

Gout

— the disease and non-drug treatment

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The word gout originates from the latin word *gutta* (meaning "drop"). The theory was that gout stemmed from evil humours literally "dripping" into areas where they did not belong. This article explains the disease and non-drug treatments in present day terminology



Gout commonly affects the joints of the foot

Gout is defined as a syndrome caused by an inflammatory response to the formation of monosodium urate (MSU) crystals which develop secondary to hyperuricaemia. It was recognised as early as the 4th century BC. Hippocrates was the first to note that gout does not occur in men before puberty or in women until after the menopause. Dutch scientist Antonj van Leewenhoek (1632–1723) described the microscopic appearance of urate crystals from a tophus and in 1847 the English physician Alfred Garrod identified uric acid in the serum of a man with gout, linking the disease with hyperuricemia.

Over the past century major advances have been made in understanding the aetiology and overall management of gout, facilitated by development of many drugs.

— Epidemiology

The prevalence of gout varies from approximately 0.2 per cent across Europe and the US to as high as 10 per cent in the adult male Maori population in New Zealand. Male Maoris are predisposed to hyperuricaemia with one in three men over the age of 40 affected. The clearance rate of renal urate in the Maori males has been shown to

be lower in those suffering with gout, suggesting a renal mechanism for their hyperuricaemia. Filipinos living in the US have a higher prevalence of gout than those living in their native Philippines, demonstrating the role of environmental as well as genetic factors. Higher social classes suffer more commonly with gout and up to one third of patients have a positive family history of a first degree relative suffering from the disease.

Gout predominantly affects males with its onset commonly in middle age. However, recent literature suggests that the epidemiology of the disease is changing. As the population ages there is an increasing prevalence amongst elderly females. This may reflect an increasing life expectancy with chronic diseases such as diabetes and atherosclerosis, and the various drugs used to treat these conditions.

Over half of the patients diagnosed with gout will admit to regular alcohol consumption. Gout is rare in children and premenopausal females and is not common in males under the age of 30. Peak age of onset is between 40 and 50 in men and somewhat later in females.

— Clinical manifestations

Today gout can manifest clinically in different ways:

- Asymptomatic hyperuricaemia — this is 10 times more common than gout

- Acute gout — particularly affecting the small joints of the feet (one joint only is affected in 90 per cent of attacks)
- Chronic gout
- Chronic tophaceous gout. Tophi are aggregations of urate crystals affecting articular, periarticular and non-articular cartilage (eg, ears)
- Gouty nephropathy, which can cause tubulo-interstitial disease (due to parenchymal crystal deposition), acute intratubular precipitation (resulting in acute renal failure) or urate stone formation

A typical acute attack of gout begins suddenly, generally overnight. Excruciating pain is noted commonly in the first metatarsophalangeal (MTP) joint (at the base of the big toe). Gout affecting joints of the foot is called podagra.

Classically the pain can be so severe the patient would be unable to tolerate the bed sheet touching the joint. In 25 per cent of attacks, joints other than the first MTP are involved, commonly joints of the lower limbs. The affected joints appear red and swollen, are hot to touch and are extremely tender. Mild attacks may peak in one to two days, whereas more severe attacks can peak within a few hours. About 90 per cent of initial attacks affect a single joint and subsequent attacks may affect the same joint or progress to involve other joints.

If the disease is left untreated the incidence of polyarticular gouty attacks

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increases. Following an initial attack approximately two thirds of patients will go on to suffer from a second attack within 12 months.

The proportion of patients who go on to develop chronic gout is not known but is thought to be dependent on the number of patients in whom hyperuricaemia is not controlled.

Tophi appear clinically as firm nodules or swellings. Overlying skin may be erythematous if there is local inflammation. Tophi can occur at any site, with the most common being the fingers or toes, the elbows and, less commonly, the ears. Patients will have usually suffered with gout for at least 10 years before tophi develop. However, there are a few exceptions when tophi can develop earlier:

- In gout secondary to a myeloproliferative disorder
- In chronic renal disease where there is disproportionate hyperuricaemia
- In elderly females on concurrent diuretic medication

— Investigations

Baseline investigations for gout include: plasma urate or uric acid, urea, creatinine, C-reactive protein, blood glucose and fasting lipids and a urine dip looking for blood or protein. Other useful tests include liver function tests and gamma-glutamyl transferase levels which can be used as a baseline for treatment with certain drugs and as an indication of alcohol consumption. As the urate level increases so does the annual incidence of gouty arthritis.

The definitive diagnosis of gout is made by examination of joint fluid and analysis

under a polarising light microscope to confirm the presence of MSU crystals. MSU crystals indicate the presence of gout as opposed to calcium pyrophosphate dehydrate crystals which are seen in pseudogout. It is important to exclude infection, which also presents as a hot swollen joint. To do this the sample is assessed for cell count and culture.

Tophi can be examined in a similar manner to joint fluid. Urate crystals are needle shaped and classically described as negatively birefringent when viewed under plain polarised light. The entire smear from the tophi will consist of these crystals, so there should be no doubt as to the diagnosis.

Early acute gout can be seen only as soft tissue swelling on plain X-rays, with definite joint abnormalities occurring after several years and gouty attacks. Various differences seen on X-rays can be used to distinguish gout from rheumatoid arthritis (RA). Gout tends to favour monoarticular or unsymmetrical joint involvement unlike RA which is by definition a symmetrical polyarthritis. X-rays of gout show a well maintained joint space and no bone fusion, unlike in RA. Juxta-articular osteoporosis is seen in early RA but not gout, and eccentric opacities can be seen in soft tissues with gout and are due to tophi. Occasionally tophi can appear as calcification, and this tends to occur peripherally. Boney erosions are seen where tophi form *in situ*.

— Aetiology

Gout is a metabolic disorder of purine metabolism. Purines can be synthesised from precursors, but significant amounts are ingested in our normal diets and subse-

quently released at cell death. Two thirds of our uric acid comes from our dietary intake. Uric acid is a breakdown product of purine nucleotides. Hyperuricaemia results from over-production (75 per cent) or under-excretion (25 per cent) of uric acid. Common reasons for a decrease in uric acid excretion include decreased renal function, diuretics, hypertension, low dose salicylates and lead intoxication. Acute attacks can be triggered by alcohol, surgical stress, trauma, acute illness and drugs (eg, diuretics, allopurinol or probenecid). The causes of gout are listed in Panel 1.

— Pathophysiology

Uric acid exists as urate ions in the blood and plasma at a normal temperature and pH. Urate is derived from dietary purines as well as degradation and turnover of the body's purine nucleotides. This explains why patients with increased proliferation or degradation of cells (eg, as seen in haematological malignancies) need prophylaxis for gout before commencing cytotoxic therapy.

Urate must be eliminated from the body to maintain a state of equilibrium. Birds and reptiles break down urate using the enzyme urase; the product is their main way of excreting nitrogen. Humans, however, lack this enzyme and the majority of urate is eliminated via the kidneys, with a small proportion being excreted via the gastrointestinal tract. Nearly all plasma urate is filtered at the glomerulus and is almost completely reabsorbed in the proximal tube. Therefore a small amount passes to the loop of Henle. There is active tubular excretion of urate, which is thought to be the most important factor in maintaining urate equilibrium. About 10 per cent of all filtered urate is finally excreted in the urine.

Formation of MSU crystals is determined primarily by urate concentration at the site of crystal formation. Local temperature and the presence of proteoglycans that maintain urate as a soluble molecule are believed to play a part.² Numerous mechanisms for the increase in urate concentration in joints have been raised. These include a decrease in the amount of water in the joint eg, dehydration which occurs at night as do acute gout attacks. A lower temperature in the peripheral joints also facilitates crystal formation, perhaps explaining why gout affects more peripheral joints.

— Non-pharmacological treatments

It is important that patients understand the diagnosis of gout and the importance of being treated. Long-term therapy is generally considered following an acute, severe attack. Drug therapy is used for the symptomatic treatment of an acute attack and to prevent further episodes of gout.³

Panel 1: The causes of gout

Primary (innate)

- Idiopathic (90 per cent of these cases are due to under-excretion of uric acid)
- Rare enzyme deficiencies, eg (Lesch-Nyhan syndrome)

Secondary hyperuricaemia

- Increased uric acid production or intake
 - Myeloproliferative and lymphoproliferative disorders
 - High purine diet
 - Cytolytic therapy
 - Acidosis, eg, ketosis of starvation
 - Extreme exercise
 - Status epilepticus
 - Psoriasis
- Decreased uric acid excretion
 - Renal failure
 - Drugs, eg, diuretics, low dose aspirin, ciclosporin, pyrazinamide
 - Alcohol
 - Lead intoxication
 - Down's syndrome

Patient information leaflets about gout and dietary advice are now widely available. Lifestyle modification, adjustment of previously prescribed medicines and drug therapy specific for gout all contribute to treatment options.

The following simple measures can contribute to a reduction in uric acid levels:

- Weight loss (if overweight)
- Reduction of alcohol intake
- Avoidance of certain foods and drinks that may induce gout (eg, foods with a high purine content)
- Increased fluid intake
- Withdrawal of drugs that may precipitate gout (eg, thiazide diuretics)

Hyperuricaemia is also a marker of cardiovascular risk, thought to be because of an association with obesity and an unhealthy lifestyle. A gout attack should be thought of as an opportunity to review the general health and lifestyle of the patient. If the patient is overweight he or she should be advised to reduce their weight gradually to a suitable sustainable level. Rapid weight loss can precipitate an increase in uric acid levels and therefore further attacks of gout.

Alcohol contributes to both obesity and purine content of the diet. Many types of beer contain guanosine, which is converted by bacteria in the gut to uric acid. When alcohol is consumed without food it is catabolised to lactate and other ketones. These breakdown products compete with urate to be excreted by the renal tubule. In addition, alcohol leads to a decrease in renal excretion of urate and causes dehydration. Binge drinking, in particular, should be avoided. Allopurinol, used in the treatment of gout, is converted to oxipurinol, which inhibits xanthine oxidase. Alcohol decreases this conversion therefore decreasing the efficacy of allopurinol in gout prophylaxis.

Fluid intake should be around two litres per day in the form of water and soft drinks. Coffee, tea and other drinks containing caffeine act as diuretics and it is important to emphasise this to the patient when giving advice about increasing their fluid intake. Also, patients should be advised to avoid foods that contain high amounts of purines, such as liver, kidney, heart, meat extracts (eg, Bovril and Oxo), crab, fish roes, anchovies, herring, mackerel and sardines.

Choi *et al* have recently undertaken a large prospective study into dietary risk factors for gout.⁴ Results from their study concluded that males in the highest quintile for meat consumption had a 41 per cent higher risk of developing gout than those in the lowest quintile. A slightly higher figure (51 per cent) was noted for consumption of seafood. The same study also found that there was no increased risk of gout in those who consumed excess amounts of purine rich vegetables (eg, peas, beans, lentils,

spinach and mushrooms) and that dairy consumption was inversely associated with the serum urate level.

During an acute attack of gout patients are advised to avoid the foods previously listed, avoid alcohol altogether, drink up to three litres of clear fluid per day and take the appropriate medicine prescribed for acute gout attacks.

— Conclusion

Gout is a painful debilitating condition that affects more men than women. It is a relatively common condition and incidence may be increasing due to our ageing population. The incidence and prevalence varies across the world. Genetics, environmental factors, lifestyle, renal function and other chronic diseases all contribute to an increased incidence and frequency of developing gout. There are many causes of hyperuricaemia. These can simply be classified as increased intake and breakdown of purines or decreased excretion. Risk factors must be considered and addressed at the initial diagnosis in order to optimise management. Patient understanding and compliance is crucial for the management of gout, which is both treatable and preventable. Education and lifestyle modification play a major role in prevention of future attacks. Recommendations for prevention of gout parallel those given for other chronic diseases, such as diabetes and ischaemic heart disease. Drug treatment is used to treat acute episodes, to prevent future attacks and for the management of chronic tophaceous gout.³

— References

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