

**A REVIEW ON GOUT****Smrithy Elsa Sam\*, Tincy Elsa Thomas and Dr. Elesy Abraham**

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**\*Corresponding Author****Smrithy Elsa Sam**Nazareth College of  
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Thiruvalla, Kerala.**ABSTRACT**

Gout is a chronic arthritic disease associated with high levels of urate in blood. The development and expression of gout depends on three key steps: (1) chronic hyperuricemia, (2) the growth of monosodium urate (MSU) crystals, and (3) interaction between MSU crystals and the inflammatory system. Epidemiological studies have continued to improve our understanding of the environmental and genetic factors which influence chronic hyperuricemia and gout. The influence of obesity, alcohol, race, sex, age, and specific dietary components will be discussed below. The primary mechanism of hyperuricemia is

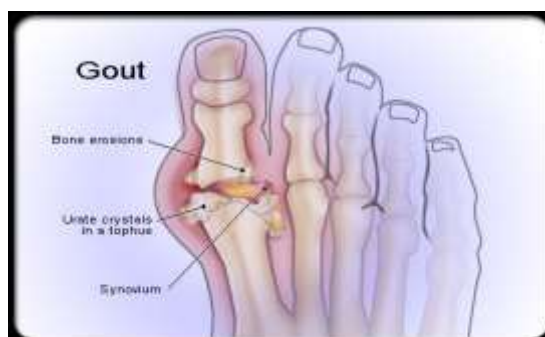
insufficient renal clearance of uric acid which in turn is dependent on transport of uric acid in the proximal renal tubule. The application of established principles of management including diagnosis through crystal identification, the gradual introduction of hypouricemic therapy with the use of prophylaxis to reduce the risk of flares, identification of a suitably low target of plasma urate, a progressive increase in therapy to achieve the target and taking steps to encourage good compliance, has the potential to improve outcomes for patients with this very common affliction. The potential role for new therapies will also be discussed.

**KEYWORDS:** gout, hyperuricemia, colchicine, allopurinol, Febuxostat, zurampic.**INTRODUCTION**

Gout is a medical condition usually characterized by recurrent attacks of acute inflammatory arthritis—a red, tender, hot, swollen joint. The metatarsal-phalangeal joint at the base of the big toe is the most commonly affected (approximately 50% of cases).<sup>[1]</sup> It may also present as tophi, kidney stones, or urate nephropathy. According to recent studies, gouty arthritis (as an indicator of gout) is the most common form of arthritis seen in general practice in adults, with a prevalence of about 1.4%<sup>[2]</sup>. Acute gouty arthritis occurs in men 95% of the time, and the first attack usually takes place between the ages of 40 and 50 (Beutler et al.,

1994). This disease occurs in woman after menopause and is uncommon before menopause. Gout cases are increasing due to ingestion of drugs especially aspirin that increases serum uric acid level<sup>[3]</sup>. It may be due to ingestion of food that has high content of purine. When purine breaks the formation of uric acid occurs. Human lack uricase, uric acid is not as easily removed, and can build up in body tissues. Uric Acid is synthesized in liver from the catabolism of purine. Uric acid is excreted through kidney if kidney is not working properly serum uric acid level increases. If concentrations of uric acid reach 7 mg/dL and above, uric acid begins to deposit in joints and inflammatory process starts in joints leading to painful gouty arthritis. This activation triggers a cascade that results in the release of interleukin (IL)-1 and other inflammatory cytokines. The release of the cytokines rapidly ignites a broader inflammatory response and the infamous redness, pain, and swelling of an acute gout flare.

Acute gouty arthritis typically presents with a sudden and severe exquisitely painful joint, most classically in the first metatarsophalangeal joint.



**Figure 1: Monourate Crystals in Joint**

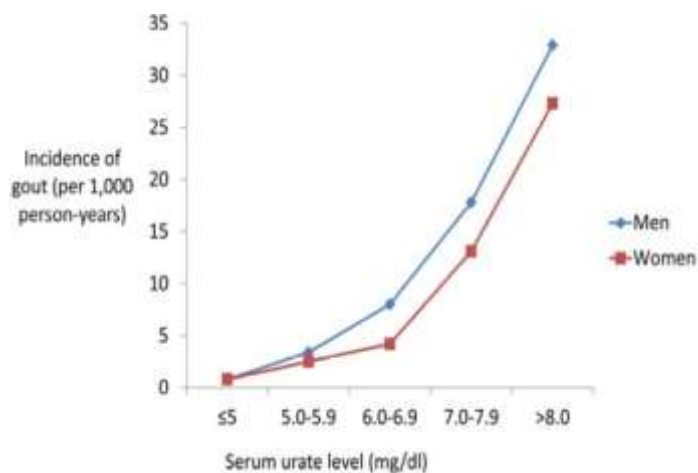
## PREVALENCE

Data from a number of countries suggest that gout is becoming more prevalent. In the USA, the National Health Interview Surveys asked participants about members of their household having gout within the preceding year. The one-year period prevalence of self-reported gout increased from 4.8/1000 in 1969 to 7.8/1000 in 1976, increasing further to 8.3/1000 in 1980<sup>[4]</sup>. Since then, the prevalence has remained fairly stable at 8.4–9.9/1000, with the most recently published estimate being 9.4/1000 in 1996. Similarly, the National Health and Nutrition Examination Survey (NHANES) found that the self-reported lifetime prevalence of physician-diagnosed gout increased from 26.4/1000 in NHANES III (1988–1994) to 37.6/1000 in NHANES 2007–2010. Furthermore, serum uric acid level (the key causal precursor of gout and primary end-point by the FDA for gout drug approval) has increased

over the interval between the two NHANES studies. Gout-related claims in an administrative claims database increased from 2.9/1000 in 1990 to 5.2/1000 in 1999<sup>[5]</sup>.

## INCIDENCE

Data from two general practice consultation databases show the incidence of gout to be stable in the UK. The earlier study, undertaken in the UK-GPRD between 1990 and 1999, found gout incidence per 10,000 patient-years to range from a low of 11.9 cases in 1991 to a peak of 18.0 cases in 1994, before stabilising at 13.1 cases in 1999. In both studies, gout incidence was higher in men than in women and increased with age<sup>[7]</sup>. The largest increase in incidence occurred in elderly. Data from two general practice consultation databases show the incidence of gout to be stable in the UK. The earlier study, undertaken in the UK-GPRD between 1990 and 1999, found gout incidence per 10,000 patient-years to range from a low of 11.9 cases in 1991 to a peak of 18.0 cases in 1994, before stabilising at 13.1 cases in 1999. In both studies, gout incidence was higher in men than in women and increased with age.<sup>[7]</sup>



**Figure 2: Incidence of Gout**

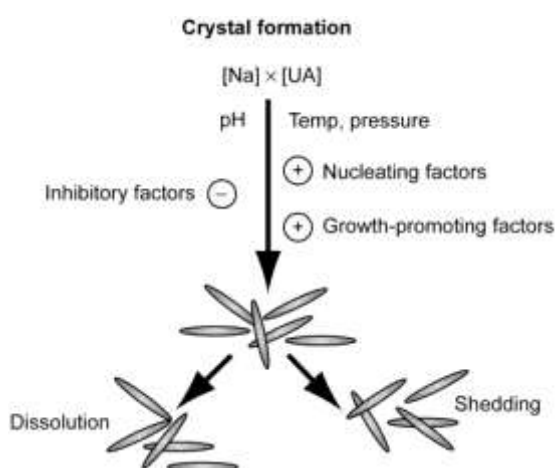
## AETIOLOGY

The crystallization of uric acid, often related to relatively high levels in the blood, is the underlying cause of gout. This can occur for a number of reasons, including diet, genetic predisposition, or underexcretion of urate, the salts of uric acid. Underexcretion of uric acid by the kidney is the primary cause of hyperuricemia in about 90% of cases, while overproduction is the cause in less than 10%. About 10% of people with hyperuricemia develop gout at some point in their lifetimes. The risk, however, varies depending on the degree of hyperuricemia. When levels are between 415 and 530  $\mu\text{mol/l}$  (7

and 8.9 mg/dl), the risk is 0.5% per year, while in those with a level greater than 535  $\mu\text{mol/l}$  (9 mg/dL), the risk is 4.5% per year<sup>[9]</sup>.

## **PATHOPHYSIOLOGY**

Gout is a true crystal deposition disease in which (i) the clinical symptoms are caused by the formation of monosodium urate (MSU) crystals in the joints and soft tissues and (ii) elimination of the crystals ‘cures’ the disease<sup>[11]</sup>. For crystals to form and gout to occur, the ionic product of sodium and uric acid must be at or above the saturation level at which MSU crystals can form. Uric acid is a weak acid with a  $\text{pK}_a$  of 5.75 and, at physiological pH of 7.40 it exists mainly in the ionized form as urate.



**Figure 3: Pathophysiology of Gout**

## **Clinical Stages**

Stage 1 - Asymptomatic Hyperuricemia

Stage 2 - Acute Gout Flares

Stage 3 - Intercritical Period

Stage 4 - Advanced Gout

## **Asymptomatic hyperuricemia**

During this stage, the blood level of uric acid is raised but the patient does not present with symptoms. Treatment is not usually required at this stage.

## **Acute gout attack**

By this stage, sodium urate crystals have been accumulating in the joints and formed deposits that cause pain, swelling and redness. The symptoms usually develop rapidly and pain becomes most intense within just 6 to 24 hours of onset. This is referred to as a “gout attack.”

Symptoms can last for between three and ten days, after which point the joint starts to feel normal again and pain subsides.

### **Intercritical Gout**

This refers to the time period between gout attacks where the patient is free of symptoms and joint function appears to be normal. However, the uric acid crystals continue to deposit in the joints and accumulate quietly, which eventually leads to another attack unless the uric acid level is reduced to below 6.0 mg/dL<sup>[14]</sup>.

### **Chronic tophaceous gout**

This is a late stage of gout. It now becomes a chronic arthritis which often results in deformity and destruction to the bone and cartilage. An ongoing, destructive inflammatory process is active, and kidney damage is also possible. With proper medical attention and treatment, most gout patients will not progress to this advanced, disabling stage.

## **RISK FACTORS**

Genetic mutations may be associated with overproduction or more often underexcretion—of uric acid because of defects in the renal urate transporter system. The female sex hormones increase urinary excretion of uric acid, pre-menopausal women have a substantially lower prevalence of gout compared with men (2.0% vs. 5.9%). Black persons have a higher risk. Consuming alcoholic drinks (particularly beer), meat (especially red meat, wild game, and organ meat), some seafood (e.g., shellfish, some large saltwater fish), fruit juice, and beverages sweetened with high-fructose corn syrup increases the risk of gout<sup>[15,16,17]</sup>. Purine-rich foods such as nuts, oatmeal, asparagus, legumes, and mushrooms do not seem to increase the risk. Consumption of dairy products appears to confer slight protection from gout.<sup>[18]</sup>

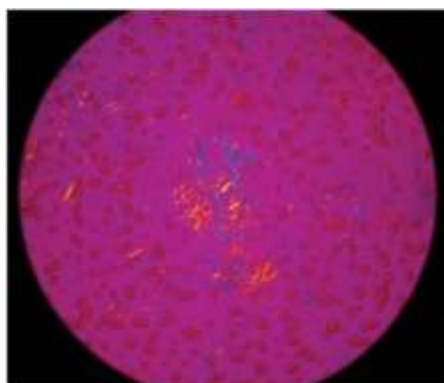
## **CLINICAL PRESENTATIONS**

Clinical symptoms of gout include severe pain (often described as “excruciating”), acute inflammation, redness, fever as high as 102°F with or without chills, long-term joint damage with successive bouts, and deposits of the urate crystals (called tophi) on or under the surface of the skin, most notably within or on the ears. Due to the inflammation and pain, affected joints typically lose significant range of motion and stability. Weight-bearing becomes difficult or impossible. Light pressure, such as the weight of a single bed sheet, can be too painful to bear for some sufferers during acute episodes. Gouty arthritis can develop very quickly, with the first episode often occurring in the middle of the night. In men, the initial

gout attack is usually monoarticular, involving only one joint, although later attacks may be polyarticular and involve multiple joints. In postmenopausal women, the attacks are commonly oligo- or polyarticular and involve the proximal joint of the big toe and (in decreasing order of frequency) the heels, knees, wrists, fingers and elbows<sup>[19]</sup>.

## DIAGNOSIS

The diagnosis can be confirmed through sampling the joint fluid by inserting a small needle into the affected joint; this procedure is performed under local anaesthetic<sup>[21]</sup>. Under the microscope, joint fluid from an affected joint will be full of tiny uric acid crystals that look like small needles. Blood tests may also be performed to check for uric acid levels and kidney tests may be done to check your kidney function<sup>[22]</sup>.



**Figure 4:** *Gout diagnosis: MSU crystals under a polarizing microscope.*

## COMPLICATIONS

Complications of gout include small lumps forming under the skin (tophi), joint damage and kidney stones. Left untreated, gout can develop into a painful and disabling chronic disorder.

**Tophi:** Gout is caused by a chemical called uric acid forming small crystals in and around the joints. These crystals also often build up under the skin and form small white or yellow lumps known as tophi.

Tophi are usually painless, but they can form in awkward places, such as at the ends of your fingers and around your toes. The development of gouty tophi can also limit joint function and cause bone destruction, leading to noticeable disabilities, especially when gout cannot successfully be treated. Tophi can develop anywhere in the body, but usually form on the heels and toes, knees, fingers, forearms and elbows.



**Figure 5: Tophi**

**Joint damage:** Without treatment, gout attacks may become more frequent and prolonged, and your likelihood of developing permanent joint damage will increase. In the most serious cases, surgery may be required to repair or replace a damaged joint.

**Kidney stones:** These occur in 10-40 percent of gout patients and about 25 percent of those with chronic hyperuricemia develop kidney disease, which sometimes culminates in kidney failure. Although, it should be noted that in most cases the kidney disease comes first and causes high concentrations of uric acid secondarily due to reduced filtering.

#### **Effect of gout on other disorders**

**Glucose intolerance and diabetes:** Although diabetes reduces the likelihood of future gout, when the relationship has been studied in the reverse direction, gout in men with a high cardiovascular risk profile, was found to increase the future risk of type II diabetes, independent of BMI.

#### **Hypertension and renal disease<sup>[15]</sup>**

Gout increases the risk of death in renal dialysis patients. The coexistence of impaired renal function and gout has important implications for therapy. In most patients with this combination, the renal disease is not due to gout. Chronic gouty nephropathy, characterized histologically by MSU crystal granulomas with foreign body giant cells, interstitial fibrosis and vascular changes, has been reported in patients with chronic tophaceous gout but appears to be extremely rare in the absence of substantial tophaceous disease. It has been suggested that deterioration of renal function in patients with gout can usually be attributed to hypertension, diabetes or unrelated renal disease. Thus, hyperuricemia has relatively little effect on renal function in most individuals but in patients with gout, allopurinol therapy may have some renal protective effect.



## TREATMENT

### 1) Non pharmacological

Primary prevention of gout involves changes in lifestyle, such as changes to diet (low - purine/weight-reducing diet) and restricting alcohol consumption. Lifestyle changes may have some effect<sup>[25]</sup>. Avoid or minimize consumption of fatty meats [red meat], sea food and fats. Consume regularly cereals, pulses, fruits, vegetables, and nuts in moderation and low fat milk and milk products. Consumption of eggs is not a risk factor but they have high cholesterol content. Tea, coffee and spices pose no risk. Carbonated beverages may contain added phosphoric acid and their regular consumption may be a risk factor for calcium oxalate renal calculi.

### 2) Pharmacological

The pharmacological treatment of gout is divided into 2 phases:

1) Treatment for acute gout;

- Colchicine, NSAIDs, Corticosteroids

2) Treatment for chronic gout or hyperuricemia:

- Uricosuric drugs: probenecid, sulphinpyrazone, benzbromarone
- Uric acid synthesis inhibitor: Allupurinol, Febuxostat.

DRUGS	DOSE	ADVERSE EFFECTS
<b>COLCHICINE</b>	<b>0.6mg</b>	Anemia, alopecia, leucopenia, diarrhea
<b>NSAIDs : Indomethacin</b>	<b>25-50mg thrice daily</b>	Headache, giddiness, mental confusion, blurring of vision
<b>CORTICOSTEROIDS</b>	<b>30mg/ day</b>	Osteoporosis, cushing's syndrome, weight gain, hypertension
<b>ALLOPURINOL</b>	<b>150mg</b>	Fever, skin rash, hepatitis, worsened renal function
<b>FEBUXOSTAT</b>	<b>10- 120mg once daily</b>	Chest pain, rashes, joint pain, and liver problems
<b>PROBENECID</b>	<b>250mg thrice daily</b>	Dyspepsia, GI irritation, nausea, vomiting, anorexia, headache
<b>SULFINPYRAZONE</b>	<b>100-200 mg thrice daily</b>	Nausea, abdominal pain, GI bleeding, rashes, aplastic anemia
<b>BENZBROMARONE</b>	<b>50-200 mg once daily</b>	GI effects, renal colic, liver damage

Figure 6: *Drugs used in the treatment of gout*



**Colchicine**

Colchicine is perceived as safer than NSAIDs in patients with mild to moderate renal insufficiency, as long as the maintenance dose is adjusted. Sodium urate crystals in joints are coated by either anti-urate IgG antibody or lipoprotein containing apolipoprotein B and then ingested by granulocytes, the latter then release a glycoprotein which amplifies neutrophil infiltration into the joint. By binding to tubulin, colchicine damages the micro-tubules in the granulocytes and interferes with mitotic spindles. It thereby inhibits the migration of cells into the inflamed area. Colchicine is an alternative for those unable to tolerate NSAIDs in gout, anti-inflammatory agent, for the treatment of chondritis and mild skin symptoms.<sup>[18]</sup>

**Non steroidal anti-inflammatory agents**

One of the strong anti-inflammatory drugs like indomethacin, naproxen, piroxicam, or phenylbutazone is given in relatively high and quickly repeated doses. Naproxen and piroxicam specifically inhibit chemotactic migration of leukocytes into the inflamed joint. After the attack is over, they may be continued at lower doses for 3-4 weeks while drugs to control hyperuricaemia take effect. They are usually not an option in persons with chronic renal disease as they can worsen renal function temporarily or permanently, cause fluid retention and increase blood pressure dramatically. NSAIDs are used to relieve pain and reduce signs of inflammation, such as fever, swelling and redness.

**Intra-articular and systemic corticosteroids**

Intra-articular corticosteroids provide the fastest resolution of the acute gouty flare. Intra-articular steroids are also very safe in patients with renal insufficiency and should perhaps be a treatment of first choice unless there is polyarticular gout. Corticosteroids have both anti-inflammatory and immunosuppressive effect. Corticosteroids act directly on nuclear steroid receptors and interrupt the inflammatory and immune cascade at several levels. By this means, they reduce vascular permeability and inhibit accumulation of inflammatory cells, phagocytosis, production of neutrophil superoxide, metalloprotease, and metalloprotease activator, and prevent the synthesis and secretion of several inflammatory mediators such as prostaglandin and leukotrienes.

Indicated in refractory cases and those not tolerating NSAIDs/ Colchicine.

**Allopurinol**

Allopurinol has potent xanthine oxidase inhibition and urate-lowering properties, allopurinol is commonly under dosed or poorly adhered to in long-term treatment. The goal is to maintain a serum uric acid level <6.0 mg/dL. During purine metabolism, the purine nucleotides are degraded to hypoxanthine and xanthine, which are then oxidized to uric acid by xanthine oxidase. Allupurinol and its metabolic product alloxanthine, inhibit xanthine oxidase and hence they inhibit the oxidation of hypoxanthine and xanthine to uric acid, lower serum and urine uric acid and increase the excretion of hypoxanthine and xanthine in the urine.

Allopurinol is used in chronic gout to prevent future attacks. Allopurinol was also commonly used to treat tumorlysis syndrome in chemotherapeutic treatments, to improve outcomes for people with inflammatory bowel disease and Crohn's disease who do not respond to thiopurine monotherapy.<sup>[19]</sup>

**Febuxostat:** It is a non purine inhibitor of xanthine oxidase. Febuxostat is a non-purine-selective inhibitor of xanthine oxidase. It works by non-competitively blocking the molybdenum pterincenter which is the active site on xanthine oxidase. Xanthine oxidase is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Febuxostat inhibits xanthine oxidase, therefore reducing production of uric acid. It is indicated in patients allergic to or intolerant of allopurinol.

**Probenecid:** Probenecid competitively inhibits the reabsorption of uric acid at the proximal convoluted tubule, thereby promoting its excretion and reducing serum uric acid levels. It increases plasma levels of weak organic acids (e.g. penicillin, cephalosporin, or other  $\beta$ -lactam antibiotics) by competitively inhibiting their renal tubular secretion. It has also found use as a masking agent, potentially helping athletes using performance-enhancing substances to avoid detection by drug tests<sup>[21]</sup>.

**Sulfinpyrazone**

It is a pyrazolone derivative related to phenyl butazone having consistent uricosuricaction, but is neither analgesic nor anti inflammatory. Sulfinpyrazone increases urinary excretion of uric acid by competitively inhibiting tubular reabsorption of uric acid, thus lowering serum urate concentration and eventually reducing urate deposits in the tissues.<sup>[22]</sup>

**Benzbromarone**

Benzbromarone, a uricosuric drug is a potent but potentially hepatotoxic agent. In a recently published study of “allopurinol-intolerant” patients, 92% of patients given benzbromarone were successfully treated to sUA<5 mg/dL compared with 65% of patients given probenecid. Benzbromarone reduces plasma concentrations of uric acid by blocking renal tubular reabsorption and possibly by increasing intestinal elimination of uric acid<sup>[23]</sup>.

**Drugs which can cause hyperuricemia**

- Alcohol
- Thiazides, Bumetanide
- Niacin
- Cytotoxic drugs
- Amiloride, Ethacrynic acid
- Levodopa
- Salicylates in low dose<sup>[26]</sup>

**NEWLY INTRODUCED DRUG****ZURAMPIC**

The US Food and Drug Administration (FDA) has approved ZURAMPIC® (lesinurad) 200mg tablets in combination with a xanthine oxidase inhibitor (XOI) for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with an XOI alone on December 22, 2015. In combination with the current standard of care, XOIs allopurinol or febuxostat, ZURAMPIC provides a dual mechanism of action to increase excretion and decrease production of uric acid, enabling more patients with inadequately controlled gout to achieve target treatment goals. The FDA approval of Zurampic was based on three phase III studies, CLEAR1, CLEAR2 and CRYSTAL. CLEAR1 and CLEAR2 evaluated the efficacy and safety of a once daily dose of Zurampic in combination with allopurinol compared to allopurinol alone.

**Mechanism of Action**

Zurampic (lesinurad) reduces serum uric acid levels by inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidney. Lesinurad inhibited the function of two apical transporters responsible for uric acid reabsorption, uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4), with IC<sub>50</sub> values of 7.3 and 3.7 μM,

respectively. URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen. OAT4 is a uric acid transporter associated with diuretic-induced hyperuricemia. Lesinurad does not interact with the uric acid reabsorption transporter SLC2A9 (Glut9), located on the basolateral membrane of the proximal tubule cell.

## Clinical studies

### Overview of Clinical Studies of ZURAMPIC

The efficacy of ZURAMPIC 200 mg and 400 mg once daily was studied in 3 multicenter, randomized, double-blind, placebo-controlled clinical studies in adult patients with hyperuricemia and gout in combination with a xanthine oxidase inhibitor, allopurinol or febuxostat. All studies were of 12 months duration and patients received prophylaxis for gout flares with colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) during the first 5 months of ZURAMPIC treatment. Although other doses have been studied, the recommended dose of ZURAMPIC is 200 mg once daily in combination with a xanthine oxidase inhibitor.

### Adverse effects

Most common adverse reactions in 12-month controlled clinical trials (occurring in greater than or equal to 2% of patients treated with ZURAMPIC in combination with a xanthine oxidase inhibitor and more frequently than on a xanthine oxidase inhibitor alone) were headache, influenza, blood creatinine increased, and gastro esophageal reflux disease.<sup>[25]</sup>

## CONCLUSION

In summary, gout is a crystal deposition disease that is associated with acute and chronic inflammation. However, it can be cured by long-term reduction in the sUA level <6 mg/dl (360 µmol/l), sufficient to dissolve crystal deposits and prevent formation of new crystals. This results in freedom from acute gout attacks, shrinkage and eventual disappearance of tophi and prevention of further tissue damage. While gout itself can be cured by lowering the sUA level below this target, joint and tissue damage that has already occurred may not be reversible, emphasizing the importance of treating the condition before such permanent damage has occurred.

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