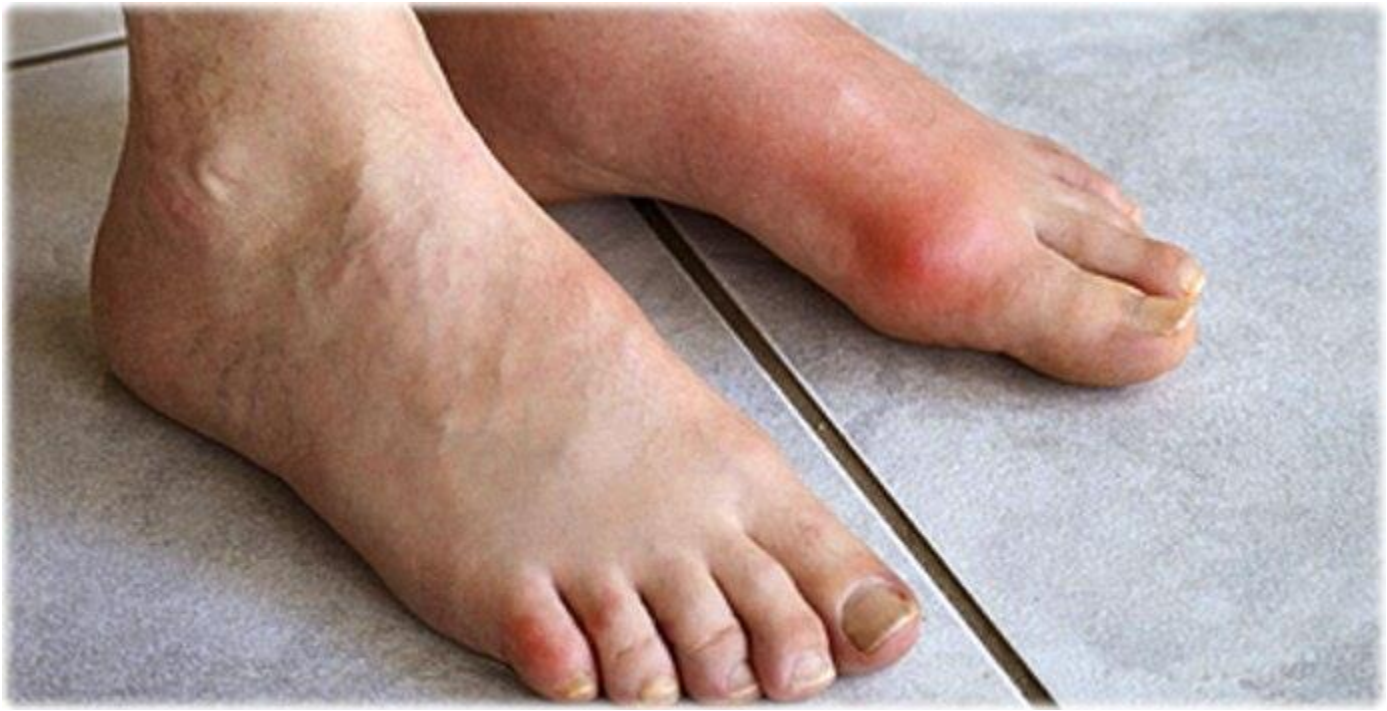


GOUT

DR. TEHMINA JALIL

Objectives

- Enlist different types of crystal-Induced arthritis.
- Describe key points of aetiology, pathogenesis, clinical features,morphological features, and complications of:

• Gout

• Calcium Pyrophosphate Crystal deposition Disease (Pseudo-Gout)

Diseases associated with crystal formation

CRYSTAL	ASSOCIATION
COMMON	
Monosodium urate monohydrate	Acute gout
	Chronic tophaceous gout
Calcium pyrophosphate dihydrate	Acute pseudogout
	Chronic arthropathy
	Chondrocalcinosis
Basic calcium phosphates	Calcific periarthritis
	Calcinosis
UNCOMMON	
Cholesterol	Chronic effusions in rheumatoid arthritis
Calcium oxalate	Acute arthritis in Dialysis patient
Extrinsic crystals/ semi-crystalline particles	
Synthetic crystals	Acute synovitis
Plant thorns/ sea urchin spines	Chronic monoarthritis, tenosynovitis

Gout

- It is a disorder caused by the tissue accumulation of excessive amounts of uric acid, an end product of purine metabolism.
- It is associated with recurrent episodes of acute arthritis, sometimes accompanied by the formation of large crystalline aggregates called tophi, resulting in chronic joint deformity. All of these result from precipitation of monosodium urate crystals.

What is Hyperuricemia?

- . Hyperuricemia is defined as
  - A plasma urate level
    - > 420 *μ*mol/L (7.0 mg/dL) in males and
    - > 360 *μ*mol/L (6.0 mg/dL) in female
  - .

Etiological factors

- Gout is more common in men than in women; it does not usually cause symptoms before the age of 30.
- Diet
- Genetic predisposition(glucose transporter 9 (*GLUT9)* gene, commonly referred to as the solute carrier 2A9 (*SLC2A9*), the product of which alters the renal excretion of uric acid.)
- Underexcretion of urate, the salts of uric acid .
- Overproduction can be the cause

Stages of gout

- Four stages are classically described:

  (1) asymptomatic hyperuricemia,

  (2) acute gouty arthritis,

  (3) "intercritical" gout, and

  (4) chronic tophaceous gout.

- Asymptomatic hyperuricemia appears around puberty in males and after menopause in women.

Classification

- Gout is traditionally divided into primary and secondary forms, accounting for about 90% and 10% of cases, respectively.
- **Primary gout** designates cases wherein the basic cause is unknown or (less commonly) when it is due to an inborn metabolic defect that causes hyperuricemia.
- **Secondary gout** the cause of the hyperuricemia is known, but gout is not necessarily the main or even dominant clinical disorder.

Clinical Category	Metabolic Defect
Primary Gout (90% of cases)	
Enzyme defects unknown (85% to 90% of primary gout)	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 Chronic renal diseases Inborn errors of metabolism	Overproduction of uric acid with increased urinary excretion Reduced excretion of uric acid with normal of uric acid with increased urinary excretion e.g., complete HGPRT deficiency .

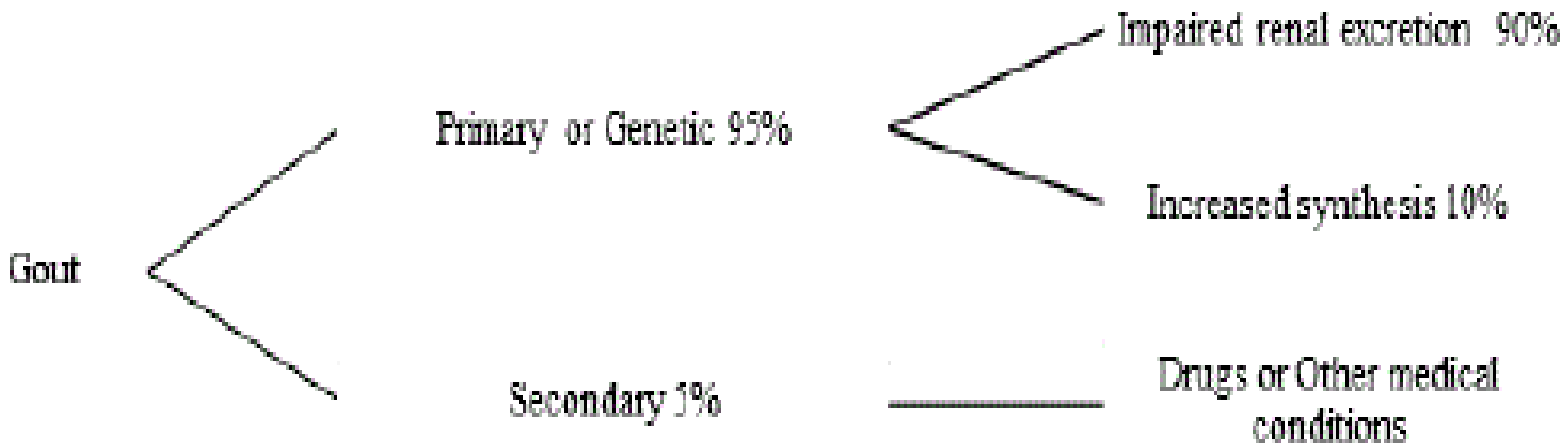


Figure 1: Classification of gout.

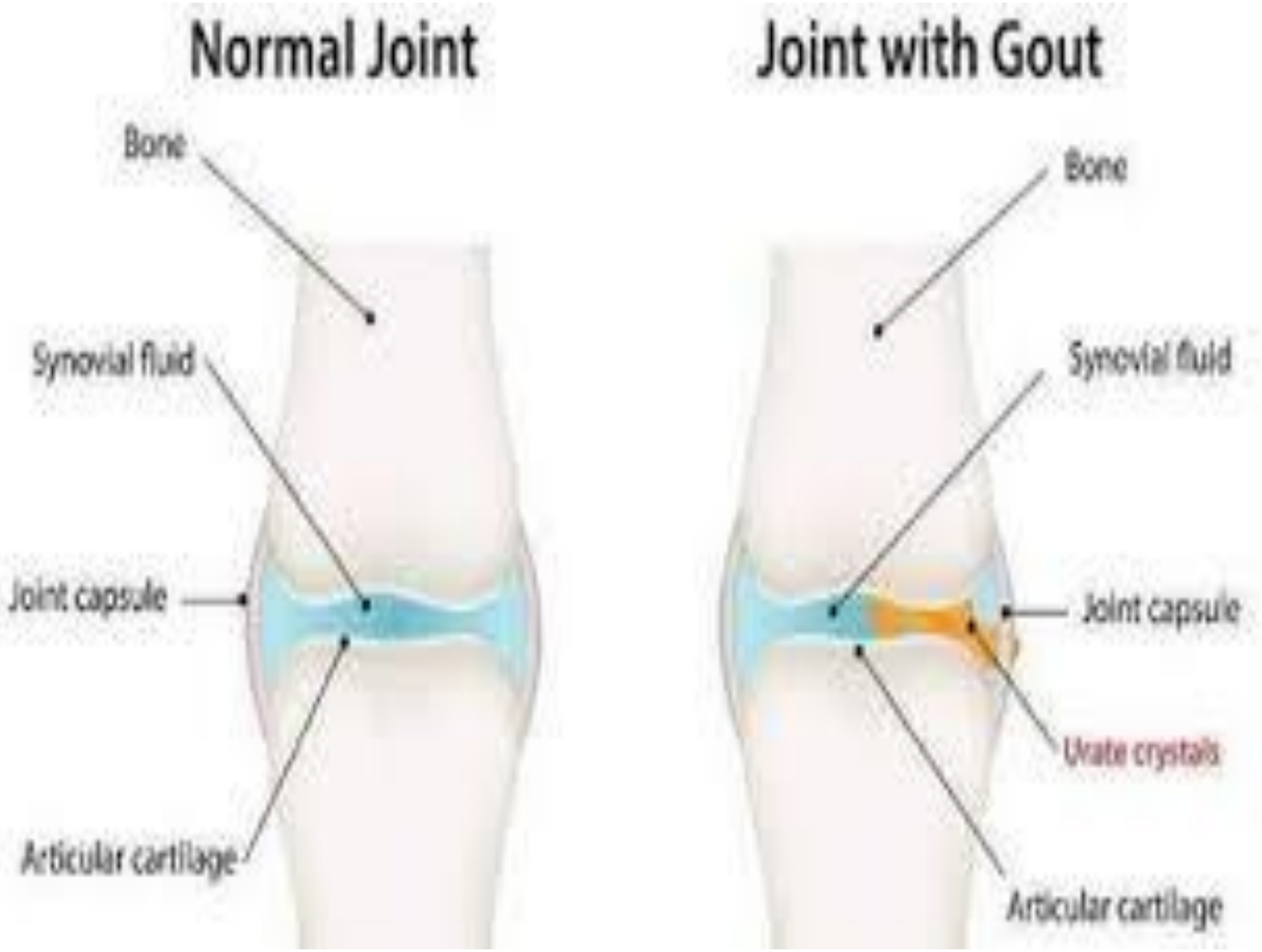
Morphology

The major morphologic manifestations of gout are

- Acute arthritis,
- Chronic tophaceous arthritis,
- Tophi in various sites, and
- Gouty nephropathy.

- **Acute arthritis** : sudden onset of excruciating joint pain associated with localized erythema and warmth; constitutional symptoms are uncommon, except possibly mild fever. The vast majority of first attacks are monarticular; 50% occur in the first metatarsophalangeal joint (great toe), and 90% in the instep, ankle, heal, or wrist. Untreated, acute gouty arthritis may last for hours to weeks, but it gradually completely resolves and the patient enters an Asymptomatic intercritical period.
- **Asymptomatic intercritical period. S**ome individuals never have another attack, most experience a second episode within months to a few years. In the absence of appropriate therapy, the attacks recur at shorter intervals and frequently become polyarticular. Eventually, symptoms fail to resolve completely after each attack, and the disease progresses to Chronic tophaceous gout.
- **Chronic tophaceous gout***:* At this stage, radiographs show characteristic bone erosion caused by the crystal deposits and loss of the joint space. Progression leads to severe crippling disease.

- Renal manifestations of gout can appear as renal colic associated with the passage of gravel and stones, and can evolve into chronic **Gouty nephropathy.** About 20% of individuals with chronic gout die of renal failure.


Normal Joint
Bone
Synovial fluid
Joint capsule
Articular cartilage
Joint with Gout
Bone
Synovial fluid
Joint capsule
Urate crystals
Articular cartilage

Uric acid synthesis

- .Uric acid is the end product of purine catabolism; consequently increased urate synthesis typically reflects some abnormality in purine nucleotide production. The synthesis of purine nucleotides involves two different but interlinked pathways: **the de novo** and **salvage pathways**. The de novo is involved in the synthesis of purine nucleotides from nonpurine precursors. While the salvage pathway is involved in the synthesis of purine nucleotides from free purine bases, derived from dietary intake and by catabolizing nucleic acids and purine nucleotides.

Pathogenesis

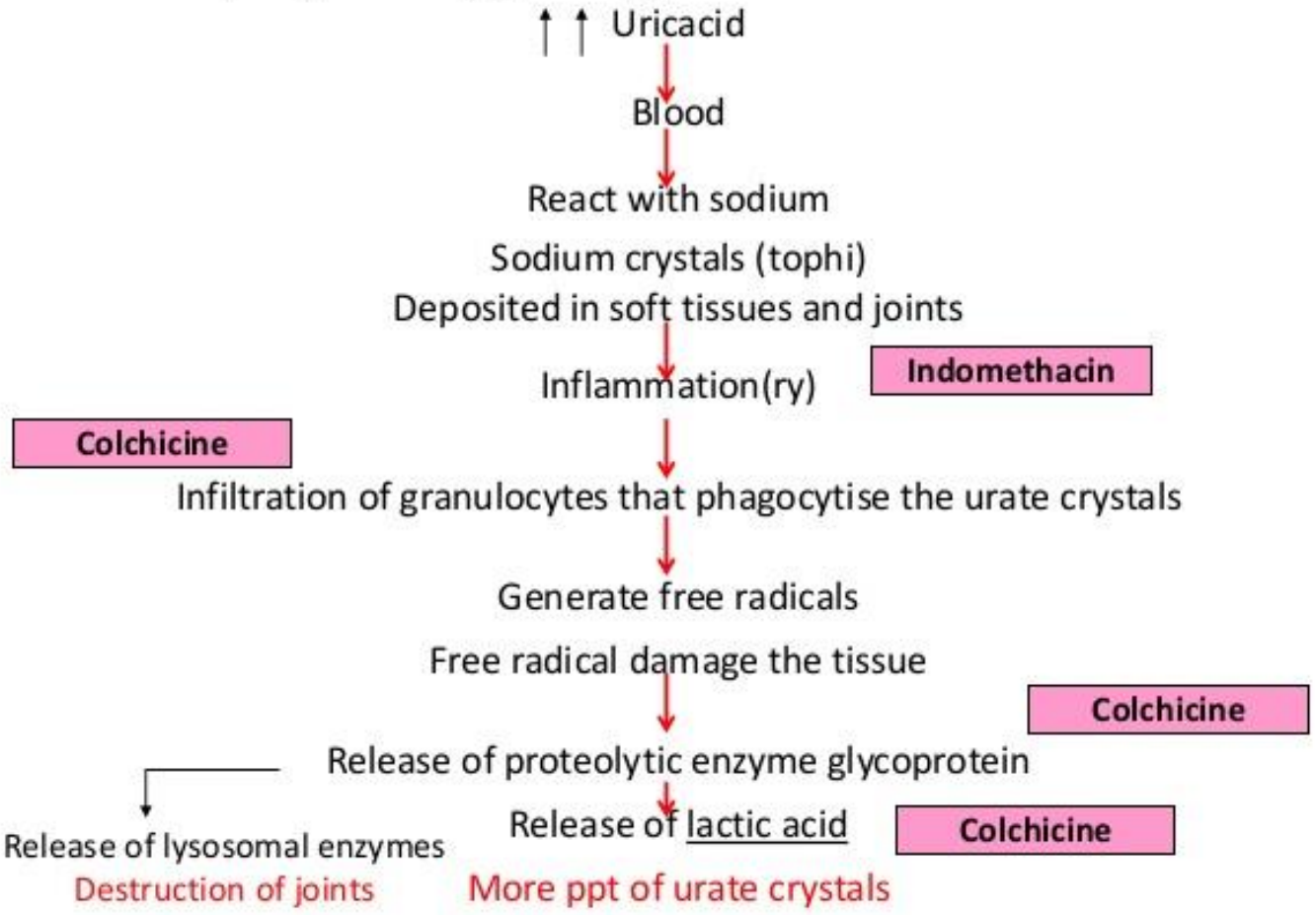
- Elevated uric acid levels can result from abnormality in purine metabolism resulting in overproduction of uric acid, reduced excretion, or both. Most cases of gout are characterized by a primary overproduction of uric acid. Less commonly, uric acid is produced at normal rates, and hyperuricemia occurs because of decreased renal excretion of urate.

- In **secondary gout,** hyperuricemia can be caused by increased urate production (e.g., rapid cell lysis during chemotherapy for lymphoma or leukemia) or decreased excretion (chronic renal insufficiency), or both. Reduced renal excretion may also be caused by drugs such as thiazide diuretics, presumably because of effects on uric acid tubular transport.

Increased levels of uric acid in the blood and other body fluids lead to the precipitation of monosodium urate crystals. This, in turn, triggers a chain of events that leads to joint injury . The precipitated crystals are directly chemotactic, and can also activate complement to generate chemotactic C3a and C5a fragments. This leads to a local accumulation of neutrophils and macrophages in the joints and synovial membranes; in attempting to phagocytize the crystals, these cells become activated, leading to the release of additional mediators including chemokines, toxic free radicals, and leukotrienes-particularly leukotriene B_4. The activated neutrophils also liberate destructive lysosomal enzymes. Macrophages participate in joint injury by secreting a variety of proinflammatory mediators such as IL-1, IL-6, and TNF.

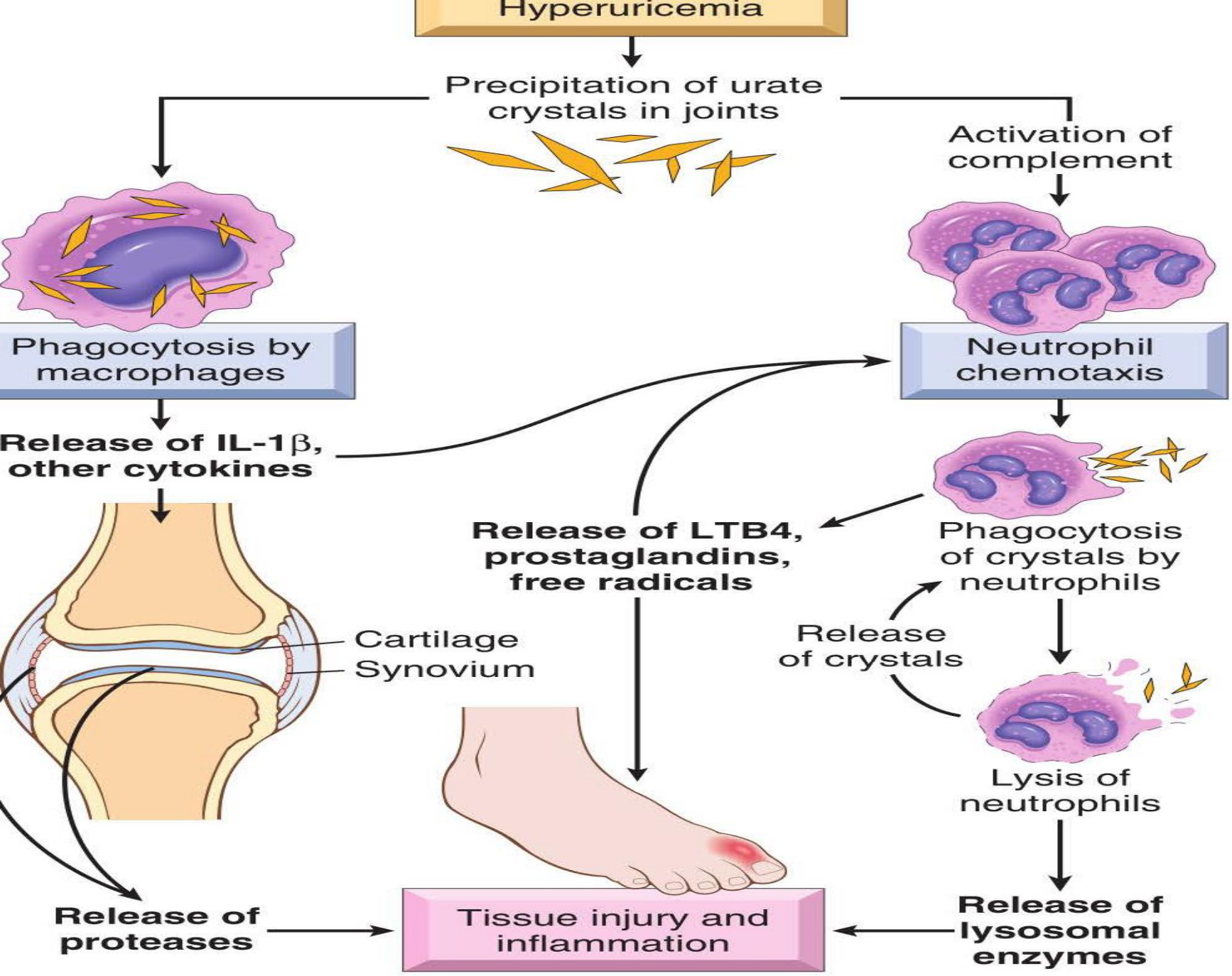
- While intensifying the inflammatory response, these cytokines can also directly activate synovial cells and cartilage cells to release proteases (e.g., collagenase) that cause tissue injury. The resulting acute arthritis typically remits in days to weeks, even if untreated. Repeated bouts, however, can lead to the permanent damage seen in chronic tophaceous arthritis

Pathophysiology of gout

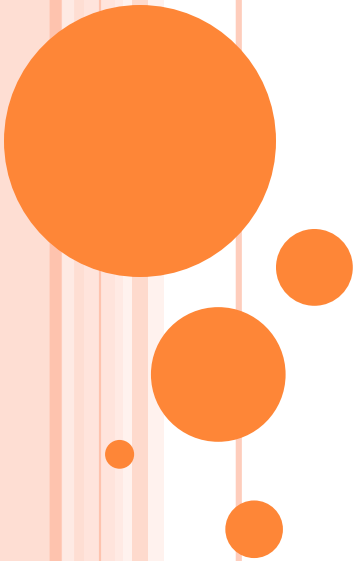


Complications

- Without treatment, an acute attack of gout usually resolves in five to seven days. However, 60% of people have a second attack within one year.
- Those with gout are at increased risk of
- Hypertension,
- Diabetes mellitus,
- Metabolic syndrome, and
- Renal and cardiovascular disease, thus are at increased risk of death.
- This may be partly due to its association with insulin resistance and obesity, but some of the increased risk appears to be independent.



gure 26-46 Pathogenesis of acute gouty arthritis. LTB4, Leukotriene B4;



Pseudogout

Pseudogout

- Calcium pyrophosphate crystal deposition disease (CPPD),also known as pseudo-gout and chondrocalcinosis, usually occurs in individuals older than 50 years of age and becomes more common with increasing age, rising to a prevalence of 30% to 60% in those 85 years or olde

Pseudogout

- **Demographics:** It is predominantly a disease of the elderly, peak age 65 to 75 years old. It has female predominance (F:M, 2-7:1).
- Prevalence of chondrocalcinosis is 5 to 8% in the general population.

Classification

- Sporadic (idiopathic),
- Hereditary,
- Secondary .

- In heriditary form we have a mutated pyrophosphate transport channel protein.

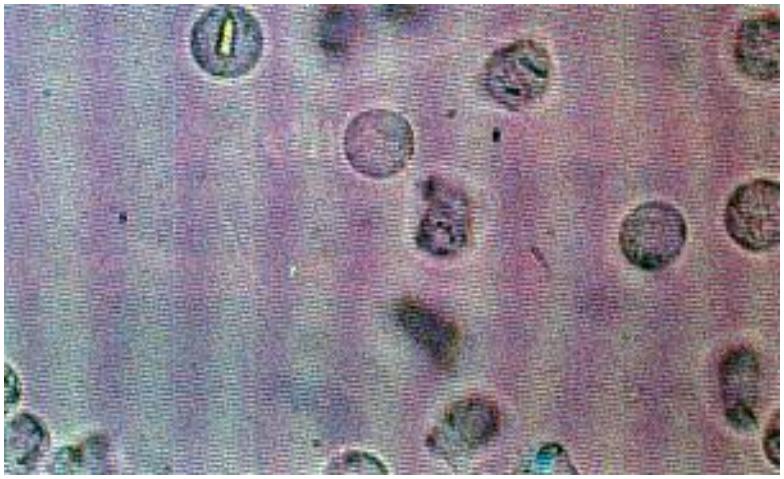
- The secondary form is associated with various disorders, including previous joint damage, hyperparathyroidism, hemochromatosis, hypomagnesemia, hypothyroidism, and diabetes.

Pathophysiology

- The basis for crystal formation is not known but studies suggest that articular cartilage proteoglycans, which normally inhibit mineralization, are degraded allowing crystallization around chondrocytes.
- As in gout, inflammation is caused by activation of the inflammasome in macrophages

Morphology

- The crystals first develop in the articular cartilage, menisci, and intervertebral discs, and as the deposits enlarge they may rupture and seed the joint. The crystals form chalky, white friable deposits, which are seen histologically in stained preparations as oval blue-purple aggregates . Individual crystals are rhomboid, 0.5 to 5 -11m in greatest dimension. Inflammation, if present, is usually milder than in gout.



Pseudogout

- **Clinical Manifestations**
- **Pseudogout:** Usually presents with acute self-limited attacks resembling acute gout. The knee is involved in 50% of the cases, followed by the wrist, shoulder, ankle, and elbow.

Pseudogout

- In 5% of patients gout can coexist with pseudogout.
- The diagnosis is confirmed with the synovial fluid analysis and/or the presence of chondrocalcinosis in the radiographs.
- Acute Pseudogout primarily affects men.
- Chronic CPPD: predominately affects women; it is a progressive, often symmetric, polyarthritis.
- Usually affects the knees, wrists, 2nd and 3rd MCP's, hips, spine, shoulders, elbows and ankles.

QUIZ

- Symptoms of gout may include…

a) Warmth, severe pain, and swelling in the joint
b) Red or purple skin
c) Peeling, itching skin at the site of the gout attack
d) All of the above

LEARNING SOURCES

- Robins 10th edition
- Internet sources

THANK YOU