Hyperuricemia (High Uric Acid) and Gout (Gouty Arthritis) — Symptoms and Treatments

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Hyperuricemia and gout are two of the most common metabolic diseases in industrial countries. The exacerbated forms of uricemia are the acute gout attack and chronic gout. They are caused by the incorporation of crystalloid salts of uric acid (urate) into the joints. In the following article, we will present all relevant facts concerning gout. This way, you are perfectly prepared for all exams in the clinical part of the medical studies and for your final exams.

Definition of Hyperuricemia and Gout

Hyperuricemia

Hyperuricemia is defined by uric acid level > 6.4 mg/dl, which corresponds to the solubility of uric acid in plasma water at 37°C and a pH of 7.4. If the uric acid level rises, the risk of gout increases simultaneously:
- At values ranging between 6.4 and 7 mg/dl: only 2% develop manifested gout.
- At values > 8 mg/dl: 40% develop manifested gout.

Clinical manifestations of gout

The clinical manifestation of gout is characterized by tissue precipitates of uric acid (joints, tophi, and kidneys). Acute gout attack represents **exacerbated hyperuricemia**.


Epidemiology of Hyperuricemia and Gout

Distribution of hyperuricemia and gout

In Western industrial nations, 25% of all men are affected by hyperuricemia. Men are affected, regardless of age, while women are affected mostly after **menopause** due to the lack of estrogens that have a **uricosuric** effect.

Gout affects 1.5% of the population. The disease primarily manifests between the ages of 40 and 60 years. Roughly, one in every 10 patients affected by hyperuricemia develops gout.

**N.B.** The overall men:women ratio affected by gout ranges between 7:1 and 9:1, according to the National Health and Nutrition Examination Survey III.
Classification of Hyperuricemia and Gout

Hyperuricemia is a metabolic disorder. It is divided into a primary (genetic) and a secondary form (due to another disease).

Primary familial hyperuricemia

Primary familial hyperuricemia accounts for 95% of all cases of hyperuricemia. It is attributed to two factors:

**Decrease of renal-tubular uric acid secretion (in 99% of the cases) due to multiple genes:** Uric acid builds up when its precipitates exceed the diminished elimination capacity of the kidney. However, following the intake of an appropriate diet, the kidneys can cope with hyperuricemia, even when it is due to genetic predisposition. Thus, for the most part, primary hyperuricemia is a genetically inherited disease, which manifests due to malnutrition.

**Genetic defects inducing excessive uric acid synthesis:** Genetic defects such as deficiency of the enzyme hypoxanthine-guanine-phosphoribosyl-transferase in Lesch-Nyhan syndrome with X-chromosome-linked recessive inheritance can lead to excessive uric acid synthesis.

Secondary hyperuricemia

- **Increased uric acid precipitation due to cell decay** occurs in myelo- or lymphoproliferative diseases, hemolytic anemia, tumor lysis syndrome, and cytostatic therapy.
- **Reduced renal uric acid elimination** occurs in renal insufficiency, treatment with medications, ketosis (fasting, a diet rich in fats, decompensated diabetes mellitus), intoxications (lead, and CO), endocrine diseases (functional disorders of the parathyroid gland, hypothyroidism, and acromegaly), lactate acidosis, and alcohol abuse.

Pathogenesis of Hyperuricemia and Gout

Development of hyperuricemia

Uric acid is the final product of purine metabolism. In purine metabolism, the nucleotide bases adenine and guanine, along with purines absorbed exogenously via consumed food, are metabolized. Every day, 350 mg of uric acid accumulates in the body and is excreted via kidneys and feces. The uric acid level in the plasma and other extracellular fluids increases in case of positive uric acid balance. Chronic precipitation and acute gout attacks occur if the solubility threshold of 6.4 mg/dl is exceeded.
Development of gout

Acute gout attack occurs following exacerbation of uric acid levels. Uric acid solubility is influenced by various factors:

- **Supernutrition**: Gout is a manifestation of metabolic syndrome.
- Alcohol consumption: Acidification of fluids in the extracellular space leads to inhibition of uric acid excretion by the kidneys.
- Fasting
- Tissue trauma
- Surgical interventions
- Medication: Diuretics and low-dose aspirin affect uric acid excretion.

Hyperuricemia often occurs in patients with hyperlipidemia, diabetes mellitus, obesity, and hypertension.

Clinical Manifestations of Hyperuricemia and Gout

Symptoms of acute gout

In almost 65% of the cases, a gout attack often occurs at night with **monarthritis**, which affects the lower extremity in 90% of the cases: gout attack in the toe basal joint (**podagra**). Gout attack may involve the thumb basal joint (**chiragra**). Most often, patients’ joints are affected for a week. Polyartritic attacks also occur in older patients.

**Signs of acute joint gout**

- Reddening, swelling, and extreme contact pain
- Fever (due to cytokine-induced systemic inflammation)
Symptoms of chronic gout

**Tophi and crystalloid arthropathy**

*Local inflammation is triggered by the accumulation of mononatrium uric acid* in the bones, cartilage, synovia, and tendons, leading to a destruction of the respective tissue and fibrotic reactions, leading to the formation of connective tissue nodes, the so-called *tophi*. Chronic damage to the joint is known as *crystalloid arthropathy*.

Tophi reflect the severity and duration of gout. They are small, non-relocatable, indolent, and firm nodes, which develop all over the body, except in the CNS.

Types of tophi

<table>
<thead>
<tr>
<th>Soft Tissue Tophi</th>
<th>Bone Tophi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm (ulna), auricle, Achilles tendon, pressure spots (heel, olecranon)</td>
<td><strong>Juxta-articular erosions</strong> in x-ray</td>
</tr>
</tbody>
</table>

**Renal manifestation**

The *kidney* is the second most frequent location of the lesion after the locomotor system. Uric acid nephropathy involves uric acid stone formation in the kidney. More than 80% are pure *uric acid stones*, and the remainder are mixed *calcium oxalate stones* or calcium phosphate stones. Stones form due to increased uric acid excretion, acidic urine and substances decreasing uric acid solubility.

**Uric acid nephropathy** occurs exclusively at very high serum levels of uric acid, leading to uric acid accumulation in the lumen of the tubules, resulting in oliguria, anuria, and vomiting. Interstitial precipitations result in mild proteinuria and low-degree kidney insufficiency.

**Course of gout**

According to the Centers for Disease Control and Prevention (CDC), the course of gout can be divided into four stages.

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic hyperuricemia (pre-gout)</th>
<th>Lasting years to decades</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>First manifestation</td>
<td>Gout arthritis or nephrolithiasis</td>
</tr>
<tr>
<td>II</td>
<td>Asymptomatic stage (intercritical phase)</td>
<td>Free from symptoms for months or years after the first attack; often recurs during the first year; intercritical phases are shorter in between attacks.</td>
</tr>
<tr>
<td>III</td>
<td>Chronic gout</td>
<td>Occurs over 5–15 years with elevated uric acid levels, polyarthritic joint changes, and nephropathy</td>
</tr>
</tbody>
</table>
Diagnosis of Hyperuricemia and Gout

A diagnosis of gout is suspected immediately when a patient with swollen anterior foot without socks, shoes or bandage limps on one foot.

If gout is suspected based on hyperuricemia, a rapid diagnosis is mostly made due to the typical symptoms. Evaluation of medical history often reveals individual or familial history of previous gout attacks.

Laboratory workup in hyperuricemia and gout

The elevated uric acid level (> 6.4 mg/dl) can be detected in the blood. Possible fluctuations due to meals should be considered. Also, the uric acid level can be within normal range despite clinical presentation of an acute gout attack.

**N.B.** In one-third of the patients with an acute gout attack, the serum uric acid is not elevated.

The following inflammatory parameters can be elevated:

- BSR ↑
- CRP ↑
- Leukocytes ↑

Imaging in hyperuricemia and gout

In the event of chronic courses, destructive changes at the joint and tophi can be detected in an x-ray. Urography can reveal uric acid stones indirectly.
Joint puncture

In case of diagnostic insecurity, a direct joint puncture can occur, especially if septic arthritis is excluded or if initial monoarthritis is present. Acute gout attack is characterized by phagocytized uric acid crystals in leukocytes (double refraction in polarization microscopy).

Differential Diagnosis of Hyperuricemia and Gout

Differential diagnosis of chronic gout

- Rheumatoid arthritis
- Arthrosis with accompanying arthritis
- Chondrocalcinosis
- Reiter’s syndrome
Differential diagnosis of acute gout

- Bacterial arthritis
- Arthritis at infections
- Traumas
- Rheumatic fever
- Gonorrhea
- Psoriasis arthritis

**N.B.** Septic arthritis is the most important differential diagnosis of acute gout.

**Therapy of Hyperuricemia and Gout**

The goals of therapy are freedom from further attacks and prevention of kidney and joint damages, accomplished via the decrease of the uric acid level to < 6 mg/dl.

**General measures for gout management**

Similar to the other metabolic diseases, a change of lifestyle is the main focus. Asymptomatic hyperuricemia up to 9 mg/dl is only treated nutritionally:

- **Diet low in purines** (giving up giblets and generally high meat consumption)
- High fluid intake to promote uric acid excretion via diuresis
- Avoidance of uric acid-increasing drugs (e.g., diuretics, low-dose aspirin, cyclosporine, and ethambutol)
- Alcohol consumption ↓ (especially beer!)
- Strive for normal weight

**N.B.** Under total fasting, catabolism can lead to a rapid increase in uric acid level and trigger a gout attack.

**Medications for gout**

If general measures are not sufficient to decrease the uric acid level below 9 mg/dl in the case of manifested gout, medication is indicated.

**Overview of gout therapeutics**

<table>
<thead>
<tr>
<th>Therapeutics</th>
<th>Uricostatics</th>
<th>Uricosurics</th>
<th>Ureolytics</th>
<th>Colchicine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td>Allopurinol, febuxostat</td>
<td>Benzbromaron, probenecid</td>
<td>Uric acid oxidase enzyme</td>
<td>Colchicum</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Inhibition of xanthine oxidase (of purine degradation)</td>
<td>Inhibition of tubular re-absorption</td>
<td>Transfers uric acid into soluble allantoin</td>
<td>Inhibition of mitosis and of phagocyte activity of the leukocytes</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Long-term therapy</td>
<td></td>
<td></td>
<td>No influence on the uric acid level, only coping with a gout attack</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Gastrointestinal symptoms, leukopenia, increase in transaminases</td>
<td>Gastrointestinal disorders, headaches, exanthema, urticaria, crystalluria</td>
<td>Fever, vomiting, nausea, diarrhea, headaches, allergic reaction</td>
<td>Nausea, vomiting, abdominal pain, diarrhea, hemorrhagic enteritis</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Inhibits the degradation of azathioprine and theophylline</td>
<td></td>
<td>ASS decreases the effect.</td>
<td></td>
</tr>
<tr>
<td>Clinical application</td>
<td>Treatment for 1-2 weeks AFTER an acute gout attack, since worsening is possible otherwise.</td>
<td>Contraindication: pregnancy, kidney insufficiency</td>
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</tbody>
</table>

**Therapy for acute gout**

In addition to medications inhibiting inflammation (NSAIDs such as diclofenac, ibuprofen, COX-2-inhibitors, and glucocorticoids), colchicine can be administered. Although the drug extracted from the autumn crocus may trigger multiple side effects (see table), it is still used to treat severe gout attacks.

Local therapy entails cooling and immobilizing the joint, if possible, to minimize most of the pain.

**Surgical interventions for gout**

Gout tophi should be treated surgically only in acute, life-threatening conditions, for e.g., if a tophus suppresses the spinal cord. Similarly, surgical intervention for kidney stones is only indicated for therapy-resistant urinary stasis due to stone impaction.

**References**


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