Gout

Zdeněk Fojtík

Gout

- A metabolic disease characterized by recurrent attack of acute inflammatory arthritis caused by elevated levels of uric acid in the blood (hyperuricemia).
- Most common rheumatic disease of adulthood
- The uric acid crystallizes and deposits in joints, tendons, and surrounding tissues.
- Hyperuricemia : overproduction/underexcretion/both

Hyperuricemia ≠ Gout

Epidemiology

- **Prevalence of hyperuricemia**

  2.3 – 41.4% in various populations.

  Corresponds with serum creatinine /BUN levels, body weight, height, age, blood pressure, and alcohol intake. (Taiwan)

  Body bulk (as estimated by body weight, surface area, or body mass index) has proved to be one of the most important predictors of hyperuricemia in people of widely differing races and cultures.

- **Incidence of Gout**

  Varies depending on population studied – 1.8 /1000 – 3.2/1000

  RR for blacks slightly higher (1.3)

Classification of Hyperuricemia and Gout

Primary Hyperuricemia and Gout with No Associated Condition

- Uric acid undersecretion(80%–90%)

  Idiopathic

- Urate overproduction (10%–20%)

  Idiopathic

  HGPRT deficiency

  PRPP synthetase overactivity

Secondary Hyperuricemia and Gout with Identifiable Associated Condition

- Uric acid undersecretion

  Renal insufficiency

  Polycystic kidney disease

  Lead nephropathy

  Drugs(Diuretics,Salicylates (low dose), Pyrazinamide, Ethambutol,Niacin, Cyclosporine, Didanosine)
- Urate overproduction

  Myeloproliferative/ Lymphoproliferative diseases / Hemolytic anemias/ Polycythemia vera/Other malignancies

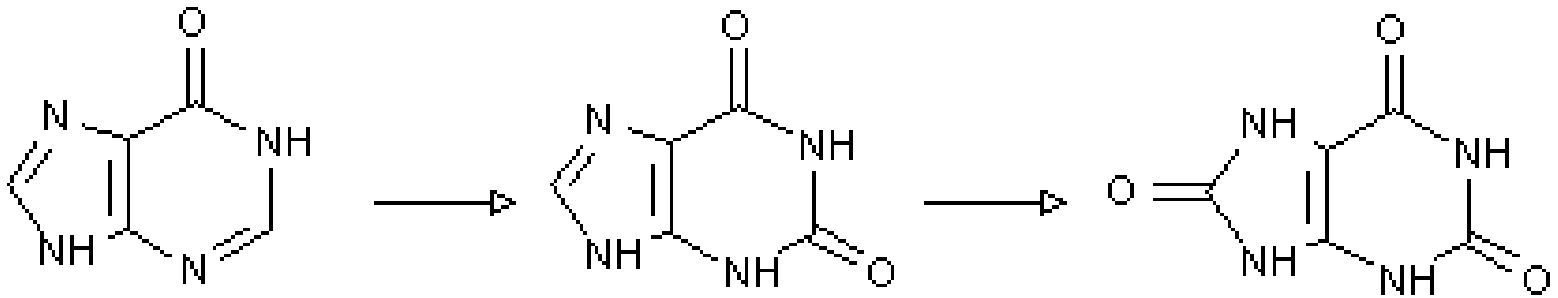
  Psoriasis/Glycogen storage disease
- Dual mechanism

  Obesity, ETOH,Hypoxemia and hypoperfusion

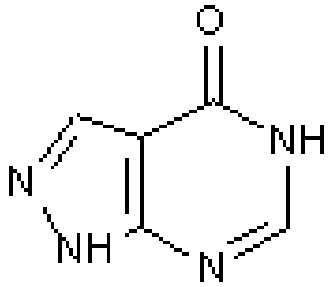
American College of Rheumatology preliminary criteria for the clinical diagnosis of gout.

Six or more of these criteria are needed to make a diagnosis:

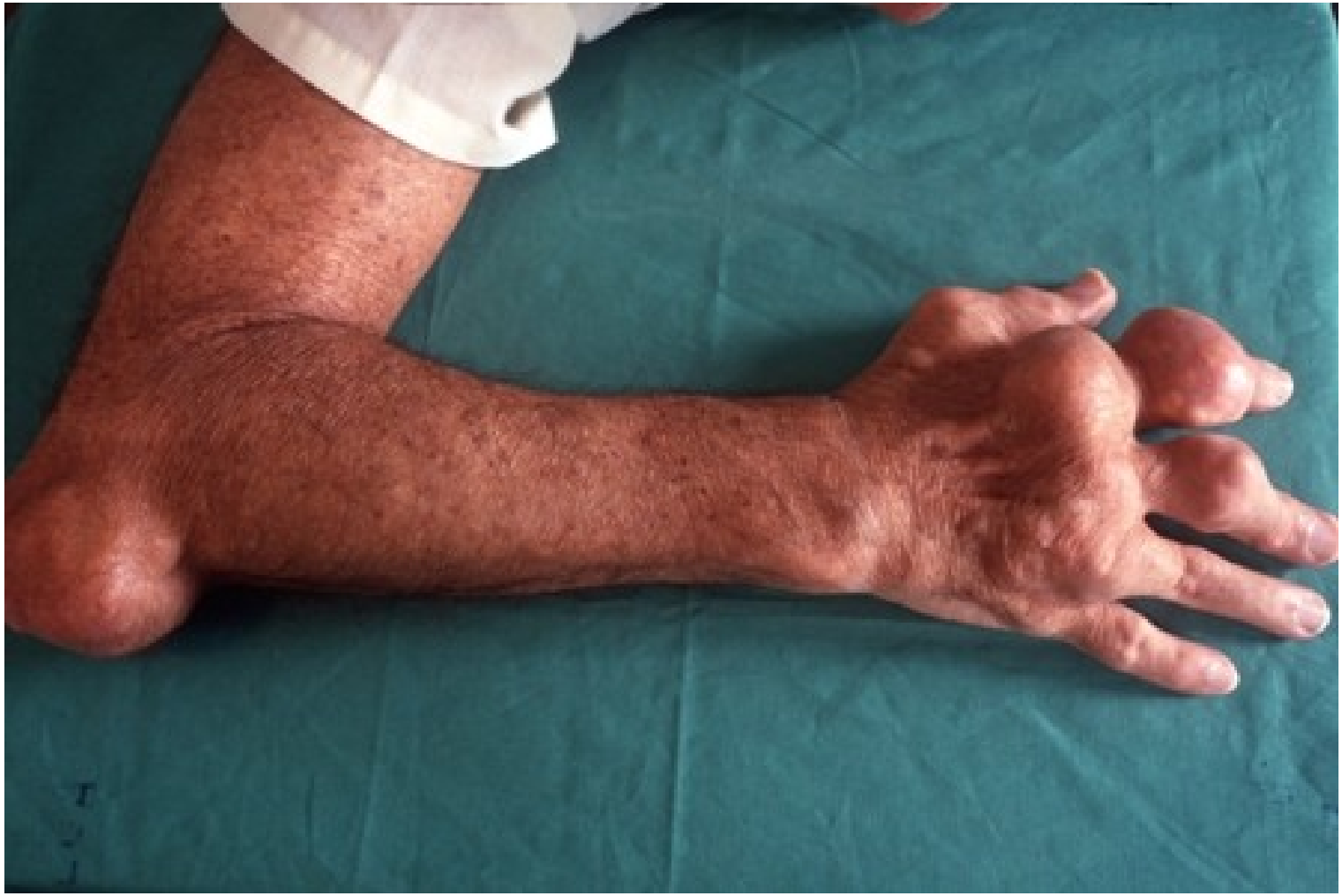
-More than one attack of acute arthritis
-Maximum inflammation developed within one day
-Attack of monoarthritis
-Redness over joints
-Painful or swollen first metatarsophalangeal joint
-Unilateral attack on first metatarsophalangeal joint
-Unilateral attack on tarsal joint
-Tophus (proved or suspected)
-Hyperuricaemia
-Asymmetric swelling within a joint on radiograph
-Subcortical cysts without erosions on radiograph
-Joint fluid culture negative for organisms during attack



Hypoxanthin Xanthin kys. močová



Allopurinol



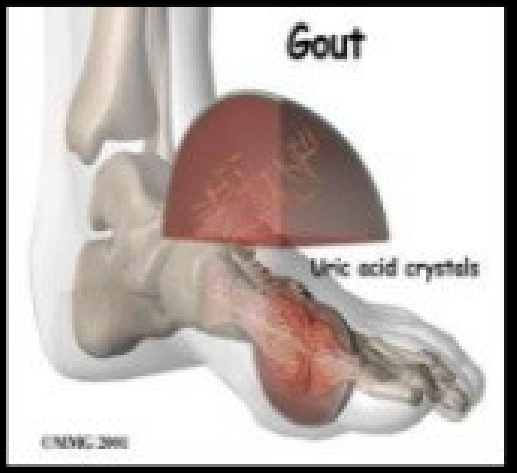
Klinický obraz a stadia

- Asymptomatic hyperuricemia
- Acute gout arthritis
- Intercritical gout
- Chronic gout with tophi

Asymptomatic hyperuricemia

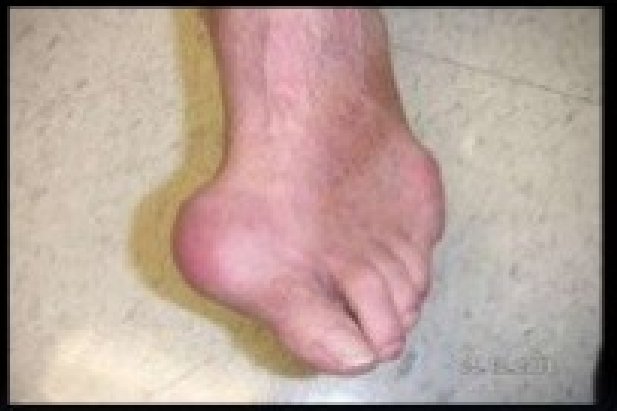
- Serum [urate] abnormally high without SSx
  - Male >420μmol/L (7mg/dL)
  - Female >360μmol/L (6mg/dL)
- Not life threatening and readily treatable
- Routine prophylactic treatment is **NOT** required
- **A/W : gout, urolithiasis, nephropathy, metabolic syndrome (HPT, DM/IFG/IGT, hyperTGemia, obesity, CKD)**
- Serum [urate] >540μmol/L (9mg/dL) were a/w greater incidence for gout
- Increased daily urinary urate excretion is a/w higher risk of urate and Ca oxalate stone formation (when >0.65mmol/L or 11mg/dL)
- Renal involvement when serum urate level is more than 2x the normal limit (0.77mmol/L or 13mg/dL in male; 0.60mmol/L or 10mg/dL) in female)

Gouty arthritis

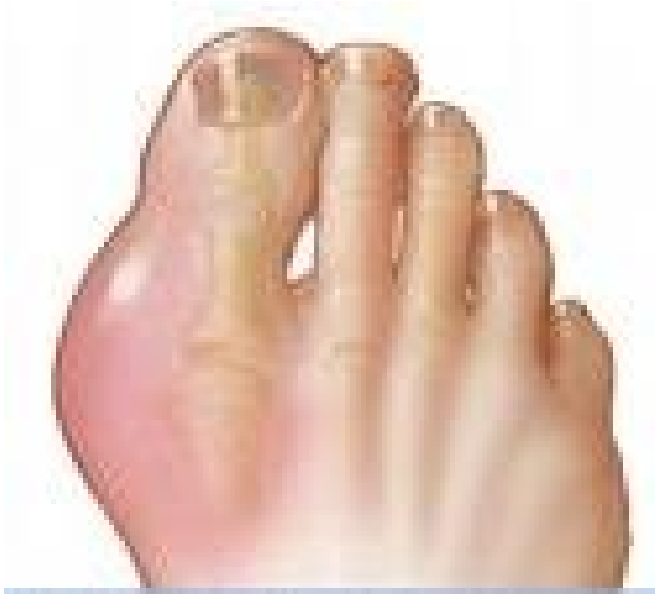


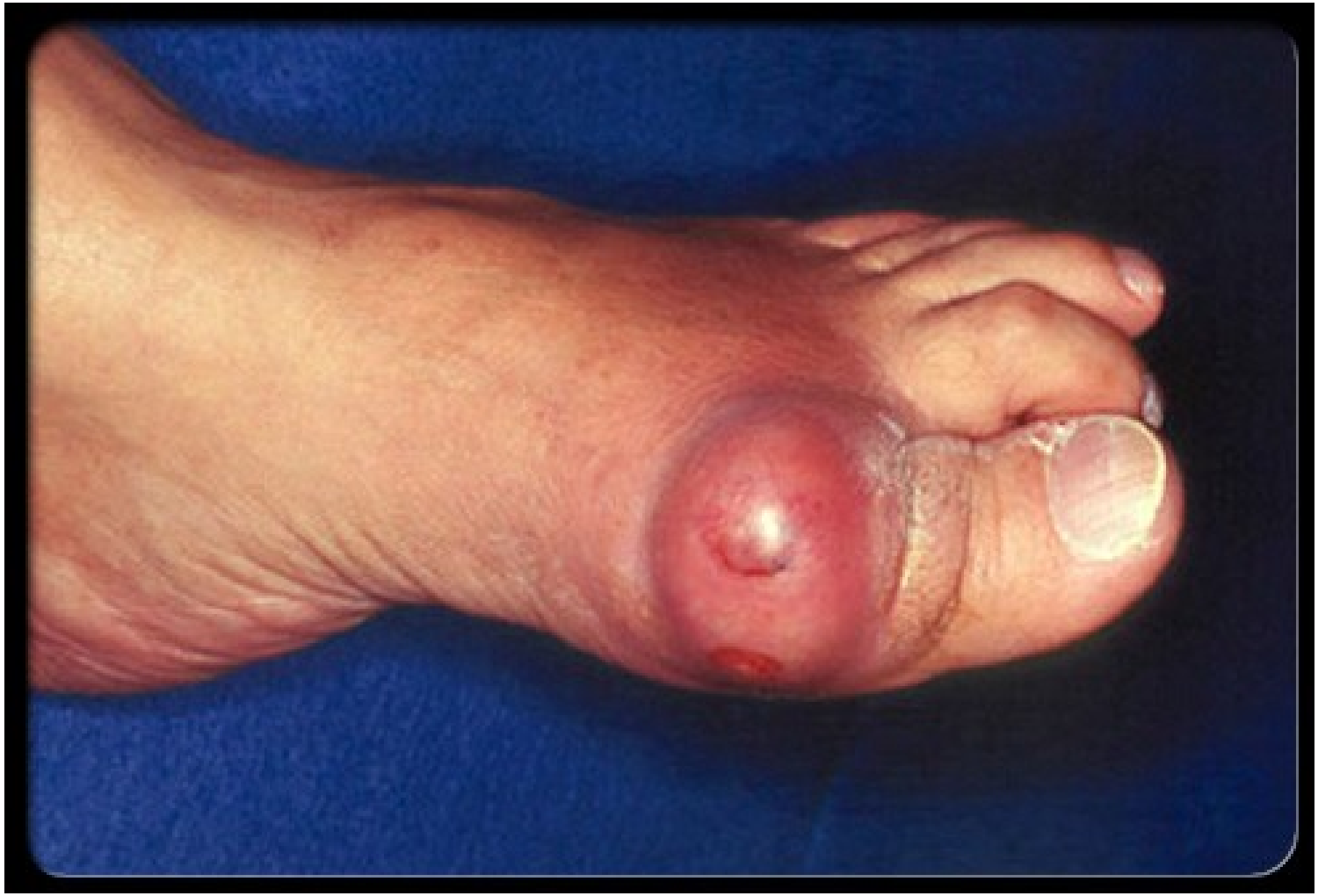
1. Acute gout

- Acute, self limiting, monoarticular
- Painful, red, hot, swollen
- Usually resolves within 2 weeks if untreated
- May occur even if serum urate is normal
- LL > UL
- Commonly affected joints
  I. 1st metatarsophalangeal joint (podagra)
  II. Forefoot/instep
  III. Ankle joint
  IV. Knee joint
  V. Wrist joint
  VI. Elbow joint
  VII. Finger joints



- Extra-articular : olecranon bursa, Achilles tendon
- O/E : erythematous, warm, swelling over involved joint with extreme tenderness +/- fever → skin desquamation
- Duration : 2 – 3 weeks, with gradual complete resolution of inflammatory signs





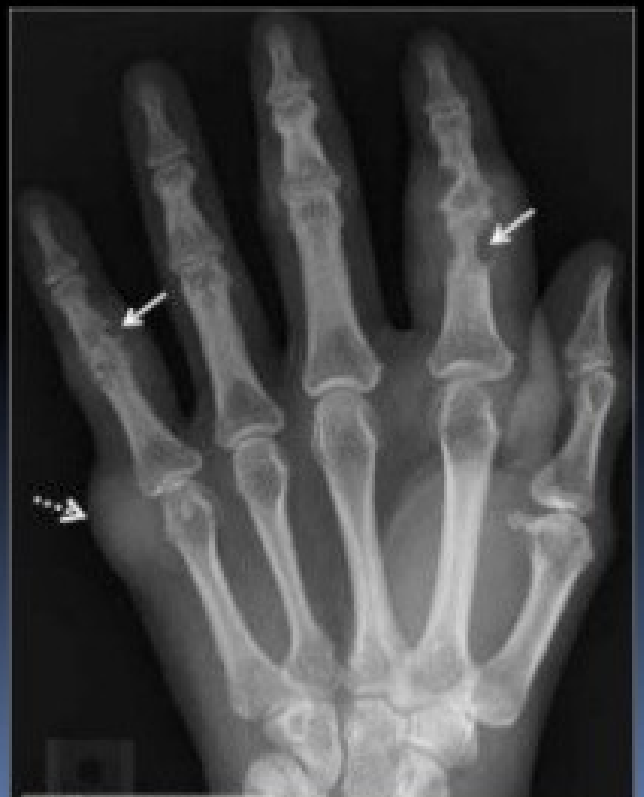
2. Intercritical gout
   - Asymptomatic period between attacks

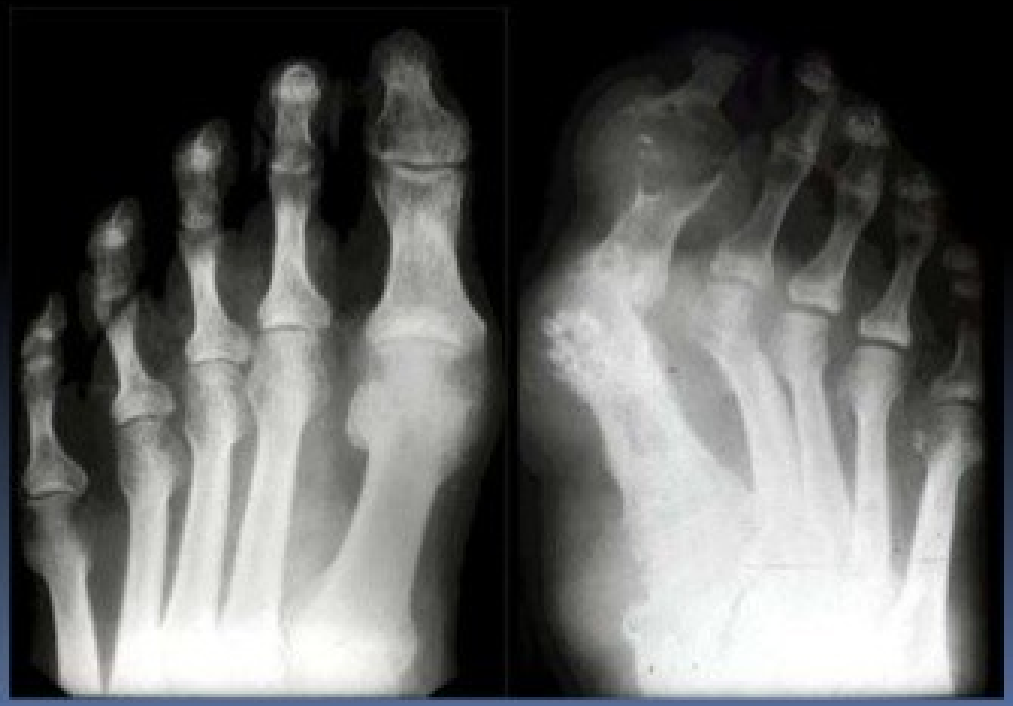
3. Chronic gout
   - Polyarticular arthritis + tophi formation
   - Articular tophaceous gout may results in destructive arthropathy and secondary OA
   - Tophaceous disease more like to occur in patients with:
     - Polyarticular presentation
     - Serum urate level >540 µmol/L (>9mg/dL)
     - Disease onset at younger age (≤40 years)
   - Sites of tophi
     - Digits of hands and feet (most common)
     - Pinna of ear (classic, less common)
     - Bursa around elbows and knees
     - Achilles tendon

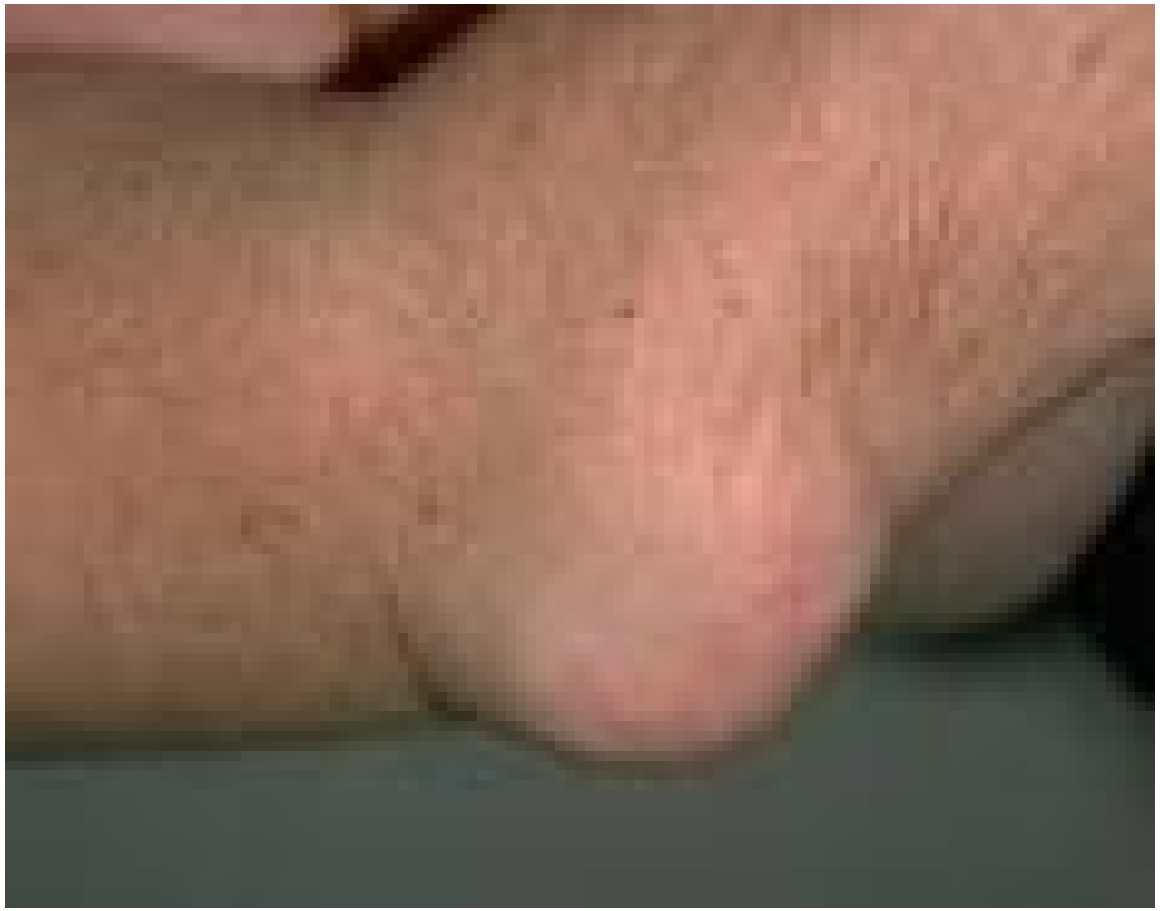
Urate/gouty nephropathy

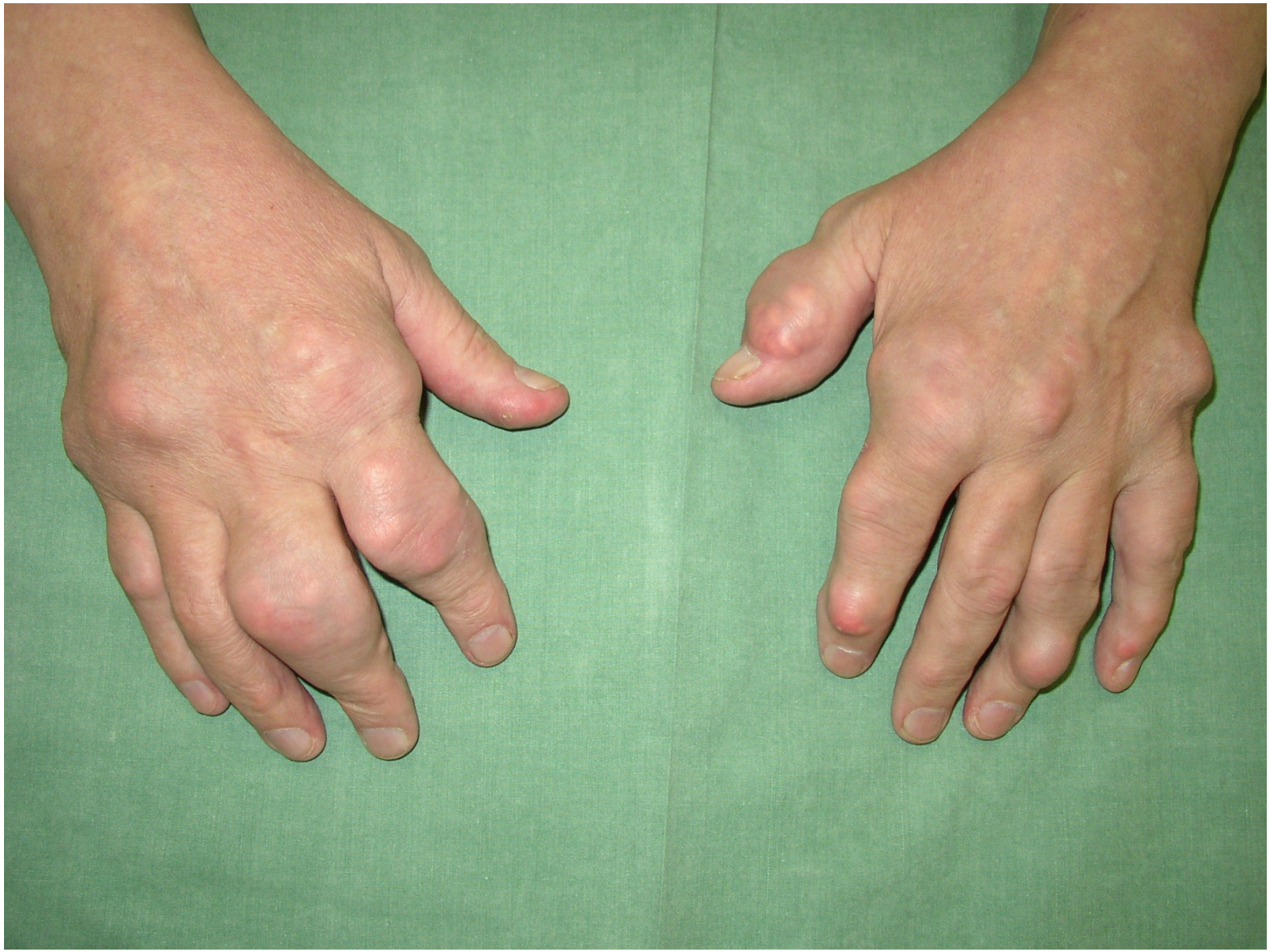
- Acute urate nephropathy
  - Urate crystals → renal tubules → obstructive ARF
  - DeH2O, low urine pH are precipitating factors
- Chronic urate nephropathy
  - Urate crystals → interstitium and renal medulla → inflammation + surrounding fibrosis → irreversible CRF
  - Renal impairment can occur in ~40% in chronic gout
- Urate nephrolithiasis
  - Stones → flank pain/ureteric colic/hematuria
  - Urate (radiolucent) / mixt. Calcium oxalate and/or calcium phosphate (radio-opaque)
  - Contributing factors : hyperuricosuria, low urine output, acidic urine
  - Urinary alkalinization (pot. Citrate or $NaHCO_3$) → dissolution of existing stones and prevention of recurrence

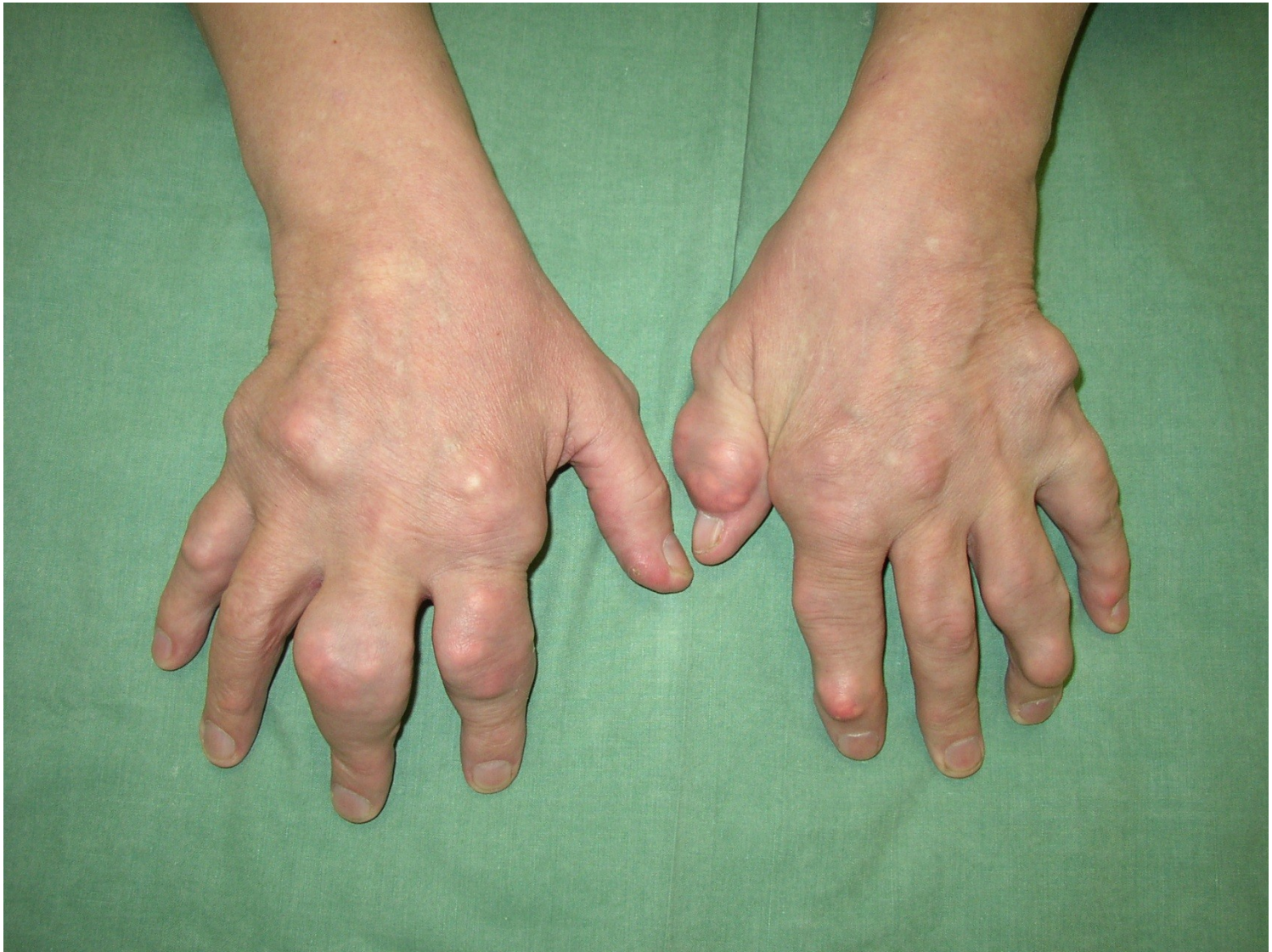
- Skeletal x-rays
  - Acute gouty arthritis : normal; soft tissue swelling
  - Chronic tophaceous gout : tophi, erosive bone lesions (punched out lesions), joint space is preserved until late stage, pathognomonic in foot and big toe











Factors affecting serum urate concentration

***Factors that decrease serum urate concentration:**

Diet: low fat dairy products.

Drugs: xanthine oxidase inhibitors (allopurinol), uricase drugs (rasburicase) and oestrogens.

***Factors that increase serum urate concentration:**

Diet: meat, fish, alcohol, obesity, and weight gain.

Drugs: including diuretics, low dose salicylates, cytotoxics, and lead poisoning.

Disease: increased purine turnover—chronic haemolytic anaemia, secondary polycythaemia; increased purine synthesis—glucose-6-phosphate dehydrogenase deficiency; reduced renal excretion—hypertension, hypothyroidism, chronic renal disease.

Management

- Lifestyle modification and dietary advice
- Management of comorbidities
- Nonessential prescriptions that induce hyperuricaemia
- Main aim :

  - To achive ideal BW

  - Prevent acute gouty attacks

  - Reduce serum urate level

- Strict purine-free diet reduced only 15 – 20% of serum urate, thus is considered an adjunct therapy to medication.

Recommendation:

- Achieve an ideal body mass index (BMI).
- Restriction or elimination of alcohol.
- Restrict consumption of high purine foods.
- Moderate intake of purine-rich vegetables.
- Consumption of low fat dairy products.
- Adequate intake of fluid of 2-3L daily.

Treatment

- Contributing factors eg. thiazide/loop diuretics; low dose aspirin may be discontinued or substituted, if appropriate

- Pharmacotherapy of **asymptomatic hyperuricemia** is NOT necessary, except :-
  - ✓ Persistent severe hyperuricemia
    - > 770µmol/L (13mg/dL) in male
    - > 600µmol/L (10mg/dL) in female
  - ✓ Persistent elevated urinary excretion of urate
    - > 0.65mmol/L/day (11mg/day), a/w 50% increased risk of urate calculi
  - ✓ Tumor lysis syndrome
    - chemotherapy/radiotherapy → extensive tumor cytolysis => require pre-hydration and allopurinol to prevent acute urate nephropathy

Treatment : Acute gouty arthritis

- Initiation within 24 hours of onset
- If on Allopurinol, continue without interruption

- NSAIDs
  - eg. Diclofenac, indomethacin, mefenemic acid etc
  - Caution in h/o PUD, HPT, renal impairment, IHD, liver impairment
  - COX-2 inhibitors (celecoxib, etoricoxib, parecoxib) = alternative for above risk factors
  - Studies have shown that etoxicoxib (Arcoxia) has equal efficacy to indomethacin

- Colchicine
  - Inhibiting mitosis and neutrophils motility and activity, leading to a net anti-inflammatory effect.
  - Alternative drug if CI to NSAIDs, but is poorly tolerated by elderly
  - Therapeutic index is narrow
  - Slower onset of action
  - Evidence base for prophylaxis is stronger than for NSAIDs (NHS Fife, Gout Management Guidelines, 2010)
  - SE (eg. N&V, abd. pain, profuse diarrhea) limit its usefulness
  - Dosage : 0.5mg – 0.6mg BD-QID

Urate lowering therapy (hypouricaemic therapy)

- Allopurinol should not be started until acute attack has resolved
- May prolong attack or lead to rebound flares if started during attack
- Should be started 2 weeks after attack is well-controlled
- Indications for ULT :
  1. Frequent and disabling attacks of gouty arthritis (3 or more attacks/year)
  2. Clinical or radiographic signs of erosive gouty arthritis
  3. The presence of tophaceous deposits
  4. Urate nephropathy
  5. Urate nephrolithiasis
  6. Impending cytotoxic chemo-/radiotherapy for lymphoma or leukemia

Management of Chronic Gout: Key facts	
First line treatment	**Second line treatment**
Allopurinol	Sulphinpyrazone Febuxostat Benzbromarone
Increase allopurinol by 100mg every 4 weeks until target reached	Uricosuric agents should be avoided in those with renal stones
Target uric acid 0.3 mmol/L. Monitor uric acid every 4 weeks until target reached	
Colchicine 0.5 mg twice daily is used for the first 6-12 months after initiating urate lowering therapy	

(NHS Fife, Gout Management Guidelines, 2010)

When to reduce ULT?????

- If serum urate <360µmol/L , and have been no gouty attacks for 1 year → can reduce T. allopurinol by 100mg.
- Check serum urate 6 monthly, if still <360µmol/L → can further reduce
- Patients that have tophi are most likely to require lifelong ULT

Risk factors for Gout	Comment
Raised serum urate	The higher the urate level, the greater the risk of gout.
Genetics	Mutations in genes for urate transporter URAT1 and fructose transporter GLUT9 are associated with gout.
Age	2% of 45-64 year old men and 6% men >75 years old have gout.
Gender	Male :Female ratio 3:1 in those > 65 years
Osteoarthritis	Gout attacks more likely in joints affected by OA while Rheumatoid Arthritis is protective
Diet and alcohol	Wine in moderation appears safe

(NHS Fife, Gout Management Guidelines, 2010)