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Hyperuricaemia and gout

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ABSTRACT Gout is increasing in prevalence throughout the world, particularly in developed countries. The causes are dietary – purine-rich foods, high saturated fats, fructose-containing drinks and alcohol. Gout is also drug-related and associated with increased obesity, hypertension, insulin resistance and metabolic syndrome. Although very readily treated, there is evidence that physicians fail to optimise the treatment and achieve low enough serum urate levels, while patients fail to comply with the treatment and dietary advice. Standard treatment of acute attacks is with non-steroidal anti-inflammatory drugs, colchicine or steroids. The standard urate-lowering agents are allopurinol and uricosuric agents. Newer urate lowering agents are now available for refractory gout. Increased understanding of the membrane transporters involved in urate excretion in the kidney and the genes that control them and of the way that sodium urate crystals cause inflammation via the innate immune system and the inflammasome offers hope for new therapeutic approaches.

KEYWORDS Gout, hyperuricaemia, inflammasone, innate immunity

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OVERVIEW

History

Podagra, gout affecting the great toe, was first identified by the Egyptians in 2640 BC and described by Hippocrates in the fifth century BC as 'the unwalkable disease'. Thomas Sydenham had gout and described it in 1649: 'the patient is awakened by a severe pain in the big toe … so exquisite and lively meanwhile is the feeling of the part affected that the sufferer cannot bear the weight of the bed-clothes nor the jar of a person walking in the room.'[1]

To the public, gout causes curiosity and mirth and is viewed as a consequence of excess alcohol and rich living. Historically it was regarded as the disease of kings and the wealthy. Evidence suggests, however, that the most important dietary elements were not port wine and purine-rich foods (red meat, offal, seafood and beer) but lead acetate used to sweeten wines. Saturnine gout (pauper's gout) was more associated with plumbers and painters because of their exposure to lead paints and pipes, but lead from sweeteners, wine and food containers meant rich man's gout was also associated with lead poisoning. Lead interferes with the renal transport of urate and reduces its excretion.

Primates lost the gene for the hepatic oxidative enzyme uricase during their evolution around 10–20 million years ago. It has been suggested that the resultant hyperuricaemia provided an evolutionary advantage, possibly because of its antioxidant properties. There may also have been an advantage to primates from its mildly hypertensive effect.[2] These advantages are probably irrelevant in humans because of dietary changes and increased urate load.

Prevalence, diet and comorbidities

The prevalence of gout is 1.4% in the UK, increasing with age to 3% in women and 7% in men.[3] In the USA it has been increasing with increasing age, and the prevalence is still rising.[4] It is usually idiopathic, with 85–90% caused by under-excretion of urate and 10–15% by overproduction. Gout is rare in pre-menopausal women, unless they are on high doses of diuretics or have renal impairment. The prevalence in Eastern countries is lower but may increase as their traditional diet gives way to more Western styles of cooking and increased meat intake. The increase in prevalence in the West is due to a variety of factors – obesity, increased alcohol intake, an increase in metabolic syndrome and the use of fructose to sweeten soft drinks[5] and total fructose intake from juices and fructose-rich fruits (oranges and apples). Diet soft drinks are not associated with a higher risk of gout. The pattern of the disease is also changing, with polyarticular attacks being more frequent; the reason for this is not clear. See Table 1 for dietary and lifestyle advice.

Clinical picture and differential diagnosis

Gout is usually diagnosed clinically – the onset of pain, redness and swelling is typically rapid, reaching its apogee in six hours. Although the first metatarsophalangeal joint is most commonly first affected, any joint can be involved. Not all pain in this joint is gout, however. Occasionally attacks are polyarticular. Gouty cellulitis occurs around an affected joint or sometimes as a sole manifestation. Gouty tophi are also diagnostic. The definitive diagnostic test, although not always practicable, is to detect typical strongly negatively birefringent, needle-shaped crystals of monosodium urate in synovial fluid under polarised light microscopy. Some crystals will be in polymorph nuclear

TABLE 1 Dietary and lifestyle advice for gout

Gradual weight loss to achieve an ideal body weight
Avoid purine-rich foods (liver, kidneys, shellfish, yeast extracts)
Change to low-fat dairy products
Increase vegetable intake
Reduce alcohol intake, avoid beers, fortified wines and spirits
Avoid fructose-containing soft drinks and fruit juices
Undertake regular exercise but avoid injuring joints

TABLE 2 Hyperuricaemia and saturation points for serum urate

Hyperuricaemia	
Men	0.42 mmol/l (7 mg/dl)
Women	0.36 mmol/l (6 mg/dl)
Supersaturation points	
At 35°C	0.36 mmol/l (6 mg/dl)
At 30°C	0.30 mmol/l (5 mg/dl)

leucocytes. Serum urate levels are usually persistently above the upper limit of normal. They may be normal during an attack, however, and in some patients they are always in the normal range but above the saturation point (see Table 2). The differential diagnosis includes septic arthritis and cellulitis, which must be excluded. Acute pseudogout affects the wrist and knee and occurs in older patients. Psoriasis causes hyperuricaemia, reflecting the high turnover of skin cells. Psoriatic arthritis can affect single joints, particularly in the feet but is distinguished by the fact that it responds less well to non-steroidal anti-inflammatory drugs (NSAIDs) and persists.

Hyperuricaemia and gout

Uric acid is the end product of endogenous and dietary purine metabolism. The typical crystals were first seen microscopically from tophi by van Leeuwenhoek in 1679 and characterised as sodium urate in the late 18th century. Serum urate concentrations are not normally distributed, being skewed to the upper range where most gout occurs. Hyperuricaemia is defined as serum urate above 0.42 mmol/l for men and 0.36 mmol/l for women. Around 10% of people with gout have levels in the normal range. Above the supersaturation level of urate (>.36 mmol/l at 35°C), monosodium urate crystals form and, in some individuals, cause a painful, self-limiting inflammatory arthritis. The most common cause of hyperuricaemia is reduced renal excretion. Some patients over-produce urate, typically in the tumour lysis syndrome and in certain inherited metabolic diseases. Hyperuricaemia, independent of crystal formation, has also been linked with hypertension, atherosclerosis, metabolic syndrome, insulin resistance and diabetes.

Hyperuricaemia is often asymptomatic. It occasionally causes acute nephrolithiasis. Clinical gout goes through distinct phases. The first attack causes severe joint pain and swelling but is self-limiting, settling within 7–10 days even untreated. The patient then enters an asymptomatic, intercritical phase. After a first attack the second is likely to occur within two years. A diet low in purines and saturated fats, alcohol reduction – particularly beer and spirits, and treatment of obesity, hypertension and dyslipidaemias are important during this phase. Interval gout comprises acute attacks, superimposed upon chronic symptoms that may be due to low-grade inflammation caused by urate crystals, or joint damage, or both. Chronic tophaceous gout occurs with or without acute attacks and is more common in renal impairment and long-term diuretic treatment. Tophi cause pain by local joint damage, by pressure or by ulceration.

Ciclosporin, used as an immunosuppressant in transplant recipients causes gout by interacting with a high affinity nicotinate transporter (hOAT10), which enhances urate uptake, and leads to hyperuricaemia. Ciclosporin interacts adversely with colchicine.

Hyperuricaemia and renal function

Not all causes of hyperuricaemia are extrinsic. The kidneys excrete 70% of daily urate production by a complex process of glomerular filtration, proximal tubule resorption and at least two phases of active resecretion, coordinated by a group of renal tubular urate transport molecules. Interfering with any part of this process causes hyperuricaemia, as does impaired renal function, whatever its origin. In some individuals, high urate levels lead to renal impairment due to renal crystal deposition and interstitial renal injury or direct toxic effects on the afferent arterioles.[6] Thiazide and loop diuretics also impair renal excretion of urate, possibly by inhibiting MRP4-mediated renal urate secretion.

Hyperuricaemia and cardiovascular disease

Urate is associated with cardiovascular risk. There is a higher prevalence of gout in individuals with an atherogenic lipid profile and low HDL-cholesterol (high density lipoprotein) levels are a strong predictor for gouty flares in hyperuricaemic patients. HDL may act by partly blocking the interleukin-1 beta (IL-1β) induced production of chemotactic factors by activated endothelial cells during acute gout. These observations reinforce the need to follow a low saturated fat diet and lose weight. Urate is an antioxidant but may also have radical forming properties, which impair endothelial function. There is insufficient evidence at present to justify urate-lowering agents in non-gouty hyperuricaemic patients, even those with high cardiovascular risks.

Hyperuricaemia and genetics

The fact that gout is in part an inherited disease has been known since Roman times. Urate transporter defects cause hyperuricaemia and gout. The urate anion transporter (*URAT1*) is mainly involved in proximal tubule

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resorption.[7] Low fractional excretion of uric acid, hyperuricaemia, and gout are associated with genetic variations in the *SLC2A9* gene, which encodes the glucose transporter family isoform *GLUT9*. This is a high-capacity uric acid transporter and is expressed in the kidney and several other tissues. *GLUT9* also transports fructose. A variant of this gene is the main cause of the increased incidence of gout in Polynesian populations. Studying these gene variations may help detect those at risk of gout, and contribute to our understanding of the role of urate in metabolic and cardiovascular diseases.

WHAT ARE THE MECHANISMS BY WHICH URIC ACID STIMULATES INFLAMMATION? THE ROLE OF THE INFLAMMASOME

Recent studies demonstrate how monosodium urate crystals trigger an acute inflammatory response in joints and periarticular tissues, although they are present in hyperuricaemic and gouty patients between attacks without causing this reaction. The explanation for this is not clear. Crystal triggering of gout is more common in osteoarthritic joints.

The innate immune system comprises a series of receptors, which recognise bacteria and viruses as 'foreign' and eliminate them by triggering the cytokine cascade. They are strongly conserved throughout evolution. Several types of receptors have been described, including the toll-like receptors (TLR) and the NOD-like receptors, also known as 'nucleotide-binding domain and leucine-rich repeat containing proteins' (NLRPs). The nomenclature is complex and still evolving. They are pattern recognition receptors and involved in diseases where there is inflammation without a triggering infection, including certain types of arthritis. The inflammasome complex comprises proinflammatory capsases and other molecules and provides a repertoire of responses to lipopolysaccharides and other ligands derived from most human pathogens. The NLRPs are intracellular sensors present in leucocytes and endothelial cells, which recognise pathogen-associated molecular patterns but also respond to endogenous 'danger-associated' molecular patterns. The best characterised component of the inflammasome is *NLRP3*. Mutations of the *NLRP3* gene cause hereditary periodic fever syndromes in humans, in which increased inflammasome activity leads to uncontrolled IL-1β production. This is clinically important because anakinra, an IL-1 receptor antagonist is a highly effective treatment for these syndromes.

The *NLRP3* gene has recently been demonstrated to play a central role in crystal-induced arthritis. Monosodium urate crystals (and calcium pyrophosphate crystals in pseudogout) are sensed extracellularly by an ill-understood mechanism probably involving *TLR2* and *CD14* on monocytes and then internalized where they activate the *NLRP3* inflammasome.[7] Activated *NLRP3* mediates the conversion of an inactive proform to (IL-1β) by activation of the enzyme Capsase-1.[9] Interleukin-1β initiates an acute inflammatory response by activating more cells and triggering an IL-8 mediated influx of neutrophils into the joint. Gout is thus one of the more common forms of autoinflammatory disease. The role of the inflammasome in a variety of arthropathies, including rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis offers exciting potential therapeutic targets for future investigation. Because of their effects in the inherited periodic fevers, the role of blocking IL-1β with anakinra has been investigated and found effective in treating refractory gout.

Uric acid may act as a potential 'danger signal' acting as an endogenous adjuvant when tissue is injured, for example during immune presentation or programmed cell death (apoptosis). Such processes lead to a dramatic local increase in purine metabolism and raised levels of tissue urate. This mechanism may mean that high urate levels offer an evolutionary advantage to primates.

TREATMENT OF ACUTE GOUT

Today, with appropriate management regimes, gout remains one of the most treatable forms of arthritis. The first attack occurs usually between the ages of 40 and 60. There is a stronger family history in those with earlier-onset gout. When attacks are infrequent, they are best controlled with short courses of relatively high doses of NSAIDs, with gastroprotection if indicated. Diclofenac and naproxen are effective, as is indometacin, although the latter has more side-effects. Colchicine is used when NSAIDs are contraindicated or not tolerated but in too high doses it can cause diarrhoea and colic. It appears to act by blocking microtubule function in polymorphs and must be given as soon as possible after the onset of the attack to be rapidly effective. Treatment is most effective when started as soon as the first sign of an attack is felt. Intra-articular or systemic corticosteroids are also effective. Low dose colchicine is useful as a prophylactic agent for gout but does not lower the serum urate levels (see Table 3).

TREATMENT OF GOUT WITH TRADITIONAL URATE-LOWERING AGENTS

Once attacks are frequent, despite a careful diet and alcohol restriction, if treatment of acute attacks produces unacceptable side-effects or if the attacks are difficult to control, the current approach is to introduce allopurinol or a uricosuric agent. The aim of treatment is to reduce the serum urate levels below the saturation point of 0.36 mmol/l (European EULAR guidelines[10,11]), above which crystal deposition can occur. Treatment aims are more stringent in the British Society for Rheumatology guidelines, suggesting a level below 0.30 mmol/l.[12] Treatment failures are common due to failure of

TABLE 3 Drugs used in acute and chronic gout

Drug	Dose
TREATMENT OF ACUTE GOUT	
NSAIDs	***with gastroprotection if indicated***
Diclofenac	100 mg immediately, then 50 mg every eight hours, tapering
Naproxen	500 mg immediately, then 500 mg every eight to 12 hours
Indometacin	50 mg every six to eight hours, tapering
Colchicine	1,000 μg loading dose, then 500 μg every eight hours, tapering
PROPHYLAXIS AGAINST ACUTE GOUT ATTACKS	
NSAIDs	***with gastroprotection if indicated***
Diclofenac	50 mg twice daily
Indometacin	50 mg twice daily
Colchicine	500–1,000 μg daily
URATE-LOWERING AGENTS (titrate dose with serum urate level)	
Allopurinol	100–300 mg, increasing to max. 900 mg daily (lower doses in renal impairment)
Benzbromarone	50 mg, increasing to 200 mg daily
Sulfinpyrazone	200 mg, increasing to max 800 mg daily (avoid in renal disease or with renal stones)
Probenecid	500 mg every eight hours (avoid in renal disease or with renal stones)
NEWER URATE-LOWERING AGENTS FOR REFRACTORY GOUT	
Febuxostat	80–120 mg daily
Anakinra	(only under specialist care)
Pegloticase	(only under specialist care)

physicians to follow treatment guidelines by not using adequate doses of urate-lowering agents to reduce the levels sufficiently, or poor patient compliance with the necessary long-term, usually life-long, treatments and/or failure to take care with their diet and alcohol intake.

The sudden fall in urate levels, which occurs with the introduction of such drugs, may lead to a severe, sometimes polyarticular attack. The reason for this is not clear but may be due to physical disruption of the crystals leading to inflammasome activation (see above). Urate lowering agents are best not started within one month of an acute attack. Use prophylactic doses of an NSAID or colchicine prior to starting them. A one to two month course of prophylactic NSAID or colchicine after urate-lowering agents are started avoids treatment-induced flares. Some specialists advise a gradual increase of dose of allopurinol from 100 mg, in 100 mg steps every few weeks to avoid such flares. Flare-ups due to poorly managed introduction of urate-lowering agents are a significant cause of poor patient compliance.

Allopurinol, a structural isomer of hypoxanthine, was introduced in the early 1960s and inhibits xanthine oxydase. It is rapidly metabolised by xanthine oxydase to oxypurinol over a few hours and then excreted through the kidneys over up to 30 hours. Urate levels fall but xanthine and hypoxanthine levels rise. Lower doses are used in renal impairment to avoid toxicity, usually a rash, which is very rarely life-threatening, or occasionally pancytopenia. Febuxostat is a new non-purine, selective xanthine oxydase inhibitor. It has been approved in Europe and the USA for treating gout, particularly in patients intolerant of allopurinol. It is safer in renal impairment as it is metabolised in the liver and not excreted by the kidneys.

Uricosuric agents increase urate excretion by binding preferentially to the proximal tubule urate reabsorption transporter *URAT1*. Sulphinpyrazone and probenecid are best avoided in renal impairment and in anyone who has had renal stones. Benzbromarone also acts by inhibiting the *URAT1* transporter and is better tolerated than probenecid. Availability of these drugs varies between countries. Losartan is an angiotensin II receptor blocker with a mild urate lowering action, which reduces the level of human *URAT1* mRNA.

Pegylated uricase (pegloticase) is used preventatively and therapeutically in patients with haematological malignancies or a high tumour load who are at risk of a sudden rise in uric acid following chemotherapy-induced tumour lysis syndrome. It is a recombinant protein derived from *Candida Spp*. Pegylation reduces its immunogenicity and prolongs its effect. It should not be used in *G6DP* deficient individuals. Pegloticase is being used on trial in refractory gout, particularly with large numbers of tophi. It produces a rapid reduction of urate load and speeds resolution of tophi. Side-effects can be troublesome and more studies are needed to establish its role in treating chronic tophaceous gout.

Because of the central role of IL-1β in acute gout, the IL-1β inhibitor anakinra has been used in some cases of refractory gout with varied reported benefit. More trials are needed. Tumour necrosis factor (TNF) is not involved so there is no role for TNF-inhibition in acute gout.

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SELF-ASSESSMENT QUESTIONS

1. A 35-year-old high-flying businessman presents with his third attack of pain and swelling of his first metatarsophalangeal joint in three years. He is overweight with a body mass index of 30. His father had gout. He has had a peptic ulcer about three years ago. His serum urate is 0.40 mmol/l. Which one of the following statements is correct?

A. Gout is unlikely because his serum urate is normal.
B. Weight reduction and dietary advice are indicated.
C. Colchicine 1,000 μg immediately and the 500 μcg every two hours will be safe and effective.
D. Colchicine 1,000 μg given after a delay of three days will be rapidly effective.
E. He needs immediate treatment with allopurinol.

2. A man with an estimated glomerular filtration rate of 48 presents with his sixth attack of gout in two years. His hypertension is under control without using diuretics, he is overweight and prone to indigestion with NSAIDs. His serum urate just after the last attack is 0.58 mmol/l. You decide to treat him with urate-lowering agents. Which is the best option for treatment?

A. Allopurinol at a dose of 300 mg combined with colchicine 500 μcg three times a day.
B. Allopurinol at a dose of 100 mg after treatment for one month with colchicine 500 μg twice a day until then.
C. Colchicine 500 μg twice a day.
D. Febuxostat 80 mg daily after treatment for one month with colchicine 500 mcg twice a day.
E. Benzbromarone 50 mg daily, after initial treatment for one month with colchicine 500 μg twice a day.

3. Which two of the following statements are correct?

A. The increased prevalence of hyperuricaemia and gout in Polynesian populations is due to a mutation of the urate anion transporter (*URAT1*).
B. The low prevalence of hyperuricaemia and gout in Polynesian populations is due to a mutation of the *SLC2A9* gene, which encodes the glucose transporter family isoform *Glut9*.
C. Mutations of the *NALP3* gene cause hereditary periodic fever syndromes in humans.
D. Mutations of the *SLCA9* gene cause hereditary periodic fever syndromes in humans by controlled production.
E. Genetic variations in the *SLC2A9* gene, which encodes the glucose transporter family isoform *Glut9* are associated with low fractional excretion of uric acid, hyperuricaemia and gout.

4. Which one of the following statements is correct?

A. Sodium monourate crystals stimulate IL-1β release by activating the *URAT1* transporter molecule.
B. Toll-like receptors are intracellular molecules that provide a repertoire of responses to most human pathogens.
C. Sodium monourate crystals activate a toll-like receptor on the surface of monocytes which directly induces IL-1β release.
D. Toll-like receptor 2 activation by sodium monourate crystals activates the NOD-like receptor *NLRP3*.
E. TNF-alpha is part of a cascade which leads to an ingress of polymorphonulear leukocytes into tissues.

5. Which three of these statements are correct?

A. Allopurinol is a non-xanthine, selective xanthine oxydase inhibitor.
B. Febuxostat is a non-xanthine, selective xanthine oxydase inhibitor.
C. Pegylated uricase works by increasing urate transport an dis commonly used in tophaceous gout.
D. Anakinra is used in refractory gout because it inhibits the action of IL-1β.
E. Probenecid is a commonly used uricosuric agent that is less well tolerated than benzbromarone as a urate-lowering agent.

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