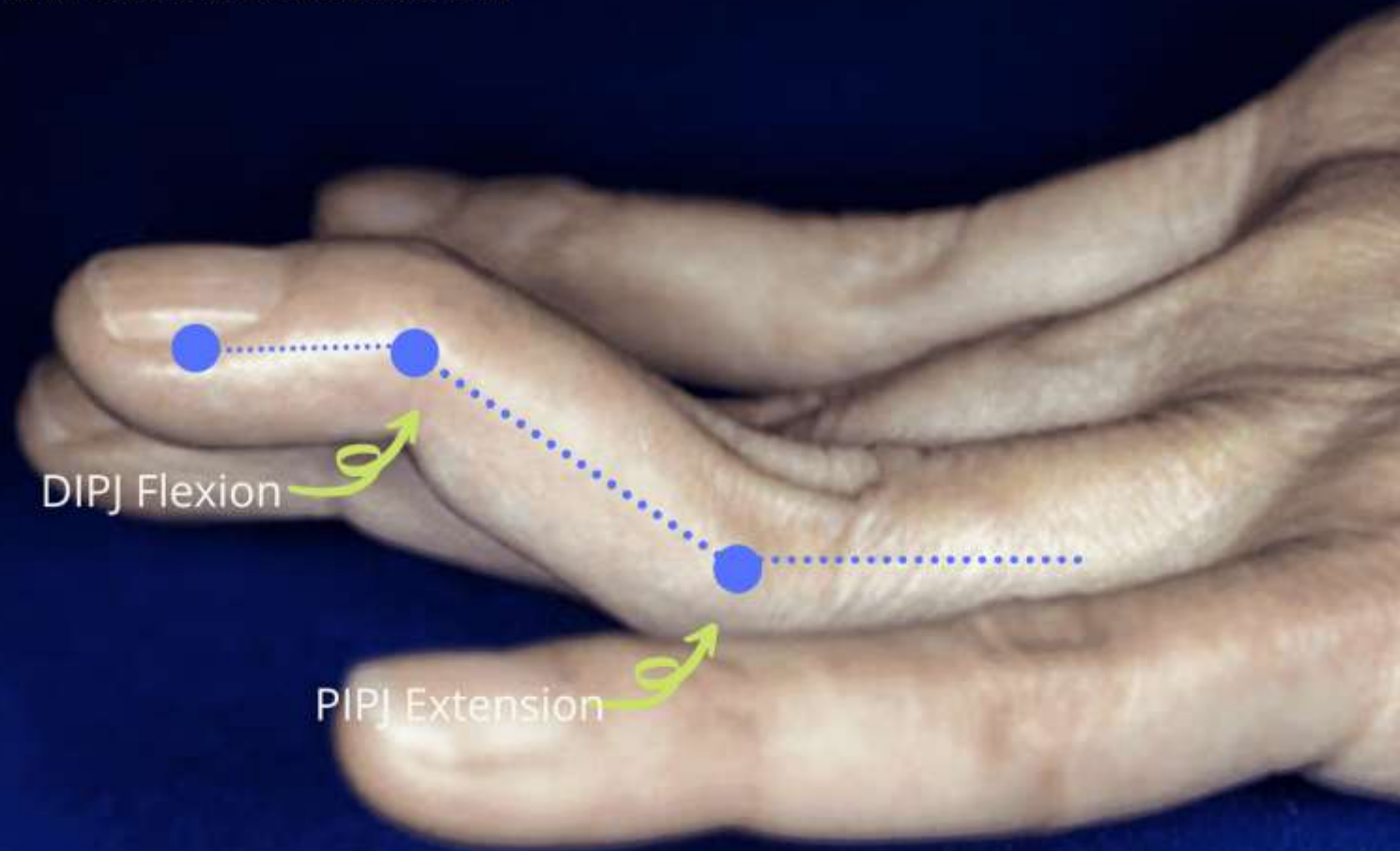
A grey rectangular box with rounded corners. A light grey arrow points downwards from the bottom right corner of the box.

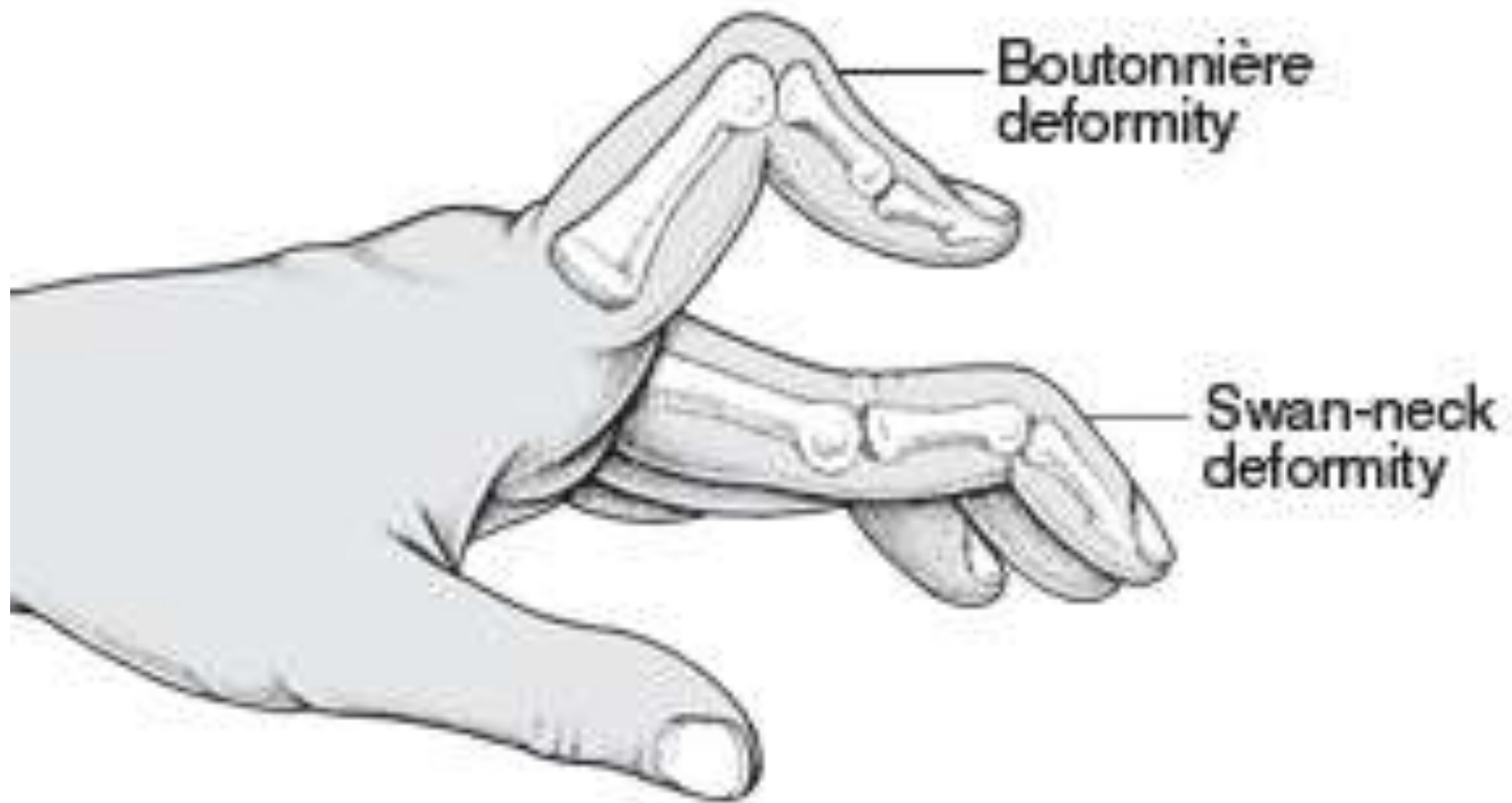


- PIP ARTHRITIS

SWAN-NECK DEFORMITY

THEPLASTICSFELLA.COM







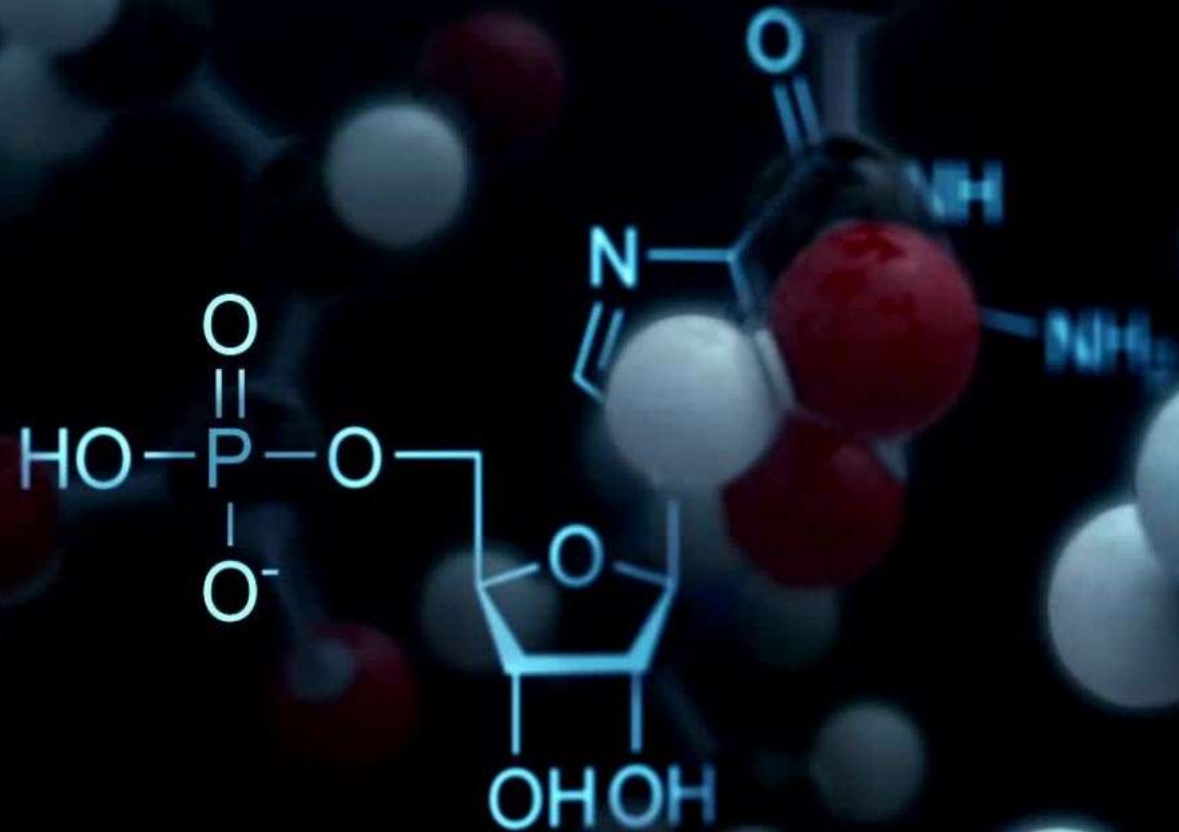


Laboratory findings :

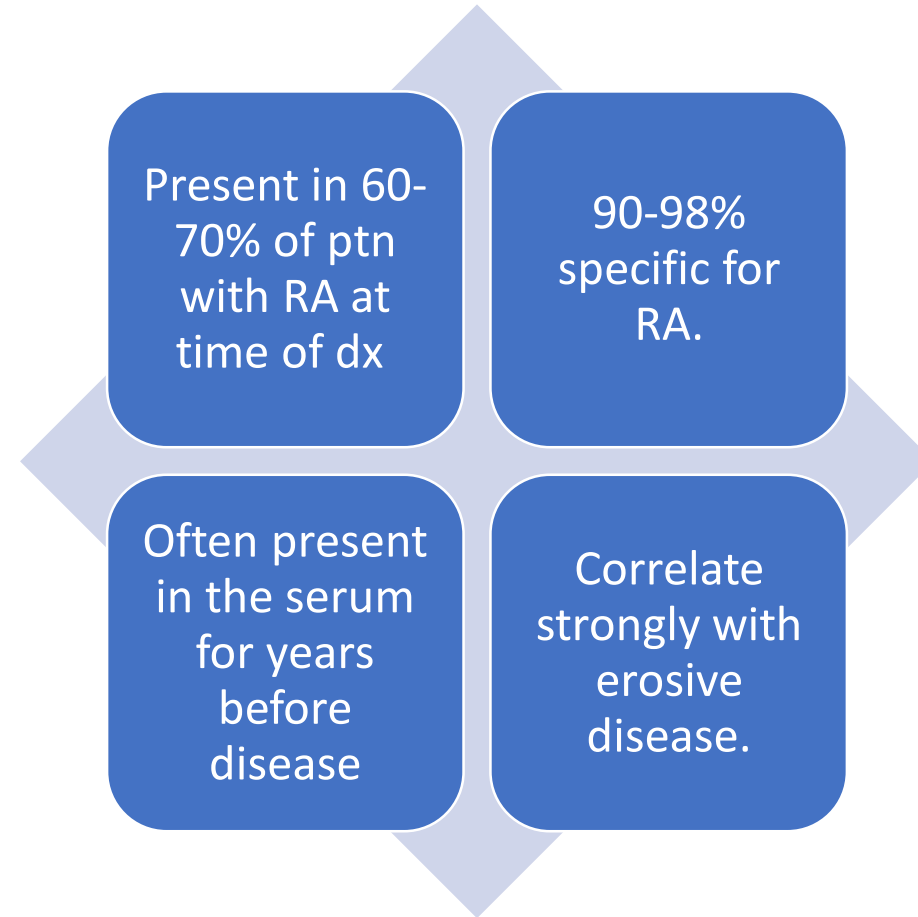
- Anemia
- Thrombocytosis
- Elevated inflammatory markers ; ESR ,CRP .
- RF
- ACCP
- ANA +VE in 30 %
- ANCA (perinuclear) 30 %

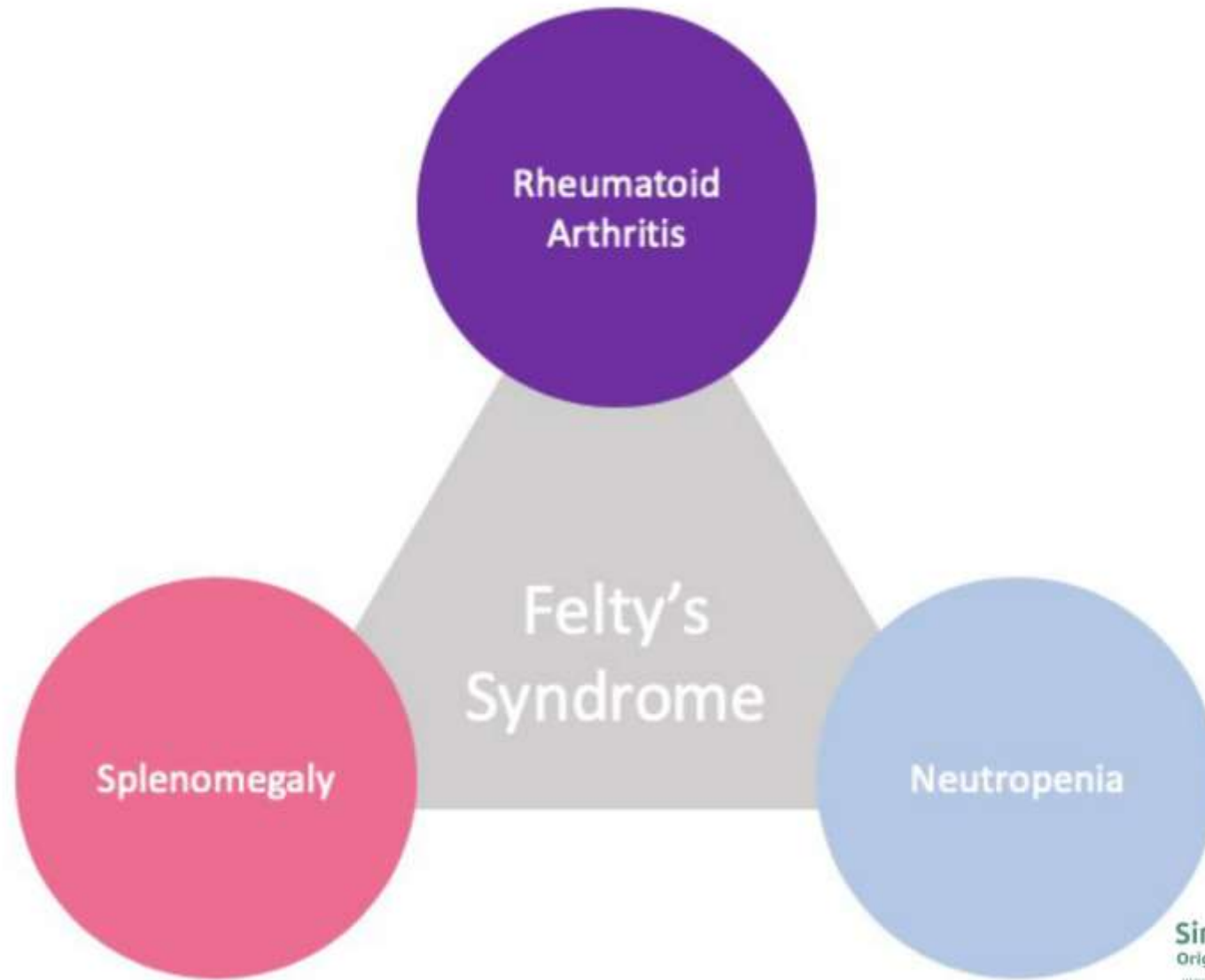
Rheumatoid factor :

- Sensitive
- Positive in 50 % of cases at presentation
- It is an autoantibody directed against autantibody ; IgM directed against Fc portion of IGG .
- Not specific can be present in Sogren, SLE, viral infxn, chronic inflammatory conditions , IBD, aging.
- Its prescence associated with more severe disease+all ptn with extra articular features are seropositive.



ACCP:



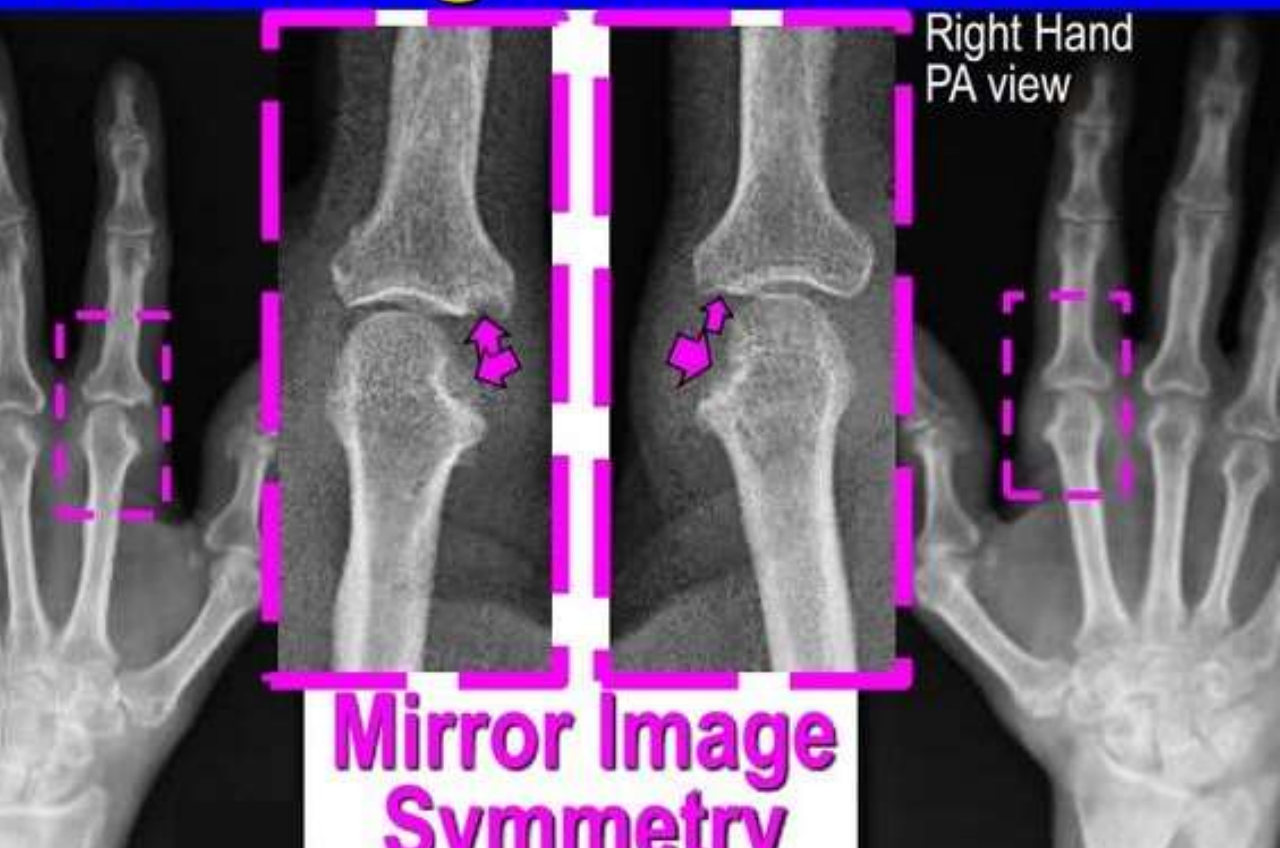




Imaging study :

- They show juxtaarticular demineralization , bony erosions.
- Radiographs of the hands and feet are an important part of the evaluation .
- Radiographs of knees , elbows, hips are not sensitive
- Radiographs of cervical spine can demonstrate c1-c2 sublaxation but MRI is the preffered method.

RA: Marginal Erosions



EULAR 2010 CRITERIA FOR DX:

2010 ACR/EULAR Classification Criteria for RA

JOINT DISTRIBUTION (0-5)

1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5

SEROLOGY (0-3)

Negative RF <u>AND</u> negative ACPA	0
Low positive RF <u>OR</u> low positive ACPA	2
High positive RF <u>OR</u> high positive ACPA	3

SYMPTOM DURATION (0-1)

<6 weeks	0
≥6 weeks	1

ACUTE PHASE REACTANTS (0-1)

Normal CRP <u>AND</u> normal ESR	0
Abnormal CRP <u>OR</u> abnormal ESR	1

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria...

→ **Prospectively** over time
(cumulatively)

→ **Retrospectively** if data on all
four domains have been
adequately recorded in the past



AMERICAN COLLEGE
OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

eular

DDX:

Viral syndroms

Psoriatic arthritis, reactive arthritis

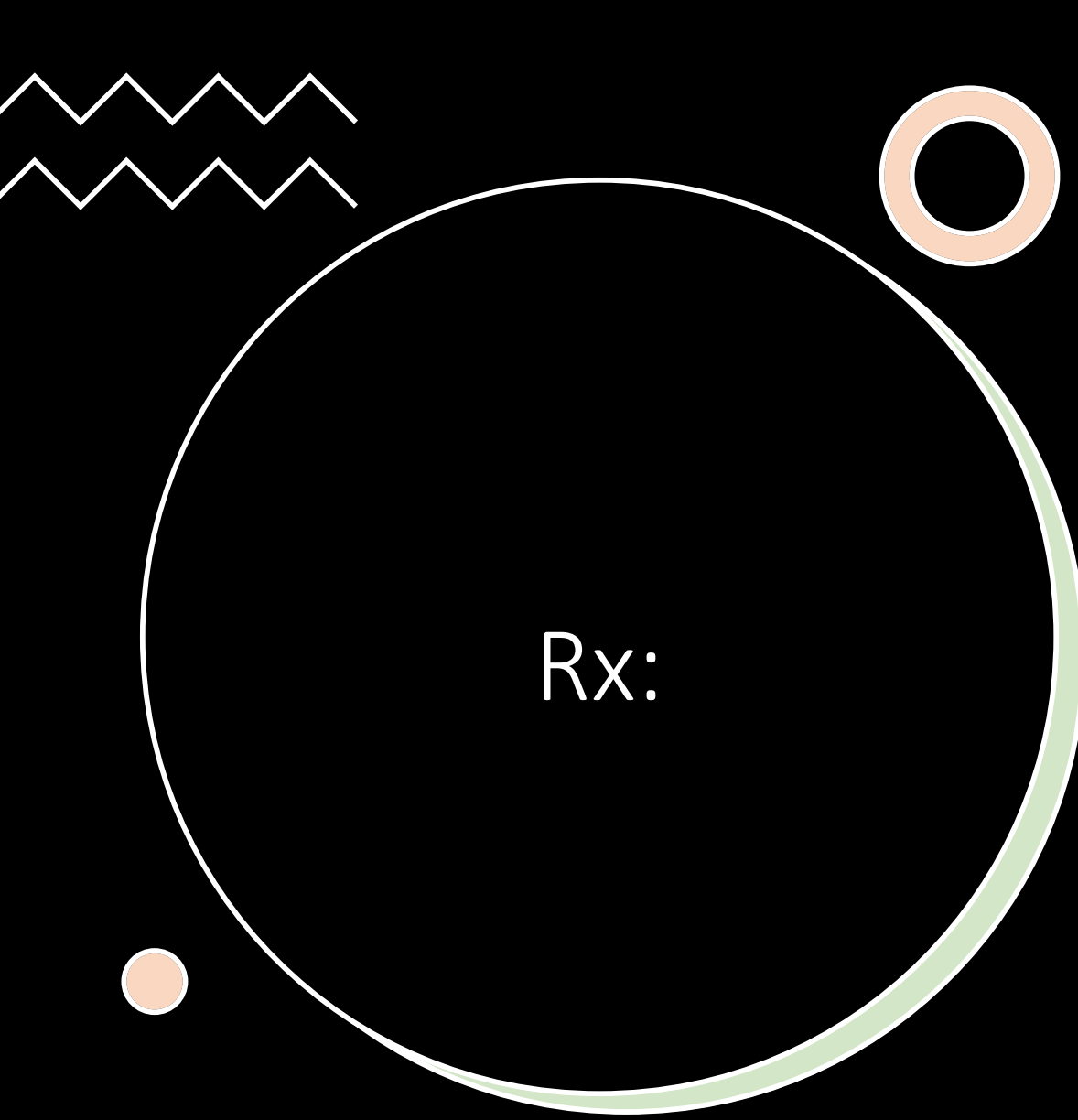
SLE

Polymyalgia Rheumatica

Paraneoplastic syndromes

Osteoarthritis

Sarcoidosis, lyme disease, rheumatic fever



Rx:

- DMARDs
- Biologic DMARDs
- Low dose corticosteroids



DMARDS;

- Methotrexate
- Hydroxychloroquin
- Sulfasalazine
- Leflunamide
- minocycline



Biologic :

Anti-TNF: Infliximab, etanercept ,
Adalimumab, Golimumab , Certolizumab

T-cell inhibitors : Abatacept

CD20 INH ; Rituximab

IL-6 inh , tocilizumab

IL-1 inh anakinra

Jak inh , tofacitinib

Disease activity scores :

Instruments	Thresholds of disease activity levels
Disease activity score in 28 joints (DAS 28) (range 0 - 9.4)	Remission: <2.6 Low activity: ≥ 2.6 to <3.2 Moderate activity: ≥ 3.2 to ≤ 5.1 High activity: >5.1
Clinical disease activity index (CDAI) (range 0 - 76.0)	Remission: ≤ 2.8 Low activity: >2.8 to 10.0 Moderate activity: >10.0 to 22.0 High activity: >22
Simplified disease activity index (SDAI) (range 0 - 86.0)	Remission: ≤ 3.3 Low activity: >3.3 to ≤ 11.0 Moderate activity: >11.0 to ≤ 26 High activity: >26

DAS28:

DAWN VISUAL DAS28 CALCULATOR
DAS 28 - Disease Activity Score Calculator for Rheumatoid Arthritis

We'd love to hear from you
Click here to give us your feedback

Enter Patient ID (for printing):

Joint Scores

Tender: 0

Swollen: 0

To enter joint scores, I prefer to:

☒ Use Mannequin

☐ Type totals

Additional Measures

☒ ESR: mm/hr

☐ CRP: mg/l

☒ Patient Global Health: 0 mm

0 - Best Worst - 100

DAS28

Calculate

Tender Joints

Swollen Joints

Click affected joints

Clear all

Clear all

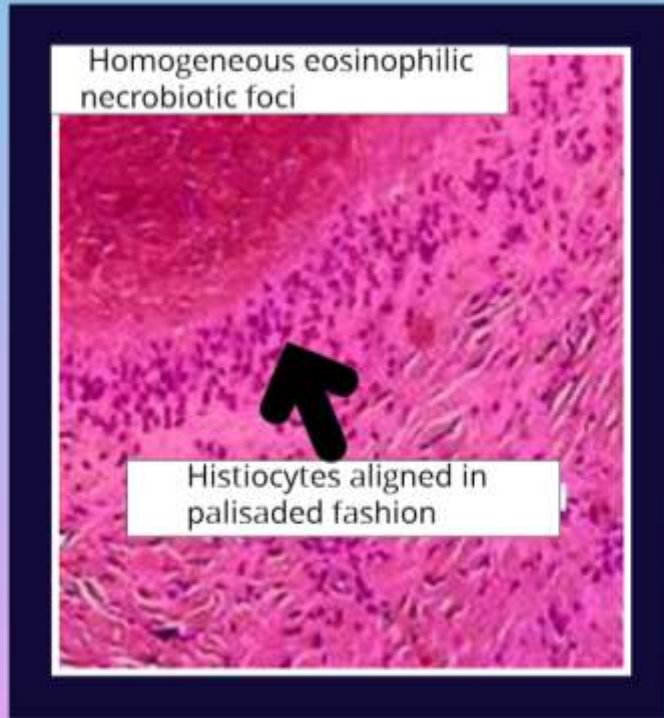
FORMULA: $DAS28(4) = 0.56 \cdot \sqrt{t28} + 0.28 \cdot \sqrt{sw28} + 0.70 \cdot \ln(ESR) + 0.014 \cdot GH$ Reference: <http://www.das-score.nl>

Click ? for safety warnings, printing help & explanation of cookie usage. WebDAS Version 4.06 [Contact us](#)

Mucosal	Sicca symptoms (ocular, oral , vaginal) Sogren syndrom
ocular	Keratoconjunctivitis sicca, episcleritis, scleritis, scleromalacia perforans, peripheral ulcerative keratitis
pulmonary	NSIP, UIP, COP, bronchiectasis, bronchiolitis obliterans , pleuritis and pleural effusion, rheumatoid nodulosis Caplan syndrome
cardiac	Pericarditis and pericardial effusion Constrictive pericarditis Valvular thickening and nodulosis Coronary vasculitis myocarditis
Haematologic and lymphatic	Anemia of chronic disease, felty syndrome, large granular lymphocyte leukemia Extremity lymphoedema uni or bilateral
neurologic	Compression nneuropathies Atlantoaxial subluxation Peripheral neuropathy Mononeuritis multiplex phachymeningitis
renal	AA amyloidosis Necrotizing crescentic glomerulonephritis

Rheumatoid nodules develop in adults and in children and is slightly more common in females

These are usually situated near bony structures close to a joint





Adults -Onset Still Disease





AOSD

- Multisystem inflammatory disease of unknown cause
- Rare ; incidence of 0.16/100,000
- Males=females
- Late teenage –early adulthood ,but 25% after age of 35 y.o.
- Starts with systemic manifestation, fever ,rash.

AOSD



Single episode(monocyclic)



Recurrent (polycyclic)lasting weeks to months



Or chronic articular disease with or without recurrent systemic flares may follow the initial systemic episode.



Fever:

Quotidian, with spikes >39 followed by return to normal without antipyretic rx.

Occasionally, the fever is double quotidian (two spikes daily)

In small percent low-grade fever persists between spikes

Associated with profound constitutional symptoms



Rash:

- Salmon-colored , macular or maculopapular eruption
- Affecting the trunk , the extremities,spares the face, palms, soles.
- Often appear during febrile attacks
- Asymptomatic but might be mildly pruritic.
- Koebner phenomenon; scratching uninvolved skin can elicit rash







pharangitis

- Non suppurative pharangitis often earliest symptom of AOSD.
- 



ARTHRITIS

Polyarthralgia is common at onset of AOSD without clinically detectable joint inflammation.

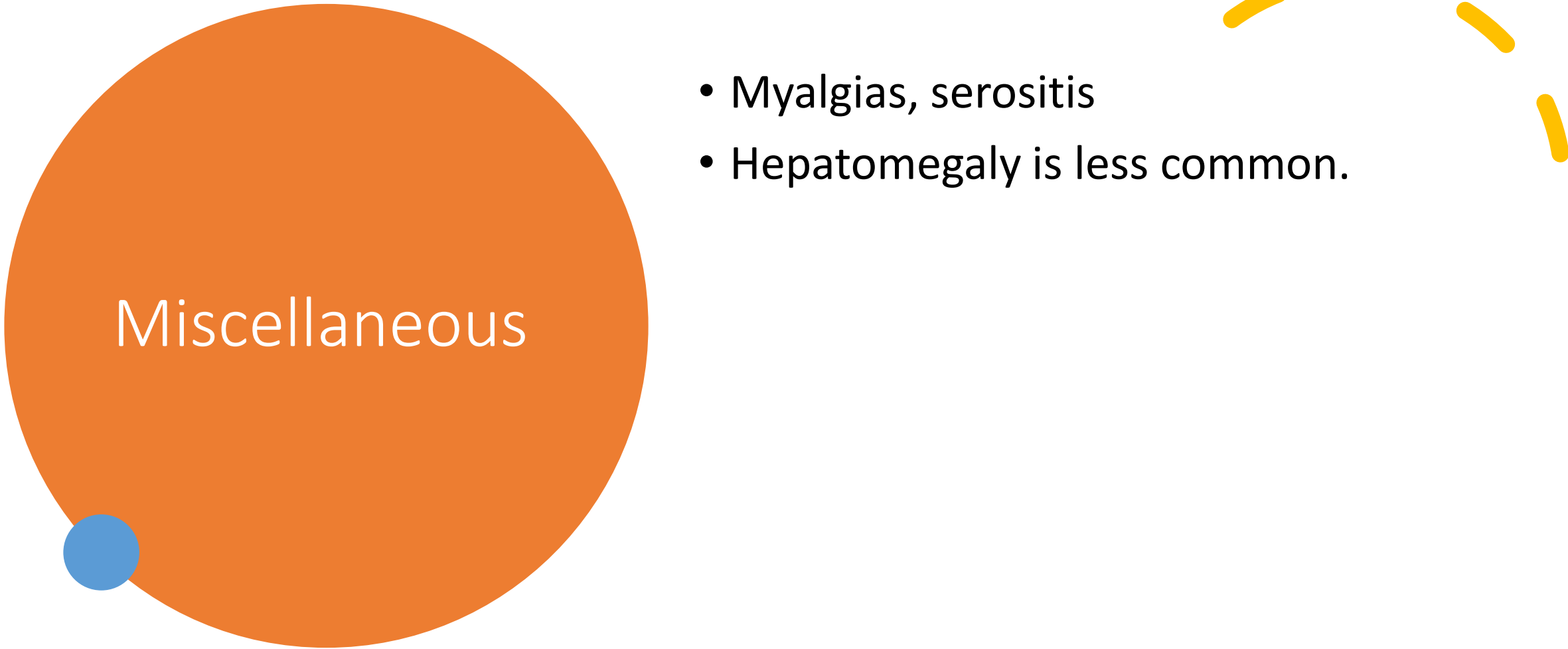
However , synovitis can develop in large joints (pelvis, knees, shoulders , hips), less common in small joints.

It can persist after resolution of fever and leads to chronic destructive arthritis in 20% of ptn .



Lymphadenopathy

- Particularly cervical L.N, and Splenomegaly are present in 50% of ptn at time of initial dx .



Miscellaneous

- Myalgias, serositis
- Hepatomegaly is less common.

Laboratory finding :

- >80% have leukocytosis , neutrophill predominant often exceed 15.000cell/mcl
- High ESR, CRP
- >90 % have elevated serum ferritin
- Elevated liver enzymes
- Normochromic, normocytic anemia
- Low albumin
- Cr , urine normal



Yamaguchi classification criteria for AOSD

Major crieteria	Fever >39 lasting more than 1 week Arthralgia or arthritis >2 weeks Characteristic rash Wbc >10.000 with neutrophill > 80 %
Minor criteria	Pharyngitis or sore throat Lymphadenopathy Hepatomegaly or splenomegaly Liver enzymes abnormality -ve test for RF, ANA
Exclusion criteria	Absence of infxn Absence of malignant disease Absence of inflammatory disease
Dx needs 5 crieteria , at least two major	

DDX

MALIGNANCY	Hodgkin disease Non-hodgkin lymphoma Renal cell carcinoma
Acute viral infxn	Adenovirus Erythrovirus,rubella, EBV, CMV,HIV Hepatitisb
Other infxns	acute lyme disease Secondary syphilis, brucellosis , relapsing fever Chronic meningococcemia,SBE, miliary TB , ACUTE FUNGAL INFXN
Autoimmune diseases	SLE Systemic vasculitidis
Hereditary periodic fever syndromes	Tumor necrosis factor associated periodic syndromes
Postinfectious disorders	Acute rheumatic fever Poststreptococcal infxn Reactive arthritis
miscellaneous	Drug hypersensitivity,schnitzler syndrome



Rx

- Systemic glucocorticoids
- NSAID
- Methotrexate in refractory cases for steroids
- Anakinra
- Tocilizumab
- Cyclosporin
- IVIG

Prognosis:

Variable

Remission occurs in one third of ptn after extended symptomatic period last up for one year

Polycyclic course relapse can occur years after initial episode with remission between flares

Persistent active clinical course with arthritis prominent symptom

spondyloarthritis:

- Sacroiliitis
- Spondylitis
- Enthesitis
- Oligoarthritis
- Uveitis

They
include:

Ankylosing spondylitis

Psoriatic arthritis

Arthritis of inflammatory bowel
disease

Reactive arthritis

Ankylosing Spondylitis:

- Typical ptns are young, white, males under the age of 40.
- M:f 3:1
- Seronegative arthritis

Clinical findings :

- **Axial spine :**

Inflammatory back pain and stiffness worsened by rest and improved with movement

Morning stiffness more than 30 min

Physical exam mostly normal

Abnormalities appear in ptn with progressive disease; loss range of motion

Loss of normal lordosis in lumbar involvement

Schober test more than 5 cm difference

Peripheral arthritis

- Hands and feet are rarely involved
- Hips and shoulders become involved in 50 % of cases.

Enthesitis

- Enthesitis of costosternal joints leads to chest wall pain that mimic pleuritic, pericardial or anginal pain .
- Achilles tendon insertion or over the attachment of plantar apponeurosis in 10% of AS .

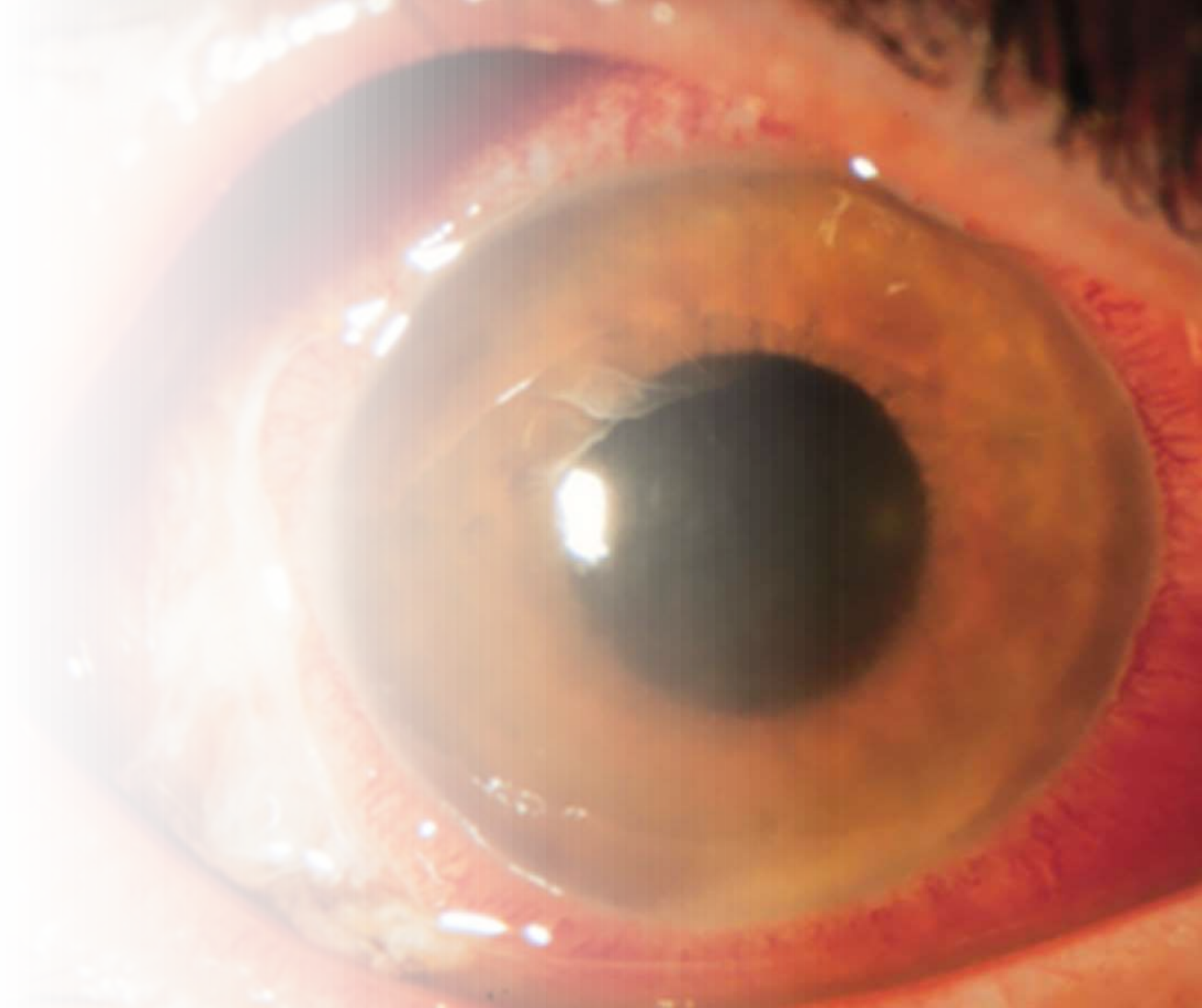


Ocular:

- Anterior uveitis in 30% of cases

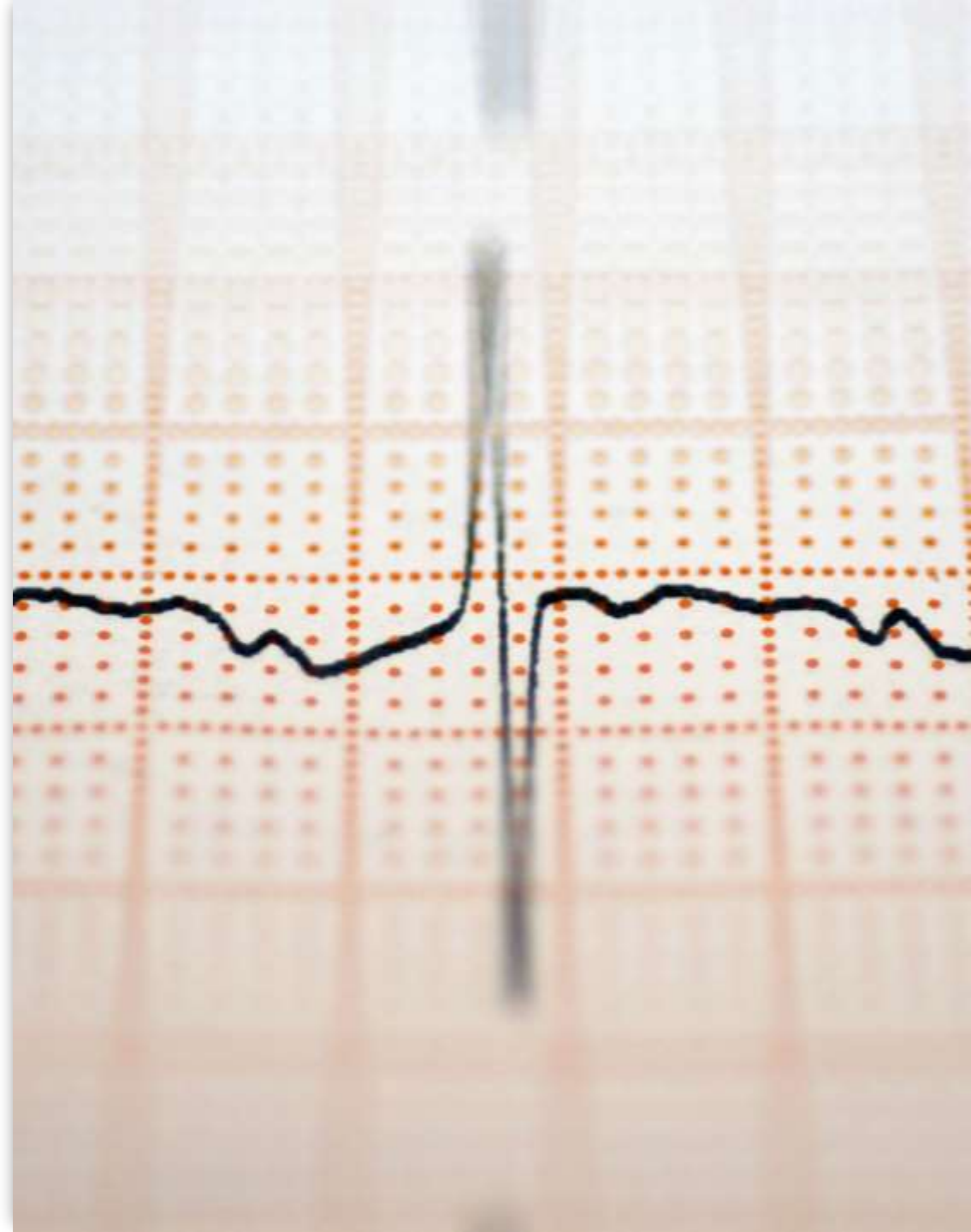


-
- Intense pain
 - Redness
 - Photophobia



cardiac

- First degree AV block
- Aortic regurgitation



neurologic

- Cauda equina syndrome is rare, due to entrapment of exiting lumbar and sacral nerves through the inflamed spinal column
- Spontaneous atlantoaxial subluxation (distance greater than 3-4 cm b/w anterior aspect of odontoid and posterior aspect of the anterior arch of atlas in the lateral maximal flexion)



others

- Secondary renal amyloidosis
- IgA nephropathy
- Apical pulmonary fibrosis

Laboratory findings :

- Usually haematologic studies are normal.
- ESR , CRP elevated in 50% of cases
- RF, ANA NEGATIVE
- HLA-B27



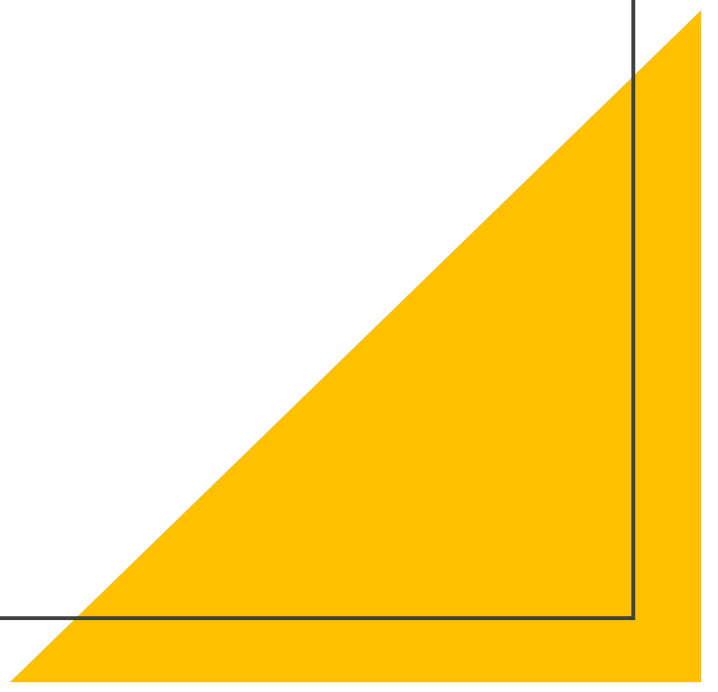
HLA- B27

- Occur in 85% of patient
- Occur in 8-10% of the normal white american population.
- But Spondyloarthritis will not develop in the vast majority of >90 % of people with HLA-B27
- HLA antigens are inherited in a mendelian dominant fashion the risk of inherited this tissue type is 50% for each of a patients children , the likely hood of developing arthritis is 20%, so without the knowledge of HLA status, every child of a ptn with HLA B27 +VE spondylitis has a roughly 10 % chance of developing spondylitis.

Imaging study

- Sacroiliac joint :
- Is the single most specific test for this disorder, it is part of entry criteria
- We need a single anteroposterior view of the pelvis.

Imaging sacroiliac joint:

- Earliest radiographic change is usually bony sclerosis on the iliac sides of joint margins.
 - Bony erosions
 - Pseudowidening
 - Fusion of sacroiliac joint
 - These changes usually bilateral and symmetrical
- 
- A large yellow right-angled triangle is positioned in the bottom right corner of the slide, with its hypotenuse running from the bottom left towards the top right.



A



B



Radiological finding in spine

- Shiny corners(erosions on anterosuperior and anteroinferior corners of vertebral bodies)
- Squaring of vertebral bodies.
- Syndesmophytes due to calcification and ossefication of the ligament structures b/w vertebral bodies.
- Can be missed with DISH (diffuse idiopathic skeletal hyperostosis).



International
society
classification
criteria for axial
spondyloarthritis:

- In patients with back pain > 3 months and age at onset < 45 years.

- Sacroiliitis on imaging

HLA B27

PLUS

PLUS

> 1 SpA feature
SpA features

> 2 other

Sacroiliitis on imaging : active inflammation on MRI
highly suggestive of sacroiliitis.

SpA Features: inflammatory back pain, arthritis,
uveitis, dactylitis, psoriasis, inflammatory bowel
disease, good response to NSAID, family hx of SpA,
HLA B27, HIGH CRP.

RX :

- NSAID : used as first line medical therapy to relieve the pain and stiffness
- DMARD:mtx , sulfasalazine , leflunamide (for peripheral arthritis they are not effective for axial spondyloarthritis)
- Anti –TNF
; etanercept, infliximab, adalimumab, golimumab .



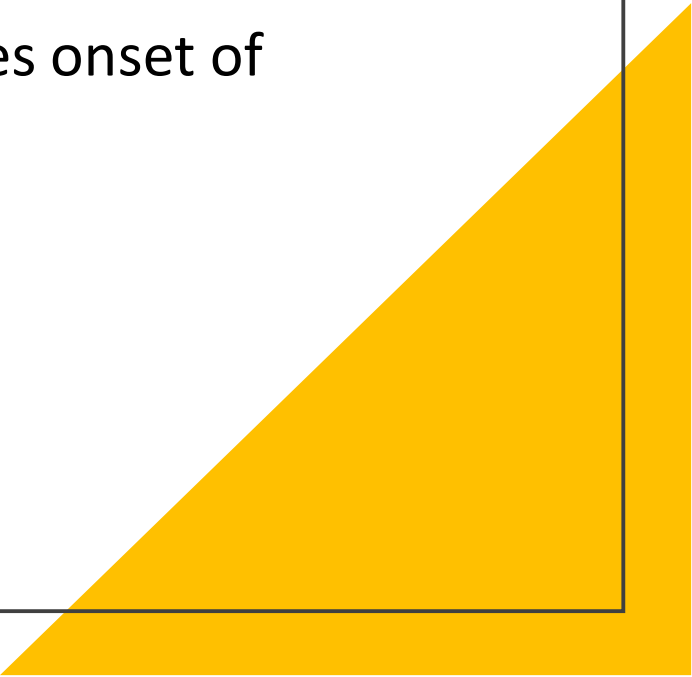
Psoriatic Arthritis

-
-

- Seronegative arthritis
- One of the spondyloarthritidis
- Chronic inflammatory arthritis associated with nail and skin psoriasis.
- Axial arthritis
- Polyarthritis affecting DIP.
- Develop in 20-30 % with psoriasis.
- Mean age 30-55 years
- Men and women are equally affected

Pathogenesis :

- Genetic susceptibility studies indicate association with HLA-B27, HLA-B13, HLA-B7, HLA-B57
- Also other susceptibility loci ; IL – 23, TNF, IL-4, IL-13,
- Infectious trigger has been suspected ; group A streptococcal infxn have been implicated in guttate psoriasis

- 
- A large yellow triangle is positioned in the bottom right corner of the slide, pointing towards the top right.
- Psoriatic arthritis typically develops after or coincident with the onset of psoriasis
 - 15-20% arthritis precedes onset of psoriasis by 2 years .

Modes of presentation :

- Asymmetric oligoarthritis
- Symmetric polyarthritis (most frequent)
- Destructive arthritis (arthritis mutilans)

Clinical findings

-
-

- Arthritis:
- Asymmetric oligoarthritis vs symmetric polyarthritis
- Involving DIP , ddx :gout , OA
- Joints involved ; DIP, KNEE , HIPS , STERNOCLAVICULAR JOINTS.
- Arthritis mutilans , represent end stage arthritis ,where loss of bony architecture allows complete subluxation , and telescoping of the involved digit (opera glass finger)





2.dactylitis:

- Sausage digits :occur in one third to one half of psoriatic arthritis
- More common in feet than hands .
- Associated with more severe radiographic damage



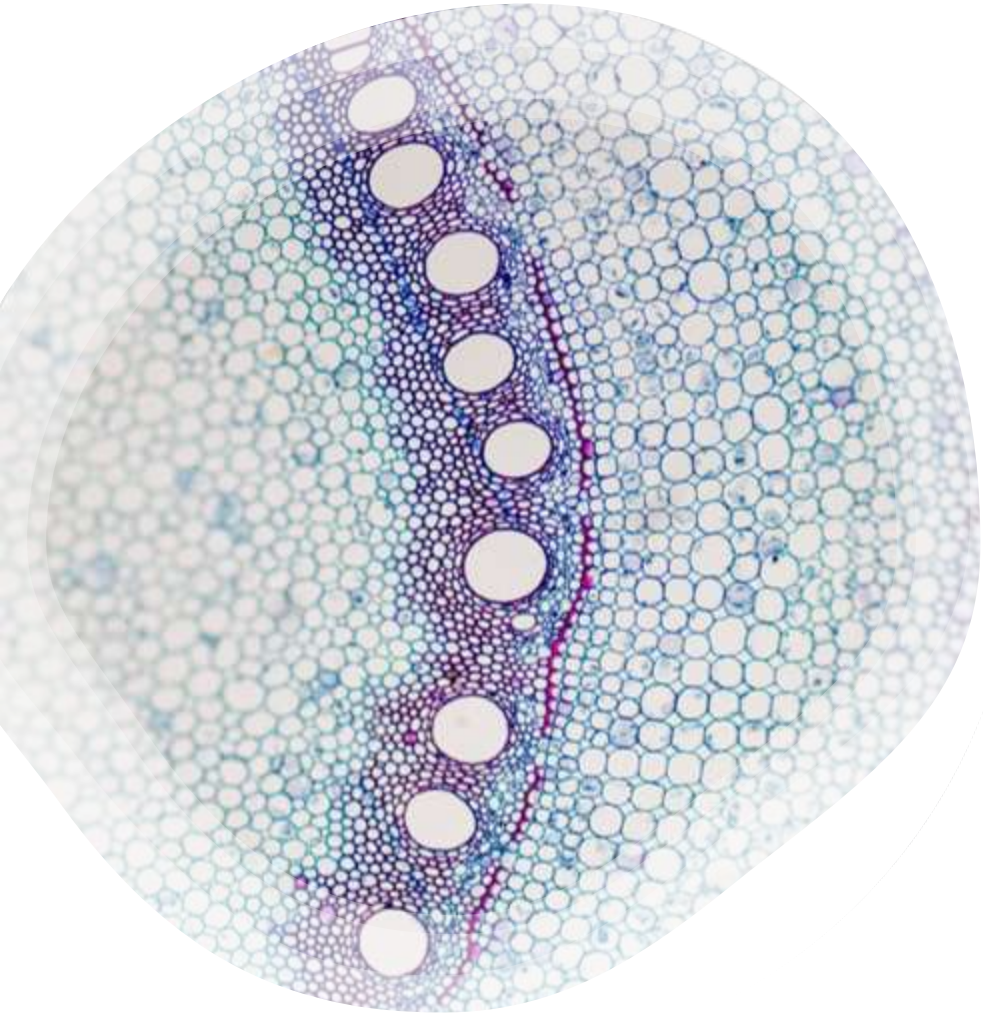
3.enthesitis

- Occure in 40 % of ptn with psoriatic arthritis

4.skin and nail changes

- Many ptn with psoriatic arthritis have only mild to moderate skin changes , no correlation between degree of psoriasis and extent of joint involvement .
- Nail involvement is common in psoriatic arthritis





5.spondyloarthropathy

- Symptomatic involvement of sacroiliac joint and axial skeleton is less common than peripheral joint .
- Sacroiliitis in psoriasis is unilateral .



Extraarticular manifestation :

- Ocular, oral , urethritis

Laboratory finding :

- 20% of ptns have hyperurecemia
- High ESR, CRP but to a lesser degree
- Up to 10 % of psoriatic arthritis have positive RF !
- ANA +VE in 10-20 % of ptns

IMMAGING

- Most common finding joint space narrowing and erosions involving DIP , PIP.
- Asymmetric manner
- Periarticular osteopenia usually absent
- Pencil in cup appearance is characteristic
- New bone proliferation at sites of erosion (whiskering)



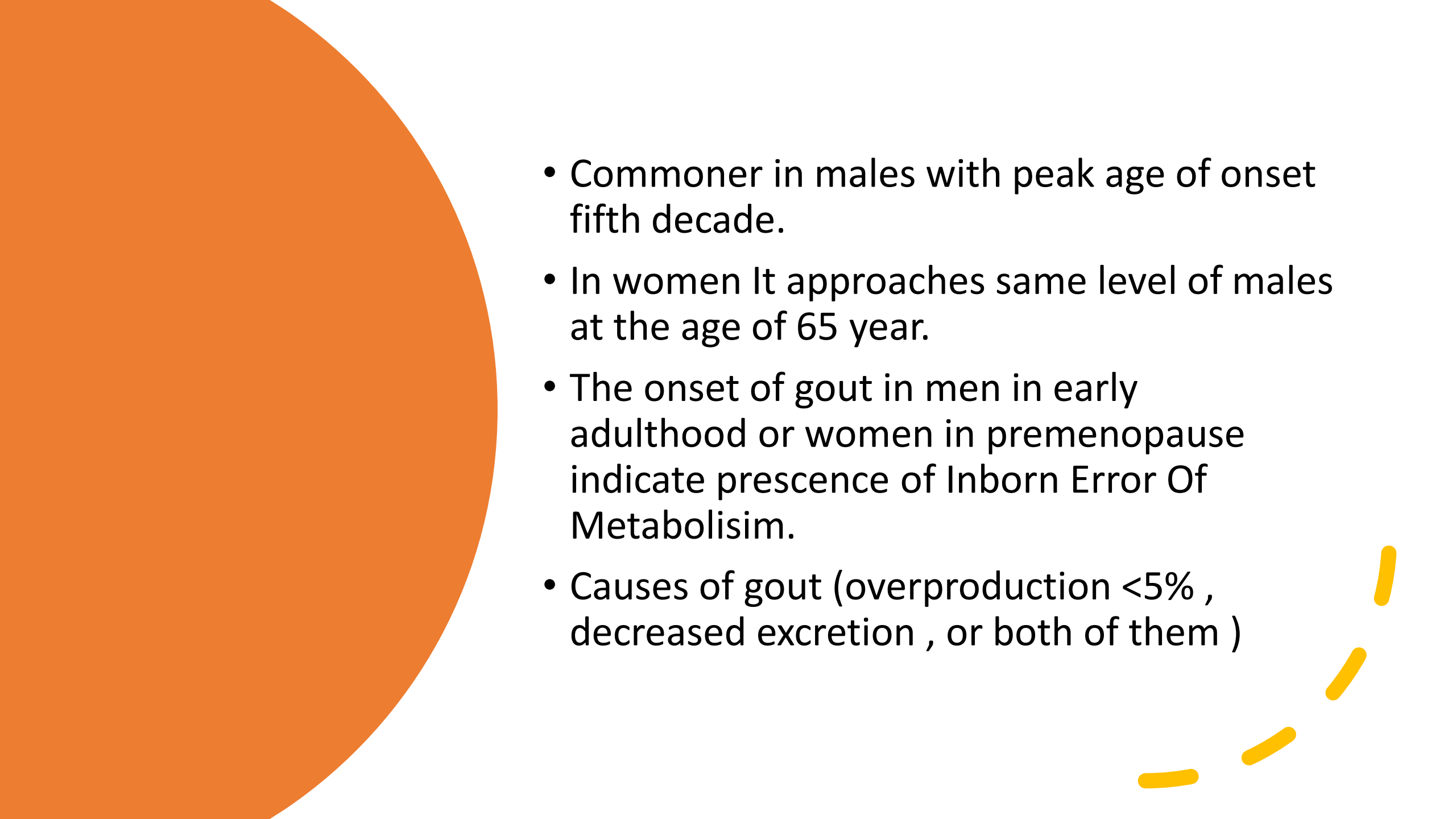
Rx

- NSAID
- MTX ; skin psoriasis+peripheral arthritis
- Sulfasalazine
- Leflunamide
- Anti-TNF
- IL-12 and IL-23 inhibitor Ustekinumab
- IL-15 Aremilast
- Jak inhibitors



gout

- Hyperurecemia is serum urate level >6.8 mg/dl
- 10% of asymptomatic American manifest hyperurecemia on at least one occasion during adulthood
- Likelihood of developing symptomatic gout and the age at which that occurs correlates with the duration and magnitude of hyperurecemia.
- In one study , persons with urate b/w 7 & 8 ml/dl had a cumulative incidence of gouty arthritis 3% while those with urate level >9 ml/dl had a 5 year cumulative incidence of 22%.
- It appears that clinical gout develops in fewer than 1 in 4 hyperurecemic persons at any time.

- 
- Commoner in males with peak age of onset fifth decade.
 - In women It approaches same level of males at the age of 65 year.
 - The onset of gout in men in early adulthood or women in premenopause indicate presence of Inborn Error Of Metabolism.
 - Causes of gout (overproduction <5% , decreased excretion , or both of them)

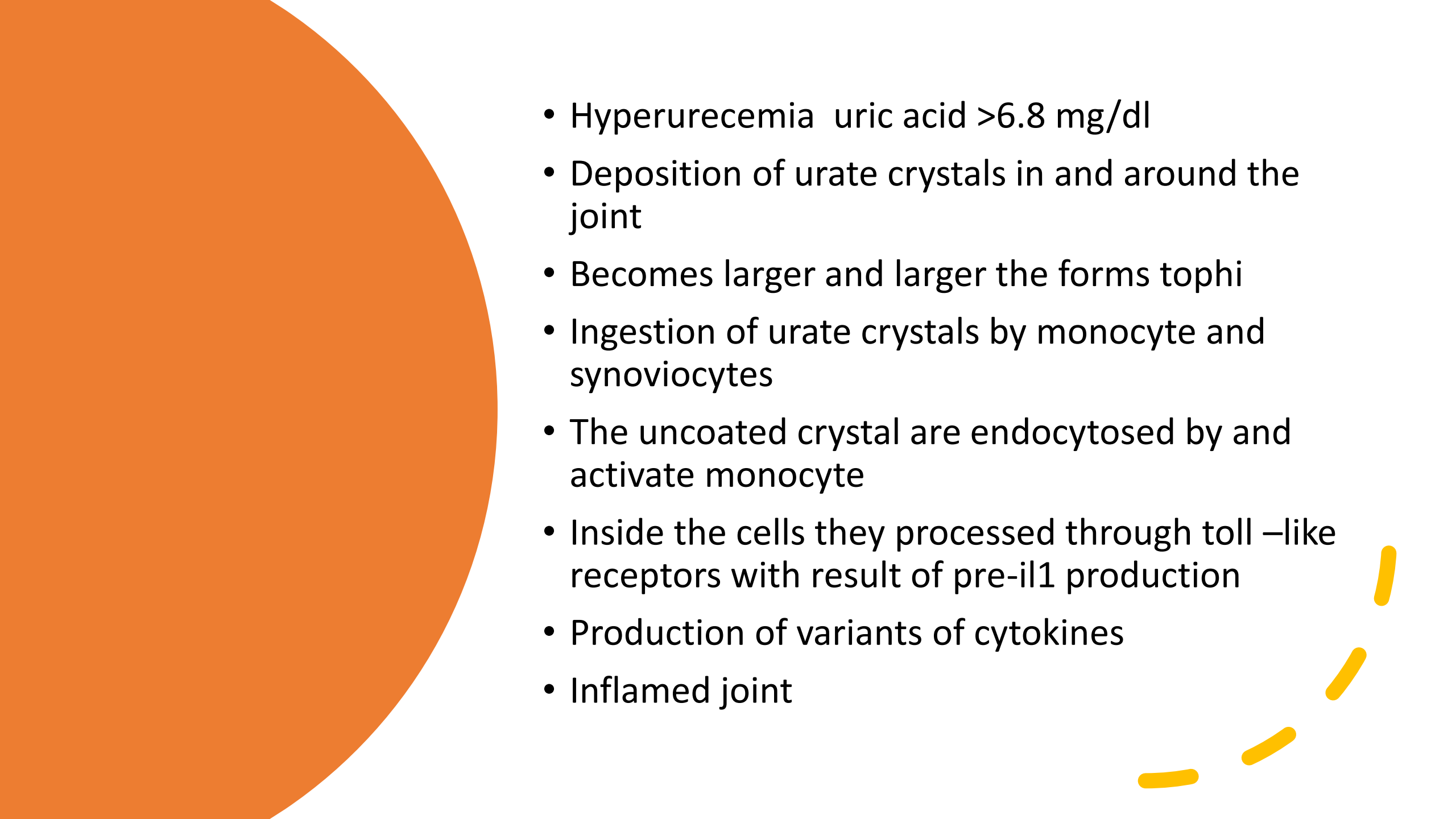


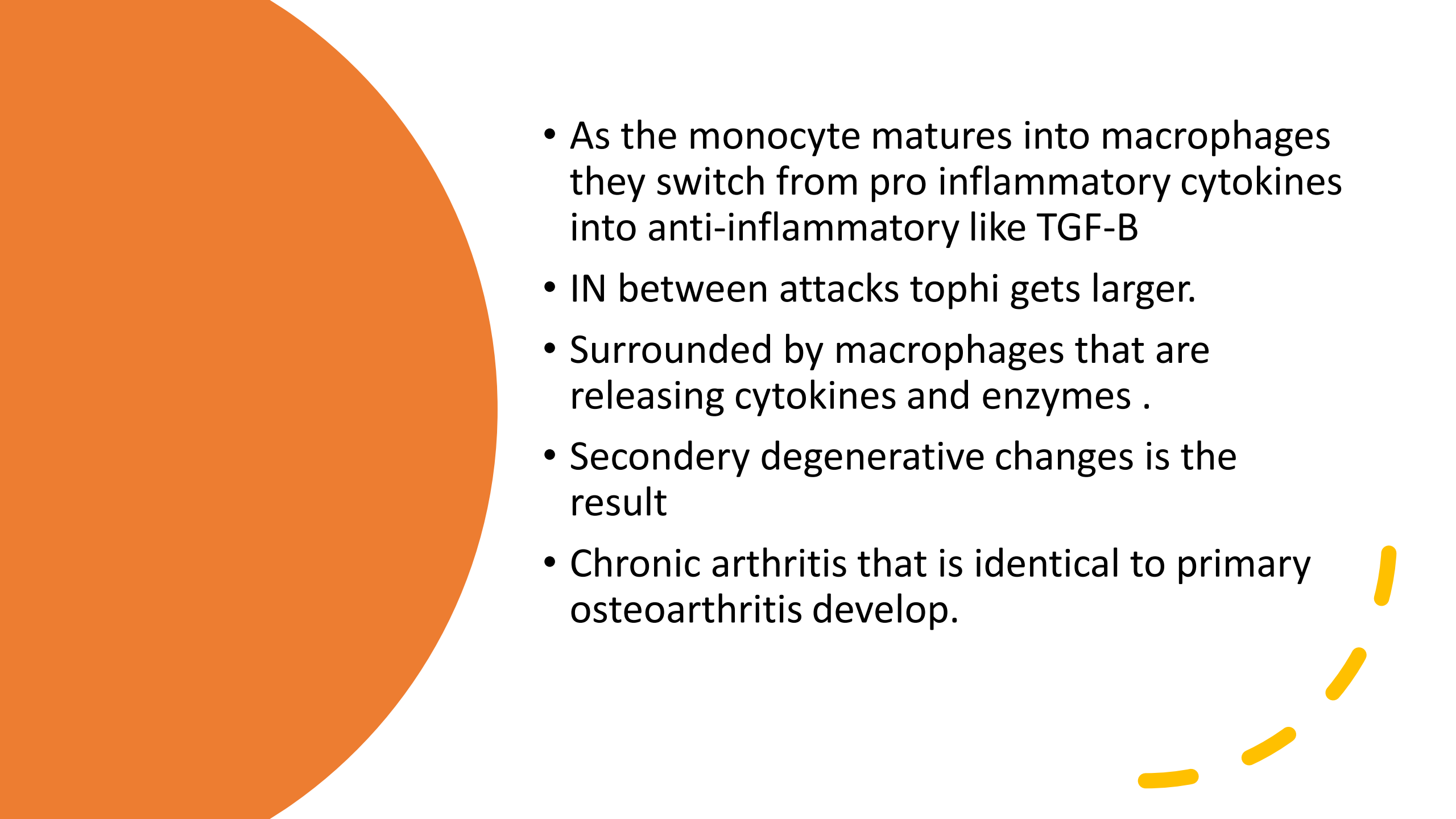
Uric Acid Overproduction

- **Primary hyperuricemia**
 - Idiopathic
 - Accelerated purine nucleotide synthesis (eg, HGPRT deficiency, PRPP synthetase overactivity)
- **Secondary hyperuricemia**
 - Excessive dietary purine intake
 - Increased purine nucleotide turnover (eg, myelo- and lymphoproliferative diseases, psoriasis)
 - Accelerated ATP degradation (eg, glycogen storage diseases, hypoxia and tissue underperfusion, ethanol abuse)

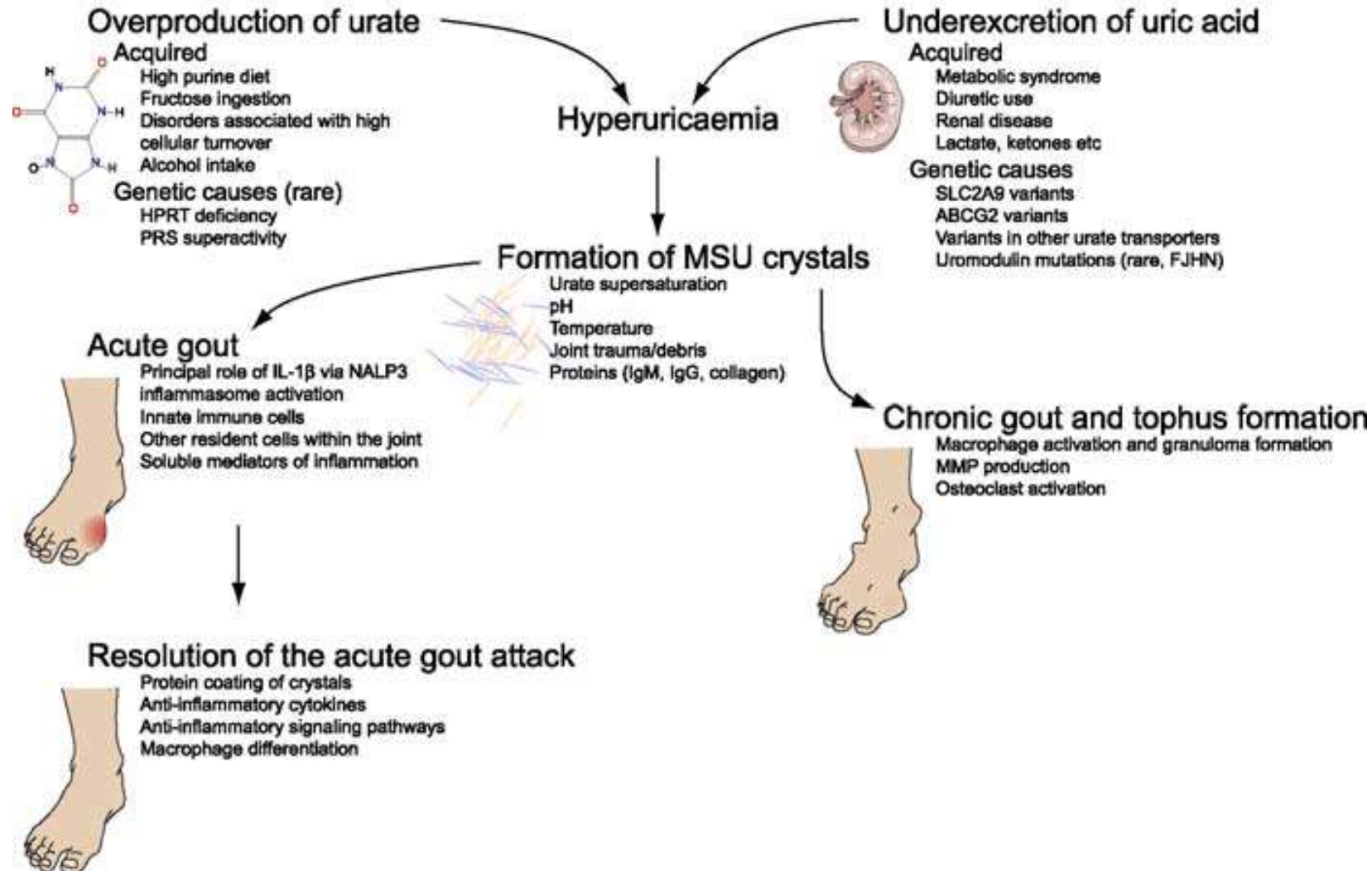
Impaired Uric Acid Excretion

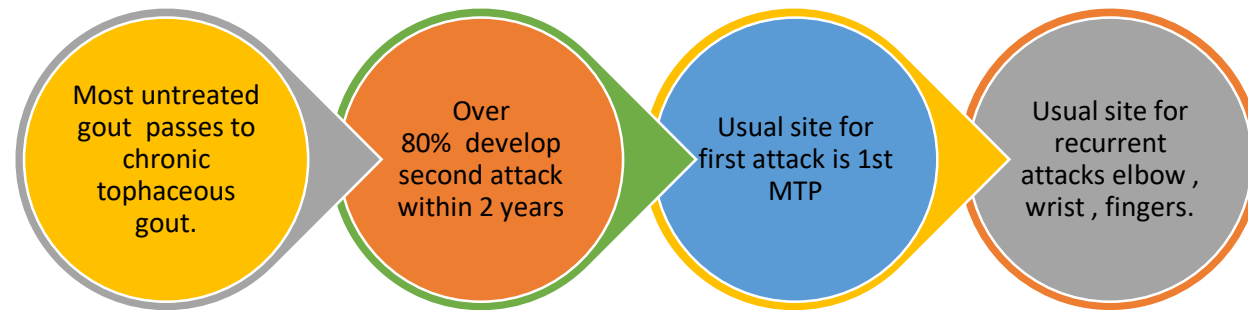
- **Primary or idiopathic hyperuricemia**
- **Secondary hyperuricemia**
 - Diminished renal function
 - Inhibition of tubular urate secretion
 - Competitive anions (eg, keto and lactic acidosis)
 - Enhanced tubular urate reabsorption
 - Dehydration, diuretics, insulin resistance (metabolic syndrome)
 - Mechanisms incompletely defined
 - Hypertension, hyperparathyroidism, certain drugs, lead nephropathy

- 
- Hyperurecemia uric acid >6.8 mg/dl
 - Deposition of urate crystals in and around the joint
 - Becomes larger and larger the forms tophi
 - Ingestion of urate crystals by monocyte and synoviocytes
 - The uncoated crystal are endocytosed by and activate monocyte
 - Inside the cells they processed through toll –like receptors with result of pre-il1 production
 - Production of variants of cytokines
 - Inflamed joint

- 
- As the monocyte matures into macrophages they switch from pro inflammatory cytokines into anti-inflammatory like TGF-B
 - IN between attacks tophi gets larger.
 - Surrounded by macrophages that are releasing cytokines and enzymes .
 - Secondary degenerative changes is the result
 - Chronic arthritis that is identical to primary osteoarthritis develop.

Key Checkpoints in Gout Pathogenesis





The Stages of Gout Progression

STAGE 1: High Uric Acid Levels

Uric acid is building up in the blood and starting to form crystals around joints

STAGE 2: Acute Gout

Symptoms start to occur, causing a painful gout attack

STAGE 3: Intercritical Gout

Periods of remission between gout attacks

STAGE 4: Chronic Gout

Gout pain is frequent and tophi form in joints



Laboratory finding

- High uric acid not mandatory
- Leukocytosis
- High ESR & CRP
- Synovial fluid analysis : consistent with moderate to severe inflammation

Wbc 5&80.000 with avg 15.000-20.000

Definitive dx by aspirating MUS (intracellular needle shape crystals) may be extracellular.

Associated hyperlipidemia, glucose intolerance

Radiology

- Distinct erosions in the involved joint with overhanging edges
- There is characteristic findings of (double contour sign) in us exam.



A



B





Podagra



complication

- Nephrolithiasis
- Joint destruction



treatment

- Providing rapid and safe pain relief
- Preventing further attacks
- Preventing formation of tophi and destructive arthritis
- Addressing associated medical conditions



- NSAID, COLCHICINE , PREDNISOLONE
- ALLOPURINOL , FEBUXOSTAT(XANTHINE OXIDASE INHIBITORS)
- PROBENECIDE
- BENZBROMARONE (URICOSURIC ACTION)
- PEGLOTICASE (THE MOST SPECIFIC)(ENZYMATIC OXIDATION OF URIC ACID)
- ANAKINRA (IL-1) INHIBITOR

- Can mimic gout , rheumatoid arthritis , osteoarthritis.
- Causes intermittent monoarthritis often of the knee or wrist.
- Dx established by CPPD crystals in joint fluid
- It is associated with other disease like haemochromatosis , hyperparathyroidism.

Calcium
pyrophosphate(pseudogout):



Linked to mutation in ANKH gene on
chromosom 5p

Through disordered inorganic pyrophosphate
transport mechanisim .

Low ratio of inorganic phosphate to inorganic
pyrophosphate favor CPPD crystal deposition.





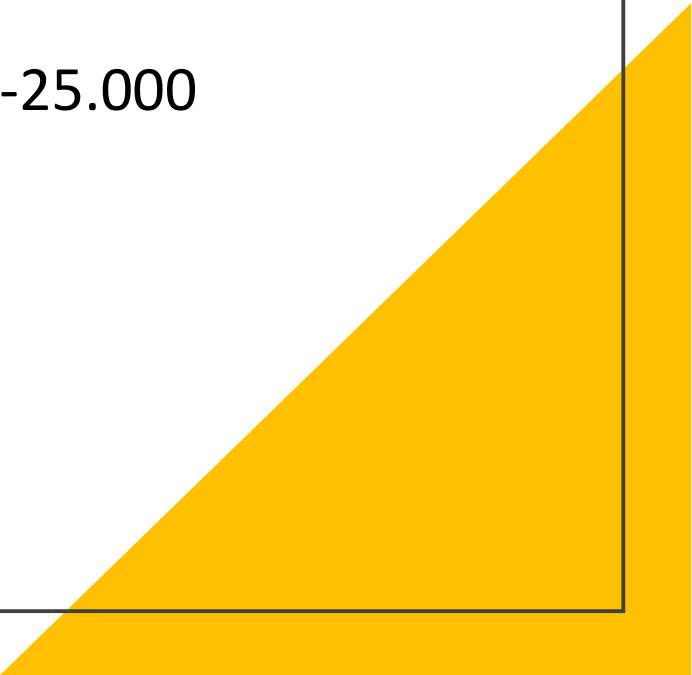
causes

- Aging
 - Genetics
 - Trauma
 - Endocrine and metabolic conditions(amyloidosis, hypomagnesemia, acromegaly, hypophosphatemia)
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Clinical findings:

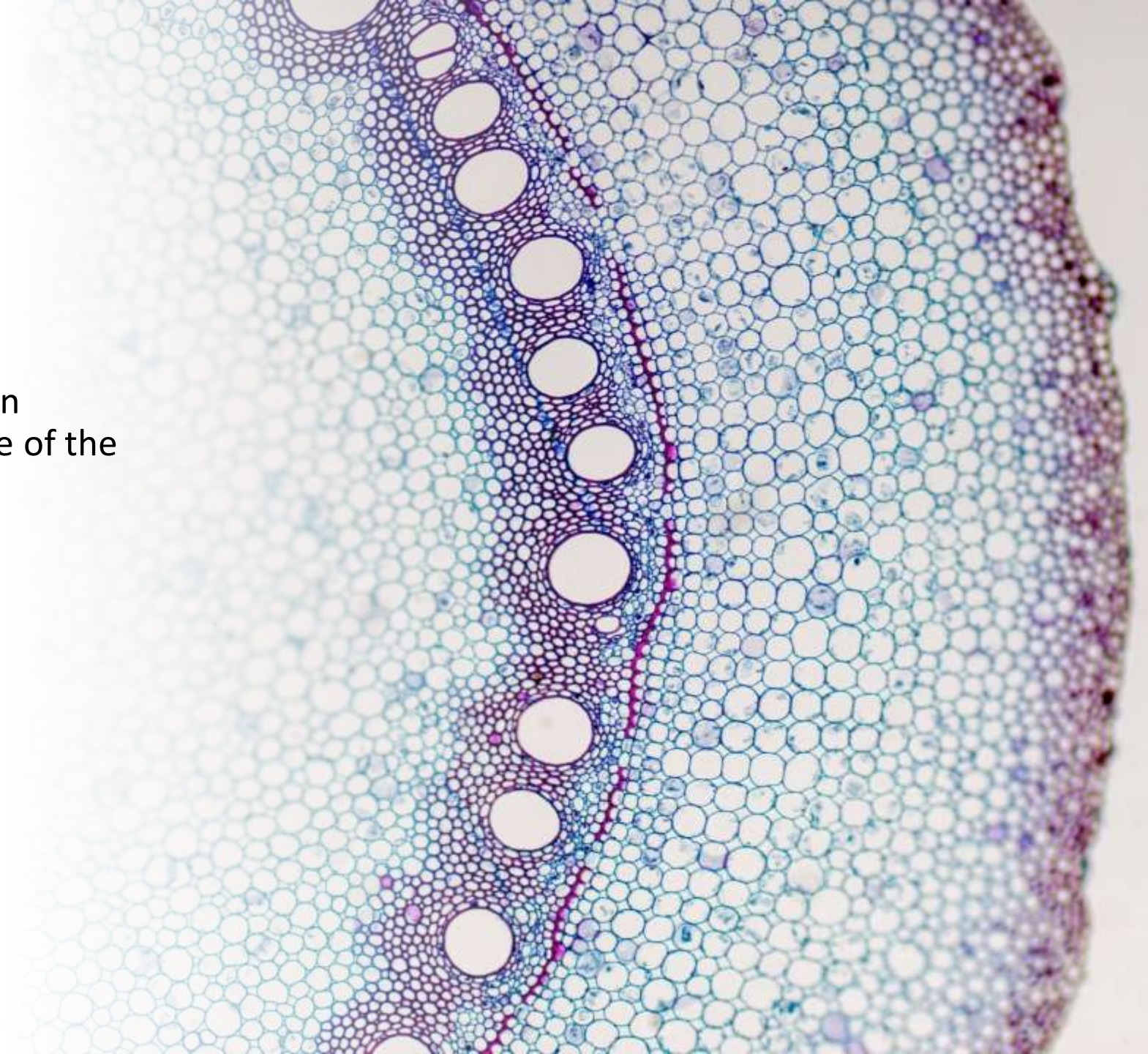
- Acute monoarticular inflammatory arthritis lasting for several days to 2 weeks affecting knees mostly , can involve 1 stMTP
- Symptoms mimicking RA can occur in 5%, small ptn of them have +ve Rf
- Nearly half of them have progressive degenerative disease termed " pseudo-osteoarthritis"
- Rarely CPPD crystal deposition occurs in axial skeleton , may lead to acute neck pain

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- CPPD CRYSTALS rhomboid – shaped and positively birefringent
 - Synovial fluid WBC 5000-25.000

radiographs

- Chondrocalcinosis esp in knees , triangular cartilage of the wrist, symphysis pubis.



- Tests should be done :
- Ca
- Ph4
- Mg, alkp
- Tsh
- Ferritin
- Ceruloplasmin

rx

- Acute attacks same as gout
- No other agents for chronic rx rather than treating primary condition