
Gout: thoughts about a treat-to-target programme

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ABSTRACT

Gout is a rheumatic disease resulting from deposition of uric acid crystals in tissues and fluids within the body. The pathogenesis involves underexcretion or overproduction of uric acid, a byproduct of metabolism of purines, resulting in a metabolic disorder commonly known as hyperuricaemia, has a relatively high prevalence in the population (0.5–1%, similar to rheumatoid arthritis). Patients with hyperuricaemia are at risk to develop acute gouty attacks which may be severely painful. The attacks tend to occur episodically over a few days up to a week or two, but gout may later become chronic. Different aims of therapy and management are well suited as targets of treatment, including reduction of purine intake, increased of excretion of uric acid, mobilisation of urate pools within the body, and reduction of acute and chronic inflammation through anti-inflammatory medications.

Introduction

Gout is a rheumatic disease resulting from deposition of uric acid crystals (monosodium urate) in tissues and fluids within the body. This process is caused by an overproduction or underexcretion of uric acid. Certain common medications, alcohol, and dietary foods are recognised contributory factors. Acute gout typically is manifested as an acutely red, hot, and swollen joint with excruciating pain. These acute gouty flare-ups respond well to treatment with oral anti-inflammatory medicines and may be prevented with medication and diet changes. Unlike most types of arthritis, in which symptoms generally are present at all times, gout is typically episodic, characterised by painful flares lasting days/weeks potentially followed by long asymptomatic periods. Gout may remit for long periods, followed by flares for days to weeks, or may become chronic. Recurrent bouts of acute gout may lead to chronic gouty arthritis.

Pathogenesis

Gout is caused by an uncontrolled metabolic disorder, hyperuricaemia, which leads to the deposition of monosodium urate crystals in tissue (1, 2). Hyperuricaemia means too much uric acid in the blood. Uric acid is a product resulting from the metabolism of purines which can be found in many foods and in human tissue. Hyperuricaemia is caused by an imbalance in the production and excretion of urate, *i.e.* overproduction, underexcretion or both. Underexcretion is the most common cause, thought to account for 80–90% of hyperuricaemia (3).

Risk factors for gout include being overweight or obese, having hypertension, alcohol intake (beer and spirits more than wine), diuretic use, and a diet rich in meat and seafood. Weight loss lowers the risk for gout (4–6). Gout is also associated with an increased risk of kidney stones (7, 8).

Clinical stages

Gout can be viewed in four stages:

1. Asymptomatic tissue deposition occurs when people have no overt symptoms of gout, but do have hyperuricaemia and the asymptomatic deposition of crystals in tissues. The deposition of crystals, however, may cause damage to joints and other organs such as the kidney.
2. Acute flares occur when urate crystals in the joint(s) cause acute inflammation. A flare is characterised by pain, redness, swelling, and warmth lasting days to weeks. Pain may be mild or excruciating. Most initial attacks occur in the lower extremities. The typical presentation, seen in about 50% of people with gout, involves the metatarsophalangeal joint of the great toe (podagra). About 80% of people with gout experience podagra at some point. Uric acid levels may be normal in about half of patients with an acute flare.

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Gout may present differently in the elderly, with polyarthritis.

3. Intercritical segments occur after an acute flare has subsided, and a person may enter a stage with clinically inactive disease before the next flare. The person with gout continues to manifest hyperuricaemia, which results in continued deposition of urate crystals in tissues and resulting damage. Intercritical segments become shorter as the disease progresses.
4. Chronic gout is characterised by chronic arthritis, with soreness and aching of joints. People with gout may also develop tophi (lumps of urate crystals deposited in soft tissue) – usually in cooler areas of the body such as elbows, ears and distal finger joints (9, 10).

Diagnosis

The gold standard for a diagnosis of gout involves aspiration and microscopic demonstration of urate crystals in joint fluid or a tophus. Urate crystals are negatively bi-refringent under polarised light. The main differential diagnosis is infection, which always must be ruled out (7, 11). Other differential diagnoses are osteoarthritis and rheumatoid arthritis. Imaging has recently been studied intensively and some new proposals are being tested to document the mechanisms of joint destruction of gout (12).

Recent data have shown that establishing a diagnosis and providing optimal management of gout may be rather inadequate (13) – in large part due to gaps of knowledge by both physicians and patients (14). Importantly, it was also shown that systematic patient education may improve this situation (15).

Epidemiologic data

One-year period prevalence estimates derived from the National Health Insurance Scheme (NHIS) were 0.94% for those 18 and older in 1996, thereby affecting about 3.0 million adults in the U.S. in 2005 (16). Lifetime prevalence estimates from National Health Insurance Scheme (NHANES) III (1988–1994) were 2.6% overall for those aged ≥ 20 years with a low of 400/100,000 in adults aged 20–29 years and a peak

of 8,000/100,000 in adults aged 70 to 79 years – thereby affecting about 6.1 million adults in the U.S. in 2005. Overall, gout was reported more often in men than in women, but prevalence increased with age for both, especially for women after menopause (17). Although both the above may be over- or underestimates because the data were self-reported, but gout appears to be increasing in frequency, with one-year prevalence estimates up from 0.85% in 1998 (18). Of interest, the incidence of gout (follow up period 26 to 34 years) among black men was almost twice that among white men: 3.1 vs. 1.8 per 1,000 person-years (19, 20). In 2004, gout and other crystal arthropathies accounted for 1.5% of 922,000 hospitalisations for a principal diagnosis of arthritis and other rheumatic conditions, and gout was listed for 2.3 million ambulatory care visits annually from 2001–2005 (21).

Treatment

Evidence-based recommendations for the treatment of gout have been published some years ago (22, 23). The goals of treatment are to end the pain of acute flares, prevent future attacks, and slow or prevent formation of tophi and kidney stones. Therapy for acute flares consists of nonsteroidal anti-inflammatory drugs, glucocorticoids, and colchicine. Diet and lifestyle (weight loss, avoiding alcohol, reducing dietary purine intake) modifications may help prevent future attacks. Changing medications (*e.g.* stopping diuretics) associated with hyperuricaemia may also help (24). Preventive therapy to lower blood uric acid levels in persons with recurrent acute flares or chronic gout usually involves allopurinol or febuxostat (25), and potentially uricosuric drugs such as benzbromaron and probenecid.

Monosodium urate crystals stimulate monocytes and macrophages to release IL-1 β through the NALP3 component of the inflammasome. Blocking interleukin-1 with the monoclonal antibody canakinumab – a drug that is approved for cryopyrin-associated periodic syndrome (CAPS) – was shown to reduce inflammation and pain in flares of patients with gout (26). Similar efficacy was shown for riloncept (27). Another

new approach is pegloticase, a recombinant polyethylene glycol-conjugated form of uricase which is a uric acid-specific enzyme lacking in humans that catalyses the oxidation of uric acid to allantoin (28).

Thoughts about treat-to-target in gout

The potential targets in the treatment strategy of gout differ according to different clinical situations and stages.

1. The first target arises when the disease manifests for the first time. It is the initial treatment approach to patients with an acute flare of gout when the clear first aim is to reduce inflammation for some weeks. The medication consists of colchicine, NSAIDs, intrarticular and systemic steroids. However, about 50% of patients may experience only one attack – and some may decide on no treatment.
2. The second target arises in the phase thereafter. The aim is to prevent more flares. This can be reached by lowering the uric acid level and keep it at a level of < 5 or 6 mg/dl.
3. The third target arises when the second aim was not reached. Patients may have two and (many) more flares of gout. In uncomplicated cases the strategy is just as described in 1. and 2.
4. The fourth target arises in the treatment approach to patients with chronic gout who have been refractory to standard therapies for various periods of time.
5. Chronic patients may be those
 - a. with >2 flares/year despite standard of care
 - b. with gout tophi who have to undergo a therapeutic trial to mobilise urate from the tissues
 - c. with gout tophi in whom no more attempts for mobilisation of urate are meaningful and/or possible anymore
6. The fifth possible target arises in patients with gout and significant comorbidity causing problems with the standard medication:
 - a. hypertension
 - b. renal insufficiency
 - c. diabetes
 - d. gastrointestinal ulcer, bleeding

Discussion

The treat-to-target (T2T) initiative that was initiated some years ago has moved the field, especially in rheumatoid arthritis, quite a bit in the last years. The process to produce recommendations on this basis has been standardised using established tools such as the systematic literature search and expert committee meetings, first publications have recently been released (29, 30). The nature of the basic thought behind T2T is strategic (31). It follows the rationale that inflammation needs to be systematically and consequently reduced to the lowest possible level to prevent structural damage.

As documented above, gout is a common inflammatory rheumatic disease that frequently requires specialist care. There are several clinical situations as described above in which clear therapeutic targets can be identified in both acute and chronic care of patients with gout, accompanied by preventive strategies. Since the last EULAR management recommendations have been published years ago this may be a good starting point to develop strategies for T2T for the management of gout.

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