The Biochemistry of Gout: A USMLE Step 1 Study Aid

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Compiled by:

Todd Kerensky

Elizabeth Ballard

Brendan Prendergast

Eric Ritchie
Introduction

Gout is a systemic disease caused by excess uric acid as the result of deficient purine metabolism. Clinically, gout is marked by peripheral arthritis and painful inflammation in joints resulting from deposition of uric acid in joint synovia as monosodium urate crystals. Although gout is the most common crystal-induced arthritis, a condition known as pseudogout can commonly be mistaken for gout in the clinic. Pseudogout results from deposition of calcium pyrophosphatase (CPP) crystals in synovial spaces, but causes nearly identical clinical presentation.

Clinical findings

Crystal-induced arthritis such as gout and pseudogout differ from other types of arthritis in their clinical presentations. The primary feature differentiating gout from other types of arthritis is the spontaneity and abruptness of onset of inflammation. Additionally, the inflammation from gout and pseudogout are commonly found in a single joint. Gout and pseudogout typically present with Podagra, a painful inflammation of the metatarsal-phalangeal joint of the great toe. However, gout can also present with spontaneous edema and painful inflammation of any other joint, but most commonly the ankle, wrist, or knee. As an exception, a spontaneous painful inflammation in the glenohumeral joint is usually the result of pseudogout. It is important to recognize the clinical differences between gout, pseudogout and other types of arthritis because the treatments differ markedly (Kaplan 2005).

Pathophysiology and Treatment of Gout

Although gout affects peripheral joints in clinical presentation, it is important to recognize that it is a systemic disorder caused by either overproduction or underexcretion of uric acid. High serum uric acid, or hyperuricemia, is the causative agent in gout; however, hyperuricemia is not pathomnemonic of gout. According to studies, 60-95% of individuals with hyperuricemia do not progress to gout (Smelser 2004). Therefore, researchers posit that other factors—such as alcohol abuse, obesity, and genetics—determine a predisposition to developing gout. Additionally, many patients with gout will not present with hyperuricemia in the clinic. It is important to reiterate, however, that all individuals with gout must have had hyperuricemia at some point in order to develop the disease (Lepsch 2005).

As stated earlier, uric acid is a normal byproduct of purine metabolism. The purine nucleotides AMP and GMP are broken down into hypoxanthine and xanthine, respectively. Xanthine is converted directly to uric acid by the action of xanthine oxidase (XO). Treatment for gout targets the enzyme xanthine oxidase by inhibiting its production of uric acid, and thus raising the concentrations of more soluble uric acid precursors, which can be excreted (see figure 1). The major drug used to treat gout is allopurinol, a structural analog of hypoxanthine. The action of allopurinol at XO is via another molecule, alloxanthine. Alloxanthine is a structural analog of xanthine made by
a reaction between allopurinol and XO. Alloxanthine is the active agent that acts as a competitive inhibitor on the XO active site.

![Diagram of the xanthine oxidase reaction and allopurinol inhibition](image)

Figure 1. The xanthine oxidase reaction converts hypoxanthine into xanthine and then into uric acid. XO is inhibited by alloxanthine, a product of the anti-gout drug allopurinol.

There are two principle ways that an individual can achieve hyperuricemia: overproducing or underexcreting uric acid. Uric acid is a normal metabolite of purine catabolism. If purines such as AMP, GMP, or adenine are overproduced, uric acid levels will rise consequently. Purine synthesis begins with ribose-5-phosphate and contains many steps that are highly feedback regulated by purine end products. PRPP synthetase and PRPP amidotransferase are the major rate determining enzymes of purine biosynthesis, and consequently, they are highly regulated. Mutations in either of these two enzymes could lead to a loss of feedback control, and thus cause overproduction of purines and eventually uric acid (King 2004). Deficiency of other enzymes in the purine synthetic pathway can cause hyperuricemia. Hypoxanthine-guanine phosphoribosyltransferase (HGPRT), for example, is an enzyme that “salvages” excess purine byproducts and converts them back into nucleotides by the following reaction:

\[
\text{hypoxanthine} + \text{PRPP} \rightleftharpoons \text{IMP} + \text{PP}_i
\]

If HGPRT is deficient, the body is unable to recycle hypoxanthine back into purine nucleotides. As a result, hypoxanthine levels build up and form uric acid (King 2004).
Underexcretion of uric acid is the other causative factor for hyperuricemia, and therefore gout. Underexcretion of uric acid typically occurs secondary to kidney disease and accounts for the minority of gout cases. The vast majority of gout is caused by overproduction of uric acid by the mechanisms outlined above (Lepsch 2005).

Although gout has been recognized and treated for centuries, the pathophysiology of gout has only been elucidated in recent years. It has long been known that gout is associated with hyperuricemia and monosodium urate crystals in joints, but it is now known that the painful inflammatory response seen in gout are the result of the lysis of polymorphonuclear cells (PMNs) that have ingested uric acid crystals. The jagged crystals rip open the plasma membrane of PMNs, releasing cytokines and other factors that initiate chemotaxis of more PMN cells. The process is represented pictorially in figure 2. (Kaplan 2005)

Figure 2. PMNs ingest uric acid crystals and rupture, causing release of chemotaxic factors that promote inflammation.
Pathophysiology and Treatment of Pseudogout

Although gout and pseudogout appear similar in the clinic, it is important to highlight the biochemical differences that account for the different treatment of the two conditions. Pseudogout arthritis is caused by the formation of calcium pyrophosphate (CPP) crystals in synovial spaces. CPP crystals are produced by nucleoside triphosphate pyrophosphohydrolase (NTPPPH) enzyme activity (Kaplan 2005). NTPPPH is found in vesicles within arthritic cartilage cells, but researchers are not certain about the etiology of these vesicles, though they suggest a genetic predisposition exists (Kaplan 2005). Research suggests that the pathophysiology of pseudogout inflammation is the same as that of gout: PMNs ingest jagged CPP crystals and rupture, causing chemotaxis of more PMNs and subsequent inflammation (Kaplan 2005).

Unlike gout, pseudogout is not a result of purine metabolism, and therefore hyperuricemia is not associated with the condition. A major consequence of the different biochemical mechanism of pseudogout is in treatment. Xanthine oxidase inhibitors like allopurinol are not effective, and therefore no effective prophylactic treatment exists.

Current Research in the Treatment of Gout


Xanthine oxidase catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid. Overproduction of uric acid can lead to hyperuricemia, which is directly linked to gout, due to the deposition of uric acid in the joints. This study aimed to identify a xanthine oxidase inhibitor, which would block the synthesis of uric acid. The authors looked at leaves of Lagerstroemia speciosa (L.) Pers. (Lythraceae), which was traditionally used as a folk medicine in the Philippines. The researchers used a bioassay-guided fractionation technique to isolate two active compounds, valoneic acid dilactone and ellagic acid. The results demonstrated that valoneic acid dilactone provided a stronger xanthine oxidase inhibitory effect than that of allopurinol, a clinical drug used to inhibit xanthine oxidase. Valoneic acid dilactone is a non-competitive inhibitor of the enzyme. This study supports the role of aqueous extracts from Lagerstroemia speciosa leaves for the treatment and prevention of gout.


This study assessed the physiologic effects of cherries in 10 healthy women who consumed Bing sweet cherries. The subjects were between the ages of 22-40 years old and each consumed two servings, 280 grams, of these cherries after an overnight fast. The authors measured plasma urate, antioxidant, and inflammatory markers by sampling blood and urine from the subjects before and after the cherry dose. Plasma urate decreased significantly over the five hour period after consumption and urinary urate per
A milimole of creatinine increased over the same period and at each sampling compared to the baseline value. Similar doses of other fruits such as grapes, strawberries, or kiwi did not affect plasma urate concentrations. This study confirmed that cherries provide anti-gout properties which can be used in recommendation for diet to help treat and prevent gout. The results however do not establish a mechanism, which may spark additional beneficial research.


The common clinical treatment for gout is the use of xanthine oxidase inhibitor, allopurinal, which is a purine analogue. At the time of publication allopurinal was the only commercially available xanthine oxidase inhibitor for the treatment of hyperuricemia and gout. As a result of this structural similarity to other purines, allopurinal inhibits other enzymes involved in nucleic acid metabolism. Takano and colleagues studied the selectivity of Febuxostat, a non-purine xanthine oxidase inhibitor. Several assays were performed using a Hitachi spectrophotometer to test the binding affinity of Febuxostat to enzymes of purine and pyrimidine metabolism. Lineweaver-Burk plots were used to interpret which type of inhibition this substance had on the enzymes. Febuxostat is a potent, high affinity mixed type inhibitor of xanthine oxidase, but had no significant effects on other enzymes in nucleic acid metabolism. These results are promising for the development of a high potent selective inhibitor of uric acid formation, which is an improvement over the current commercially available product.

**Case Studies**

Clinical Presentation #1:
A 58-year-old man woke up in the early morning due to a pain in his right wrist. He had never undergone a medical check-up. The pain was moderate at first, however, by the time he visited the emergency room, the pain was severe. Tenderness, swelling, and redness overlying the right wrist were remarkable which limited the range of motion. Laboratory studies showed elevated C-reactive protein (8.2 mg/dl), serum uric acid (8.8 mg/dl; normal 2.4-7 mg/dl) and mild leukocytosis (10,900/mm³). Detailed history-taking revealed that he had experienced several episodes of mild acute pain in the first metatarsophalangeal joint of his right foot. A diagnosis of acute arthritis of primary gout was made based on the following findings: more than one attack, maximum inflammation that developed within 1 day, monooarticular arthritis, redness observed over the joint, a past history of unilateral and painful attack in the first metatarsophalangeal joint, hyperuricemia and asymmetric swelling according to the criteria proposed by the American Rheumatism Association. Resolution of the attack occurred within five days after the initiation of diclofenac sodium 25 mg (a NSAID) three times a day (Kamimura, 2004).
Clinical Presentation #2:
A 55-year-old man has a 10-year history of ankle pain. Asymmetrical joint pains and swelling fluctuated at irregular intervals. Symptoms subsided in between but never completely ceased. Swelling and tenderness were present with no warmth or erythema. Three years after onset, pain spread to small joints of hands, knees, ankles, shoulders and elbows, with morning stiffness lasting over four hours. Two months prior to admission he presented with multiple nodular swellings on feet, hands, wrists and elbows. Patient's past medical history is significant for hypertension, diabetes mellitus, chronic ethanolism and renal stones.

creatinine 1.6 mg/dl
serum uric acid 10.9 mg/dl

Fluid from a nodular swelling was alkaline with WBC 25000 cells/cmm and monosodium urate crystals. Diagnosis of chronic tophaceous gout with rheumatoid arthritis was made (Khosla, 2004).

Questions:

1. What effect would the medication prescribed to Patient #1 have on serum uric acid levels?
   A. increase
   B. decrease
   C. no effect
   D. not enough information to determine

2. Which of the following compounds would be effective in reducing this patient’s uric acid load.
   A. allopurinol
   B. xanthine
   C. hypoxanthine
   D. guanine
   E. pyrophosphate

3. The painful inflammation of the first metatarsalphalangeal joint this patient experienced is characteristic of which of the following disorders?
   A. gout
   B. pseudogout
   C. rheumatoid arthritis
   D. A & B
   E. A, B, & C
4. This patient’s pain is caused by:
   A. accumulation of monosodium urate crystals in the joints
   B. accumulation of calcium pyrophosphate crystals in the joints
   C. cytokines and other chemotactic agents released from lysed leukocytes
   D. inflammatory effects of uric acid in the blood

5. Which of the following was not a factor in the development of gout in Patient #2?
   A. chronic alcoholism
   B. kidney stones
   C. genetics
   D. diabetes
   E. age
   F. weight

6. Which of the following is true regarding patient #2?
   A. His hyperuricemia is sufficient information to make the diagnosis of gout.
   B. Allopurinol would be more effective at reducing his serum uric acid than Febuxostat.
   C. Elevated levels of white blood cells in his skin nodules are due to the chemotactic properties of monosodium urate.
   D. Compromised kidney function is probably contributing to his hyperuricemia.

7. What enzyme is responsible for the production of uric acid in this patient?
   A. xanthine oxidase
   B. nucleoside triphosphate pyrophosphohydrolase
   C. hypoxanthine-guanine phosphoribosyltransferase
   D. PRPP synthetase

8. The elevated uric acid in this patient could be salvaged via which of the following pathways?
   A. Conversion of uric acid to xanthine via xanthine oxidase
   B. Conversion of hypoxanthine to IMP via hypoxanthine-guanine phosphoribosyltransferase
   C. Conversion of monosodium urate to calcium pyrophosphate via nucleoside triphosphate pyrophosphohydrolase
   D. Conversion of hypoxanthine to xanthine via xanthine oxidase
Answers and explanations:

1. **C.** A nonsteroidal anti-inflammatory drug would alleviate this patient’s painful inflammation but would have no effect on his circulating serum uric acid levels. Thus this represents an alternative to therapy with xanthine oxidase inhibitors.

2. **A.** Allopurinol is converted to alloxanthine in the body, a competitive inhibitor of xanthine oxidase. This would reduce the amount of uric acid formed by xanthine oxidase and thus lower serum uric acid levels. B, C, and D would all increase serum uric acid and E is not a metabolite in the synthesis of uric acid.

3. **D.** Podagra, inflammation of the first metatarsal phalangeal joint is a hallmark of both gout and pseudogout but is not common as an isolated finding in rheumatoid arthritis.

4. **C.** Although elevated uric acid is the ultimate cause of this patient’s condition his pain is mediated by the inflammatory response to cytokines and other agents released by leukocytes lysed by the ingestion of monosodium urate crystals.

5. **D.** Diabetes does not predispose this patient to developing gout, however all of the other answer choices are key factors in its formation.

6. **D.** Decreased kidney function can reduce the excretion of uric acid and thus lead to gout although this cause is not as common as defects in purine metabolism. Hyperuricemia alone is not sufficient to diagnose gout, Febuxostat has been shown to be more specific and more effective than allopurinol in xanthine oxidase inhibition, and compounds released from lysed PMN’s are responsible for the aggregation of WBC’s in this patients nodules.

7. **A.** Xanthine oxidase produces uric acid from xanthine as part of the metabolism of purines.

8. **B.** Hypoxanthine-guanine phosphoribosyltransferase can convert hypoxanthine, a precursor in uric acid synthesis, to IMP and thus shuttle metabolites away from uric acid formation and into purine synthesis. Deficiencies in this enzyme can be causative agent in gout.
Works Cited


Kaplan J. “Gout and Pseudogout.” Emedicine.com. 2005


