

# PATHOPHYSIOLOGY OF GOUT

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*These lecture notes accompany my lectures on pathophysiology in the study module "Musculoskeletal system" at Innsbruck Medical University. The English version serves two purposes: as a learning aid for international students and to encourage German-speaking students to familiarize themselves with medical English; the lectures are delivered in German. The translation from the original [German version](#) is my own; I am afraid it will occasionally sound appalling to native English speakers, but it should at least be intelligible.*

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Gout is an inflammatory reaction to monosodium urate crystals. In the human body, urate is constantly near its limit of solubility, in a flux balance between production and elimination.

## URIC ACID PRODUCTION

Uric acid is formed by breakdown of purines from nucleic acids. By two hydroxylation reactions, xanthine oxidase transforms hypoxanthine via xanthine to uric acid. In animals, uric acid is further metabolized to highly water-soluble allantoin by opening the larger of the two rings with the help of the enzyme uricase. While the human genome still contains the gene for uricase, it has been inactivated by mutation in a hominid ancestor. Gout is therefore an exclusively human (or rather, primate) problem.

Obviously, uric acid production is a function of purine intake. Nutrients high in purines include meat, especially offal, sea food and beer, which contains guanine. [High consumption of fructose](#), as in fructose-sweetened beverages or cereals, seems to increase serum urate levels. Fructose is metabolized in the liver in an ATP-dependent process. Part of the "spent" AMP is disposed of, and the adenine broken down to uric acid. In contrast, coffee, dairy products and vitamin C lower urate levels.

It has been known since a long time that fasting strongly elevates serum urate levels. As we will see in a minute, the ketoacidotic state typical of fasting causes increased renal reabsorption. But production of uric acid is increased, too, via a mechanism resembling the one seen in fructose consumption. In fasting, more ATP is broken down, causing AMP to be metabolized to uric acid. In addition, the normal equilibrium between cell death and proliferation in our organism is skewed towards cell death, causing breakdown of more DNA. A typical situation where involuntary fasting may result in a gout flare is surgery, where a certain period of fasting is required by anesthesia.

In patients with leukemia or lymphoma receiving their first rounds of chemotherapy, breakdown of cells may cause marked hyperuricemia and acute gouty arthritis.

## URIC ACID ELIMINATION

As its name implies, uric acid is eliminated mainly via the kidneys. A smaller part is excreted via the intestines.

In the kidney, about 10% of filtered load is excreted, but this percentage is highly variable. The excreted amount is the net result of simultaneous reabsorption and secretion processes. In the proximal tubule, cells use SLC22A12 (synonym: URAT1, urate transporter 1) to reabsorb filtered urate anions in exchange for intracellular organic anions such as lactate or ketone bodies. In a metabolic state of lactic acidosis (alcohol) or ketoacidosis, in which lactate or ketone bodies are actively secreted, urate reabsorption is thus increased: both feasting and fasting raise urate levels and abet gout flares. Working in the opposite direction, purine nucleoside transporter ABCG2 and voltage-driven transporter SLC17A3 pump urate back into the lumen. At the basolateral membrane, voltage-dependent SLC2A9 transfers urate from the cell into the blood.

Solute carrier SLC2A9 is expressed by all cells of our body. While in the proximal tubule cell, relative concentrations cause it to export urate, it is very well able to import urate into other cells. SLC2A9 is a target gene of [p53, the guardian of our genome](#). Via p53, DNA damage by reactive oxygen species leads to induction of SLC2A9 and thereby to increased import of radical-scavenging urate. There are indications that the loss of uricase gene function may have enabled primates to live longer lives by better shielding cells from oxidative damage.

Renal excretion of urate is heavily influenced by genetic factors. Logically, polymorphisms making SLC22A12 less efficient increase renal excretion of uric acid, while problems with outward transporters result in hyperuricemia. A SNP (single nucleotide polymorphism) in ABCG2 results in amino acid exchange Gln141Lys. This substitution changes a conserved position in the intracellular ATP-binding domain and cuts the protein's urate transport rate by about 50%. This SNP is quite frequent, with about 10-20% of Europeans and 30- 50% of Asians carrying the allele. Presence of the allele roughly doubles the risks of hyperuricemia and gout. Missense mutations in SLC17A3, too, were reported to cause hyperuricemia and gout.

Urate excretion via the intestines is mediated by ABCG2, too. Thus, SNPs reducing the efficiency of this transporter negatively impact elimination via both kidneys and intestines.

Estrogen has a uricosuric effect by modulating expression of renal urate transporters, substantially decreasing serum urate levels in premenopausal women.

## HYPURICEMIA

One key problem for our understanding of gout is the fact that only a minority of individuals with hyperuricemia develop gout. More than 10% of the population in affluent countries has hyperuricemia (21% of males but only 3% of premenopausal females), however, only about 0.5% develop gout. Hyperuricemia is defined as serum levels of 6.8 mg/dl or more, the limit of uric acid solubility under physiologic conditions. Above this level, monosodium urate (MSU) crystals are forming somewhere in the body. The higher the serum levels over time,

the higher the probability of an eventual attack of gout. Hyperuricemia is in 90% caused by inadequate renal elimination

Crystallization is dependent on pH, the presence of nucleating partners and the temperature. Urate is less soluble in synovial fluid than in plasma and articular cartilage, especially in peripheral joints, is colder than adjacent tissue for lack of blood supply. Therefore, crystallization is likely to initiate in small peripheral joints.

While we routinely determine serum levels of uric acid in patients with a suspected diagnosis of gout, in many cases, the numbers we get back from the laboratory are not very helpful. People at very high levels may have no trouble at all, while in patients suffering an acute attack of gout, serum levels frequently have dropped to normal values.

Do we have to worry about asymptomatic hyperuricemia? We don't yet know for sure, but there are indications that hyperuricemia may promote hypertension and vascular disease.

## GOUT

### **Gouty Arthritis**

The "crystal-clear" way to diagnose gout is to aspirate some synovial fluid from the affected joint and look for the birefringent needle-like crystals in the polarizing microscope. However, for the danger of infections and other potential complications, it is not terribly popular to puncture a joint. Therefore, in most cases diagnosis is based on clinical presentation, which is quite characteristic: severe pain developing within hours, tenderness, warmth, swelling and erythema, e. g. in the first metatarsophalangeal or metacarpophalangeal joint. Frequently, gout flares up following rich meals and alcohol consumption, in the middle of the night.

How do the urate crystals lead to inflammation? The main waypoints, hammered out by genetic techniques, are uncontroversial: monosodium urate activates the NALP3 inflammasome, causing activation of caspase 1 and production of IL-1 $\beta$ . Yet, on closer inspection, the details are far from clear.

To begin with, MSU crystals are in the extracellular space, while NOD-like receptors, which on activation form inflammasomes, reside in the cytoplasm. How do they interact? Macrophages take up the crystals, but then, the crystals are in the endosomal compartment, not in the cytosol. NOD-like receptors are cytosolic sensors that recognize either microbial PAMPs (pathogen-associated molecular patterns) or molecular features characteristic of distressed cells, so-called danger signals. Distressed cells may bleed K<sup>+</sup> or break down RNA and DNA, leading to formation of uric acid.

One model that has been proposed works like this: Macrophages take up MSU crystals. Following fusion with acidic lysosomes, the decrease in pH causes the release of sodium from the crystals. Intracellular osmolarity increases, causing the cells to swell by influx of water. This has a short-time dilutive effect on intracellular K<sup>+</sup> concentration, activating NOD-like receptor NALP3. Activated NALP3 units aggregate to form an inflammasome, which in turn activates caspase-1 to cleave proIL-1 $\beta$  into IL-1 $\beta$ .

Still, that does not explain why flares of gouty arthritis occur only now and then despite continuous presence of MSU crystals and why attacks typically occur at night, following rich and alcoholic meals. There are indications that an increase in free fatty acids contributes to macrophage activation via Toll-like receptor 2 (TLR2). Toll-like receptors are pattern recognition receptors, too, but TLR2 and TLR4 have been shown to be partially activated by high levels of free fatty acids. The combination of a rich meal with alcohol intake is ideal to raise free fatty acids, as alcohol is metabolized to fatty acids. In addition, these conditions may intensify sleep apnea, which might promote a gout attack via hypoxia-related increased breakdown of ATP and simultaneous dips in pH by hypercapnia.

IL-1 $\beta$  is just the leading ingredient of a macrophage-released cocktail that also includes TNF $\alpha$ , IL-6, CXCL8 (IL-8) and other inflammatory mediators. CXCL8 attracts neutrophils. These are activated and contribute to acute arthritis with production of reactive oxygen species, lysosomal enzymes, prostaglandins and leukotrienes.

### **Tophaceous gout**

MSU crystals may form not only in the synovial fluid, but also in synovial membranes, peri-articular tissues like tendons, ligaments and bursae and elsewhere in the body, e. g. in the skin. Around these urate aggregates forms inflammatory reactive tissue that basically constitutes a foreign-body granuloma, altogether called a tophus. The reactive tissue consists of macrophages, multinuclear giant cells, lymphocytes and proliferating fibroblasts.

### **Nephropathy**

At the plasma pH of 7.4, 98% of uric acid is in the ionized form of urate. In the renal medulla, where pH may go down below uric acid's pK<sub>a</sub> of 5.75, uric acid formation is favored. Uric acid is less soluble than urate, so the renal medulla is especially conducive to uric acid crystallization which may lead to intratubular precipitations and interstitial tophi. Low volume and low pH of urine favor further development of urate stones.

Acute uric acid nephropathy is acute renal failure due to obstruction of tubules with uric acid crystals. It is mostly seen in leukemia and lymphoma patients with tumor lysis syndrome at the beginning of therapy.

Whether chronic "gouty nephropathy" is more than an occasional observation at autopsy, remains to be seen. In contrast, chronic nephropathy is clearly present in patients suffering from the rare X-linked Lesch-Nyhan syndrome, which is caused by a deficiency in the "spent-purine recovery" enzyme HGPRT (hypoxanthine guanine phosphoribosyltransferase). As purines cannot be reused in these patients, massive uric acid overproduction leads to chronic hyperuricemia and uricosuria.

Regarding kidney stones, about 10% consist primarily of uric acid.

### **Gout attack as part of the tumor lysis syndrome**

Initial therapy of leukemia, lymphoma or a malignant tumor can result in massive simultaneous cell death. In this condition, one of the problems is large-scale breakdown of DNA in the presence of impaired renal function, resulting in a spike of hyperuricemia and

gout attacks. In this case, short-term prevention is possible by injecting uricase from another organism.

## PHARMACOLOGY CROSS REFERENCE: THERAPEUTIC STRATEGIES

Patients need treatment in two different situations: during an acute flare of gout to alleviate symptoms and, in case of repeated acute attacks, during the interval to reduce the likelihood of another attack. A constraint to be kept in mind is renal function: some of the drugs below are contraindicated if creatinine clearance is reduced.

### **Options to alleviate acute attacks:**

**Colchicine** has been used to treat gout since antiquity. It is a toxin from autumn crocus (*Colchicum autumnale*) that binds to tubulin and inhibits its polymerization. Microtubules are required for vesicle transport and for the mitotic spindle. Colchicine works well to alleviate the excruciating pain of an acute flare, but its use is a balancing act against its toxic side effects. Obviously, the oral drug reaches its highest concentrations in the gastrointestinal tract, causing nausea and other gastrointestinal symptoms. It is contraindicated at reduced creatinine clearance. Colchicine is most useful if patients have it at home, so that they are able to take it quickly in response to a flare.

**Nonsteroidal antiinflammatory drugs (NSAIDS)** inhibit cyclooxygenase enzymes and with that, synthesis of pain-potentiating prostaglandin E<sub>2</sub>. They, too, are contraindicated in renal disease.

**Glucocorticoids** or **corticotropin (ACTH)** may be used in patients with reduced creatinine clearance. For their immunosuppressive effect, a potential infectious nature of the arthritis in question has to be excluded. Glucocorticoids may be injected directly in to the inflamed joint. Glucocorticoids inhibit expression and release of many cytokines, including IL-1 $\beta$ .

**Anti-IL-1 $\beta$ -therapy:** The importance of IL-1 $\beta$  in the pathogenesis of gouty arthritis is underlined by the effectiveness of medications countering IL-1 $\beta$ . However, compared to conventional therapy, these pharmaceuticals are extremely expensive and have the additional drawback of neutralizing a protein that is important for fighting infections. Apart, their effectiveness might encourage people to maintain unhealthy eating and drinking habits.

- **Anakinra** is a recombinant form of human IL-1 receptor antagonist, a protein that competitively blocks the IL-1 receptor. It was the first anti-IL-1 pharmaceutical, originally developed for rheumatoid arthritis, but gained little traction in that indication because anti-TNF $\alpha$  medication was more effective. In anecdotal cases, it was observed to be extremely effective in curbing flares of gout, which lead to renewed interest in anti-IL-1 $\beta$ -therapy. Use of anakinra itself is limited by its very short half-life.
- **Canakinumab** (Ilaris, Novartis) is a monoclonal antibody against IL-1 $\beta$ . It has been approved in the EU for patients with frequent flares of gouty arthritis who do not respond to the drugs above or are unable to tolerate them. In a trial testing Canakinumab for cardiovascular benefits (CANTOS), participants developed more infections.

## Options to bring down serum urate levels:

As we have seen, levels of urate depend on production as well as elimination. Urate-lowering therapy may be initiated on either end, with pharmaceuticals available to either inhibit urate-producing xanthine oxidase or to enhance renal elimination. During the first weeks or months of urate-lowering therapy patients are at increased risk of a flare of disease, possibly by mobilization of urate from tissue deposits. Prophylaxis with NSAIDs or colchicine is attempted to prevent these flares.

### -Xanthine oxidase inhibitors:

**Allopurinol** is a purine analog structurally resembling hypoxanthine: just a single nitrogen is shifted within the smaller of the two rings. It competes with hypoxanthine for the xanthine oxidase binding site. With inhibition of xanthine oxidase, less uric acid is produced and more hypoxanthine and xanthine are eliminated via the kidney. To minimize the risk of acute flares during therapy initiation, it has to be started in increments of 100 mg. It has to be dosed individually: at the typical dose of 300 mg per day, many patients remain underdosed and still demonstrate hyperuricemia. Patients with HLA allele HLA-B\*58.01 are at increased risk for a hypersensitivity syndrome, which might be caused by allopurinol-modification of the MHC binding pocket, paralleling the hypersensitivity mechanism shown for HIV-medication Abacavir. The hypersensitivity syndrome may manifest as Stevens-Johnson or Lyell syndromes with high lethality. Should this risk be taken to prevent attacks of a painful, but usually self-limiting disease?

**Febuxostat** is a non-purine inhibitor of xanthine oxidase. It is hoped to avoid the grave but rare complications of allopurinol; whether that holds true will take years to establish. Flare prophylaxis seems even more important than with allopurinol and cardiovascular side effects may be more frequent.

### -Uricosuric drugs:

Uricosuric agents enhance uric acid elimination, primarily by inhibiting urate anion reabsorption in the proximal tubule. Of the three potential candidates, in most countries, only one is licensed; which one, varies according to country. This is an indication that all three have their problems. Obviously, they all rely on adequate renal function and become useless below a certain level of creatinine clearance. More excretion means higher concentrations in the urine and therefore, increased risk of urolithiasis, especially in acid urine.

- **Probenecid** is registered for gout in many countries, e. g., Germany, Switzerland and the USA, but not in Austria. It has been used previously to increase serum levels of antibiotics and it interferes with excretion of many drugs.
- **Benzbromarone**. This is the only one of the three registered in Austria, and only in combination with allopurinol, which does not seem to make too much sense. As monotherapy, it's available, e. g., in Germany, but not in Switzerland or the USA. Side effects are gastrointestinal symptoms, especially diarrhea. Benzbromarone was associated with very rare yet severe liver damage, causing one big drug company to take its product off the market.
- **Sulfinpyrazone** is the third drug that was in the past used for this purpose, but it has been discontinued in most countries.

## **-Injecting uricase to break down uric acid**

Reintroducing uricase, the enzyme lost in evolution, at first glance seems like a brilliant idea, but the problem is that our immune system never learned to tolerate it. Over time, we are bound to raise antibodies against it, in the best case making it ineffective, in the worst case producing more problems than we had before. So, it's either for desperate situations or for short-term indications. Two forms are used:

- **Pegloticase:** recombinant porcine uricase with polyethylene glycol (PEG) modification for chronic tophaceous gout refractory to conventional treatments. Pegylation reduces immunogenicity and increases half-life of the enzyme from a few hours to almost two weeks. The many long PEG chains wrap the enzyme in sort of a ball of wool, hiding its surface from B cell receptors and impeding access by proteases. In contrast, the small urate molecule easily diffuses between PEG chains into the enzyme's active center.
- **Rasburicase:** recombinant uricase from *Aspergillus flavus* for lymphoma patients, to prevent gout attacks and acute uric acid nephropathy due to massive tumor cell lysis at the initiation of chemotherapy.

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