Gouty arthritis: an approach for general practice

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Abstract

Gout is a common crystal-induced inflammatory arthritis, the prevalence and clinical complexity of which is increasing in the face of a growing aged population with multiple co-morbidities. Recent epidemiological studies emphasise that lifestyle factors strongly influence the development of hyperuricaemia and gout. Moreover, there is growing evidence that gout is an independent risk factor for cardiovascular disease. Acute attacks of gout are extremely painful and disabling, and if repeated attacks go untreated, chronic deforming arthritis ensues. Early diagnosis and appropriate therapy is essential to reduce long-term disability. Identification of monosodium urate crystals on synovial fluid analysis is the gold standard in gout diagnosis. Nonsteroidal anti-inflammatory drugs and oral or intra-articular corticosteroids remain central to the treatment of acute attacks. Prophylactic colchicine use, during the intercritical period, reduces gout flares, a common complication on initiation of urate-lowering therapy (ULT). Allopurinol is the treatment of choice when ULT is indicated. Gout management is suboptimal in many patients because of non-adherence to treatment and underutilisation of available treatments. Treating to target: a serum uric acid level < 0.35mmol/l, prevents crystal deposition in joints and soft tissues, thereby preventing acute attacks and ongoing inflammation, as well as decreasing the size and number of tophi. Treatment strategies should include attention to cardiovascular risk. The family practitioner is paramount to gout management which should be individualised. Emphasis should be placed on ongoing education and prevention.

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Introduction

Gout is an inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in and around joints, which occurs against a background of chronic hyperuricaemia. It is recognised as one of the oldest diseases afflicting man, dating back to ancient Egypt, 2640 BC. More than 2 500 years ago, Hippocrates dubbed it "the unwalkable disease".[1] Today, despite advances in our understanding of the pathophysiology of the disease, and the availability of inexpensive, effective treatment, gout still remains a major cause of disability.[2]

Gout is the most common cause of inflammatory arthritis in men over 40 years of age, while the prevalence in postmenopausal women continues to rise.[3,4] With the growing pervasiveness of the disease and mounting recognition of its association with cardiovascular morbidity and mortality, it is imperative to recognise and treat these patients early.[4,5] Recurrent attacks of acute arthritis, if not treated appropriately, eventually lead to chronic destructive arthropathy, tophi and renal disease. This impacts on the quality of life of the patient, while decreased productivity leads to an increased burden on economies and managed care services. Gout accounts for six per cent of the total healthcare costs relating to the elderly.[6] Most of the deformity and disability of this potentially curable disease can be attributed to suboptimal management. Primarily, this stems from poor patient education and compliance, under-utilisation of available drugs, drug interactions and co-morbidities. Current management guidelines address these problems and aim to assist in patient care.

The increasing burden of gout, coupled with the development of novel, innovative therapies has renewed interest in this often trivialised medical condition. The family practitioner is at the forefront of diagnosis and gout management. Rheumatologists are involved in < 2% of cases.[7] This review aims to provide a practical approach to the diagnosis and management of gout in the primary care setting, and highlights vigilance of the at-risk population and the importance of cardiovascular morbidity in these patients.

A rising prevalence: the population at risk

Epidemiological studies conducted in several countries suggest that the prevalence of gout is on the rise. Currently,

it is estimated to affect 1-2% of the population worldwide, although higher rates have been reported in certain populations. In the US alone, there are an estimated 6-8 million people with a lifetime history of gout.[3-5] In South Africa, where gout was once thought to be uncommon, there is a noticeable increase.[8,9] Men are affected more than women. Older age confers greater risk in both gender groups.[3-5]

The growing epidemic has been attributed to diet and lifestyle changes as a consequence of urbanisation, as well as an increasing ageing population. The aged gout population has multiple co-morbidities and this has added to the clinical complexity of the disease.[3-5]

The role that is played by diet and lifestyle, as risk factors for gout, has been known for a long time. Hence, gout was often dubbed the "disease of kings".[1] Recent large population-based studies have confirmed that purine-rich foods such as red meat, seafood (particularly shellfish), and alcoholic beverages (especially beer with its high guanosine content, and spirits to a lesser extent), confer a high risk of gout. Fructose-sweetened drinks are also a significant risk factor. Conversely, low-fat dairy (particularly yoghurt), coffee intake, high doses of vitamin C and vegetable purines derived from lentils and wine have a neutral effect.[3-5]

Some commonly used medications can cause hyperuricaemia and cause or precipitate gout. These include diuretics, thiazides and loop diuretics, low-dose aspirin, cyclosporine (in transplant patients), and the anti-tubuerculosis agents, pyrazinamide and ethambutol. Diuretics have been implicated as the leading cause of secondary gout in postmenopausal women and are a common trigger of acute gout. The associations tend to be stronger with longer use and higher doses.[3-5,10,11]

Although not an absolute risk factor for gout, there is a propensity for MSU crystals to deposit on osteoarthritic cartilage. Similar joint sites are involved in both gout and osteoarthritis and are unaffected by disease duration. This suggests that this is not a secondary phenomenon.[3-5]

There is also a strong genetic predisposition for gout in some cases. Polymorphisms of genes, encoding for specialised urate transporters within the renal proximal tubules implicated in the reabsorption of urate [urate transporter 1 (URAT1) and glucose transporter T9 (GLUT9], have been associated with hyeruricaemia and gout.[3-5,12]

Gout commonly occurs in the setting of the metabolic syndrome. Its component features are hypertension, obesity, dyslipidaemia, insulin resistance or type 2 diabetes, and renal and cardiovascular disease. A body mass index ≥ 35 is associated with a threefold increased risk of gout. Whether the role of these conditions is causal, consequential or an epiphenomenon is yet to be determined.[3-5]

Conversely, gout is an independent risk factor for all-cause mortality and cardiovascular morbidity and mortality beyond that which would be expected from its strong association with traditional co-morbid cardiovascular risk factors. As such, gout should be considered as a useful red flag for the screening and detection of cardiovascular disease, diabetes and kidney disease.[5,13]

Hyperuricaemia: the primary risk factor of gout

Hyperuricaemia is defined physiologically as a serum urate level ≥ 0.38mmol/l, above which physiological saturation threshold is exceeded which promotes the deposition of MSU crystals in tissues. In the vast majority of cases, it arises from under-excretion (90%) and rarely from overproduction (10%) of uric acid (Table I).[13] Uric acid accumulates and precipitates in the form of MSU crystals within joint tissues over time, forming complex microtophi. Fluxes in uric acid concentrations induce an inflammatory cascade that manifests as an acute gout flare.[13,14]

A common misconception is that hyperuricaemia and gout are interchangeable. Only a minority of patients with hyperuricaemia develop clinical gout, but increasing serum uric acid levels are associated with increased gout risk, such that a serum uric acid of ≥ 0.54mmol/l is associated with a

Table I: Causes of hyperuricaemia

Uric acid under-excretion (90%)	Uric acid overproduction
Clinical disorders: Renal failure, hypertension, metabolic syndrome and obesity	*Inherited enzyme defects:* HGPRT deficiency and PRPP synthetase overactivity
Nephropathies: Lead nephropathy, polycystic kidney disease, medullary cystic kidney disease and familial juvenile hyperuricaemic nephropathy	*Increased cell turnover:* Myeloproliferative and lymphoproliferative disorders, polycythaemia vera, haemolytic disorders and psoriasis
Drugs increase urate reabsorption through trans-stimulation of URAT1: Pyrazinamide and low-dose salicylate	*Purine-rich foods*
Agents decreasing renal urate excretion, through URAT1 or other mechanisms: Diuretics, ethambutol, insulin and beta blockers	*Drugs:* Cytotoxics and warfarin

HGPRT: hypoxanthine-guanine phosphoribosyltransferase, PRPP: 5-phospho-alpha-d-ribosyl pyrophosphate, URAT1: urate transporter 1

61.1% risk of gout.[15,16] Conversely, during an acute attack of gout, serum uric acid levels are normal in approximately a third of cases. As highlighted above, it is not the absolute level of uric acid that precipitates a gout attack. Rather, it is the acute changes in the uric acid levels.

Clinical aspects of gout

The acute attack and intercritical period

After a variable period of months to years of asymptomatic hyperuricaemia, gout commonly presents as an acute attack of monoarthritis. Classically, it affects the first metatarsophalangeal joint, termed

"podagra". Less frequent sites include the mid-foot, ankle, knee and hand joints. Onset is abrupt, usually in the early hours of the morning. It results in an extremely painful and tender, red, warm, swollen lower-limb joint. It is often clinically difficult to distinguish it from acute septic arthritis. In rare instances, more than one joint is affected. The pain peaks within 12-24 hours and resolves after days or weeks, with or without treatment. Fever, chills and malaise may be present. Triggers of an acute attack include trauma, surgery, dehydration, an alcohol binge, ingestion of a meal with high purine content and drugs that reduce urate excretion. Once the acute attack resolves, there is a quiescent period, followed by a second attack, usually within two years. Subsequent attacks last longer, occur more frequently and have atypical features, such as upper-limb and polyarticular involvement. The asymptomatic period between attacks is referred to as the intercritical period.

Chronic gouty arthritis

Progression from the initial attack of acute gout to a chronic destructive arthropathy generally occurs over a decade of poorly controlled hyperuricaemia. It is usually polyarticular. Associated deformities in the small hand joints often closely mimic rheumatoid arthritis. This stage is characterised by low-grade background inflammatory pain. A frequent associated feature of this stage is the presence of subcutaneous deposits or tophi. Tophi can occur anywhere, including the helix of the ear, the olecranon, Achilles tendon, over Heberden's nodes and finger pads. Skin may ulcerate and extrude a white, chalky substance. Other more unusual sites include the spine, eyes, heart valves and carpal tunnel (See Figure 1 a-c).

Diagnosis[16-21]

Early recognition is imperative to avoid destructive complications. Synovial fluid (SF) analysis is the gold standard for diagnosis and should be performed whenever possible. The presence of negatively birefringent, needle-shaped MSU crystals confirms the diagnosis of gout, but is the basis of diagnosis in only 15% of all cases.[5] As mentioned previously, an important differential diagnosis to consider in a patient with gout presenting with monoarthritis, is septic arthritis. This is a medical emergency and can both mimic and coexist with gouty arthritis. The SF should always be sent for microscopy (Gram stain) and culture when septic arthritis is suspected.

In the primary care setting, joint aspiration is not always feasible. In this case, diagnosis is made on clinical grounds. The 1977 American Rheumatism Association classification developed for research purposes, and the more recent 2006 European League Against Rheumatism (EULAR) recommendations, are useful guides from which the primary care physician can diagnose gout (Tables II and III). Efforts are ongoing to improve diagnostic accuracy in a nonspecialised setting. Where the diagnosis is uncertain, SF analysis is essential and patients should be referred appropriately.

Other important differential diagnoses to consider include pseudogout (calcium pyrophosphate deposition disease), inflammatory osteoarthritis and pauciarticular presentations of systemic rheumatic diseases, including rheumatoid arthritis, psoriatic and reactive arthritis.

Uric acid quantification is of limited value in the diagnosis of acute gout and is normal in one third of cases. Levels should be repeated once an acute attack has subsided.

Figure 1 a

Figure 1 b

Figure 1 c

Figures 1 a, b and c: Tophi deposited on first metatarsophalangeal joint and big toe, fingers and helix of the ear

Table II: American College of Rheumatology Classification criteria[20]

Six of the 11 following criteria:

- Maximum inflammation within one day
- More than one attack of acute arthritis
- Monoarticular arthritis
- Redness over joints
- Involvement of the first metatarsophalangeal joint
- Unilateral metatarsal joint attack
- Unilateral tarsal joint attack
- Suspected tophus
- Hyperuricaemia
- Asymmetric swelling within a joint on X-ray
- Subcortical cysts with no erosions on X-ray

Table III: European League Against Rheumatism 2006 recommendations for the clinical diagnosis of gout

In acute attacks, the rapid development of severe pain, swelling and tenderness that reaches its maximum within just 6-12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation, although not specific to gout.
A clinical diagnosis alone is reasonably accurate, but not definitive without crystal confirmation with regard to typical presentations of gout, such as recurrent podagra with hyperuricaemia.

Radiography is of limited value in acute gout. In patients with longstanding disease, certain characteristic features are visible: eccentric soft tissue prominences (tophi) and typical erosions (extra-articular, punched-out, with overhanging edges and sclerotic rims). Changes are usually asymmetrical and affect typical joints. Joint involvement and deformity occur much later in the course of the disease (Figure 2).

Figure 2: Plain radiograph of the fingers showing typical punched-out erosion, overhanging edges (left) and eccentric soft-tissue swelling with secondary osteoarthritis of the middle digit

Ultrasonography, computed tomography and magnetic resonance imaging are newer available tools for the early diagnosis of gout and where atypical sites are affected. Ancillary tests include full blood counts (septic arthritis or underlying haematological disorder), renal function testing and metabolic screening (lipogram and blood glucose). Twenty-four hour urine estimation of uric acid is not a routine test and should be reserved for specialist use.

Special subgroups[17]

Early onset gout

A small subset of patients develop gout at a young age (< 25 years). Because these patients usually have an underlying primary medical condition and tend to present with a more accelerated course, early specialist referral is indicated. Possible causes include Lesch-Nyhan syndrome or Kelley-Seegmiller syndrome (enzyme deficiency disorders of purine salvage pathway), glycogen storage diseases and haematological conditions, such as leukaemias, lymphomas and haemoglobinopathies.

Renal disease

Renal disease is commonly associated with gout. Renal dysfunction can predispose to gout, as seen in patients with chronic kidney disease on dialysis. Consequences of longstanding hyperuricaemia and gout include acute and chronic nephropathy, as well as an increased risk of renal calculi: both uric acid and calcium stones.[3-5,17]

Management[22-31]

The principles of management include symptom control for acute attacks and long-term management in order to prevent joint damage and renal complications. This is achieved through risk-factor modification and urate-lowering therapy (ULT). Management must be individualised and take into account potential co-morbid diseases. Current guidelines from the British Society of Rheumatology (BSR) and EULAR are available to assist with care of patients with gout.[22-24]

Acute attack

The goal in acute gout is rapid relief of pain, inflammation and functional incapacity. Nonsteroidal anti-inflammatory agents (NSAIDs)[22-25] are the first-line therapy. Initially, where possible, maximum doses should be prescribed. Once the acute attack subsides, doses can be tapered. Head-to-head studies show few differences between various drugs in this class. Naproxen is favoured in patients with associated cardiovascular disease. A proton-pump inhibitor can be co-prescribed or selective cyclo-oxygenase 2 inhibitors may be used instead in patients with gastrointestinal side-effects, like dyspepsia,

In cases where NSAIDs are contraindicated, such as the elderly, patients with renal or peptic ulcer disease, corticosteroids are indicated. Joint aspiration and intra-articular steroid injection (IAS) is highly effective, providing rapid relief of pain and inflammation. Where multiple joints are affected or if joints are not amenable to IAS, intramuscular methyl prednisolone (160 mg) or oral steroids can be used. Prednisone at doses of 30-40 mg/day for five days with a gradual tapering over 10-14 days has been shown to be as effective as NSAIDs. Importantly, oral corticosteroid use is reserved strictly for refractory cases or where NSAIDs are contraindicated.[22-25]

Colchicine in high doses (1 mg stat followed by 0.5 mg every 3-4 hours, up to a maximum of 3 mg/day), although effective for the acute management of gout, is seldom prescribed today because of the associated acute gastrointestinal toxicity, abdominal cramps and diarrhoea: "Makes you run before you can walk".[22,26]

During an acute attack, no attempt should be made to alter serum uric acid levels. Hence, ULT (most commonly allopurinol) should not be started in patients who are not on ULT and the dose of ULT should not be altered.

Adjuncts to medical management

Resting the affected joint and the use of ice packs may be helpful.[22,23]

Newer drug treatments

Crystal stimulation of interleukin-1 is integral to the inflammatory attack on synovial joints. Anti- interleukin-1 drugs (rilonacept, canakinumab and anakinra) have been shown to be effective in refractory cases, with a low side-effect profile. Due to the high cost and availability of effective oral treatments, their role in gout management is yet to be established.[6,22]

Secondary gout prevention

Nonpharmacological therapy

Patient education and risk-factor modification[22-25,27]

Patient education and risk-factor modification is essential for all stages of gout management.

Important areas of lifestyle and risk modification include:

- *Weight reduction*: This should be controlled and gradual as crash diets can precipitate acute attacks.
- Increasing fluid intake to produce > 2 l urine per day.
- *Diet modification: Alcohol, particularly beer, must be restricted, h*igh-purine-content meats (red meat and organ meat) and seafoods (shellfish) consumption should be reduced, fructose-sweetened drinks should be avoided and low-fat dairy products encouraged.
- *Considering vitamin C supplementation (500 mg-2 000 mg daily, in divided doses)*: Caution must be taken when prescribing high doses of vitamin C due to the low gastrointestinal tolerability and risk of renal calculi formation.[4,27,30,31]
- *Where possible, substituting drugs that cause hyperuricaemia*: Taking low-dose aspirin for cardioprotection should not be stopped.

Pharmacological therapy

Indications for ULT include:

- Two attacks/year
- The presence of tophi
- Destructive changes on plain X-rays
- Renal complications of calculi or urate nephropathy.

Currently, there is no evidence to support the use of ULT for asymptomatic hyperuricaemia, except in patients with a strong family history of gout.[22-24]

Treat to urate target

The aim of therapy is to decrease uric acid levels below the physiological saturation threshold of ≤ 0.35 mmol/l and more refractory cases to < 0.3 mmol/l.[22-24] This prevents further acute attacks, joint damage and systemic complications. With time, this will shrink tophi.

During patient consultation, decisions should be made regarding long-term ULT and emphasis placed on adherence to drug therapy. Patients at high risk of non-adherence, especially younger recently diagnosed male patients, should be specifically targeted.

Allopurinol, a xanthine oxidase inhibitor, is the drug of choice and prevents the conversion of xanthine to uric acid. It should be introduced one to two weeks following an acute attack, at a low dose (100 mg nocte), slowly increasing at 100 mg increments, while monitoring serum urate levels four weekly. This assists in reducing flare risk with ULT initiation. The most commonly prescribed dose of 300 mg is inadequate in reaching the target uric acid level in two thirds or more patients. Therefore, doses need to be titrated up, with cautious monitoring of renal function and adverse effects, up to a dose of 700-900 mg daily. Once target urate level is reached, less frequent monitoring is appropriate (6-12 monthly).

Common adverse effects include rashes, deranged liver function tests and bone marrow suppression. A life-threatening hypersensitivity reaction (fever, malaise, a severe erythema multiforme rash and multi-organ failure) occurs mostly in the elderly and in patients with renal dysfunction. The dose should be adjusted for renal dysfunction, with a starting dose of 50 mg and similar increments. The most important adverse effect of any ULT is the precipitation of acute flares. Patients should be reassured of this prior to initiation of therapy.[14,22-25]

Colchicine at a dose of 0.5mg twice daily or 0.5 mg daily, or a NSAID for six months after initiating ULT, reduces the risk of gout flares. Colchicine acts by suppressing urate crystal-induced activation of NALP3 inflammasome. Potential colchicine toxicities include neuromyopathy and bone marrow suppression. Toxicity is enhanced by concomitant use of erythromycin or statin therapy.[25]

When to refer to a rheumatologist?

Referral to a rheumatologist is sometimes necessary:

- *Allopurinol hypersensitivity or gout refractory to maximal doses:* In these cases, an alternative ULT is to be tried. Probenecid is the only uricosuric drug that is available locally. Several alternative drugs are either in development or have been registered for clinical use in other parts of the world, including febuxostat (a non-purine xanthine oxidase inhibitor), and a pegalated uricase, pegloticase. Losartan has a weak uricosuric effect in patients with hypertension.
- *Allopurinol desensitisation:* Allopurinol desensitation for mild intolerance should only be attempted by a specialist.[22]
- *Young patients, patients with renal disease, and patients with extensive tophi:* These patients require specialist care.

Key points

- Gout prevalence and clinical complexity is on the rise.
- Gout is a major cause of disability.
- Multiple risk factors are implicated in gout.
- Hyperuricaemia is the most important risk factor.
- Not all individuals with hyperuricaemia develop gout.
- Hyperuricaemia and gout should serve as a red flag for cardiovascular risk factors and morbidity.

Conclusion

Gouty arthritis is increasingly common. The majority of patients present to general practice. The general practitioner should have a good working understanding of this condition in order to meet the needs the patient. Patient co-operation is integral to the effective management of gout. Specialist referral is indicated for certain patient subgroups and in treatment-refractory or treatment-intolerant cases. Exciting new drugs are being developed and this has revitalised interest in this ancient disease. Gout cure can be achieved if the treat-to-a-target principle is followed.

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