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Gout: is it all crystal clear?

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INTRODUCTION

Uric acid is a normal constituent of human body. It is an antioxidant and a negative phase reactant that initiates inflammation in the intracellular space. However, it is important to remember that hyperuricemia and gout are not synonymous. All hyperuricemic patients (uric acid level>7mg/dL) do not suffer from gout. Asymptomatic hyperuricemics usually needs no treatment as most people with hyperuricemia never develop gout. Conversely, a few gout patients have normal uric acid levels. Asympotomatic hyperuricemia is often seen in metabolic syndrome and has a confusing and mixed relationship with coronary artery disease. Hyperuricemia is also regarded as a marker of activity in other diseases like AIDS and eclampsia. Aspirin in low dose precipitates gout but in high doses, it ameliorates pain and acts as a uricosuric agent.

Gout presents as arthritis, bursitis and/or tendonitis. Many a time, it is a diagnosis of exclusion, e.g., in tarsal joint pain and knee pain, reactive arthritis is suspected first. Polarized microscopy gives the surest diagnosis but is not available everywhere. Misdiagnosis of gout is common as is the inappropriate or improper use of urate lowering drugs like allopurinol. At the same time, gout is one condition where the cause and pathophysiology are very well understood, the diagnosis can be made with certainty and available therapies are very effective.

Causes of Hyperuricaemia

Hyperuricemia may be caused by either increased urate production (10%), or decreased urate excretion (90%). On a 'purine-free diet', a person with normal renal function excretes uric acid < 600 mg/day. Increased urate producers excrete uric acid above this level. Those who excrete lower amounts have decreased urate excretion. If the assessment is done on a 'regular diet', 800 mg/day may be used as the discriminative value. Anti-cancer treatment and high protein diet are causes of high uric acid production. Drugs responsible for decreased urate excretion are thiazides, loop diuretics, pyrazinamide, cyclosporine, nicotinic acid, low-dose aspirin, ethambutol and levodopa. Obesity, metabolic syndrome and alcohol are other common causes of hyperuricemia.

Management of asymptomatic hyperuricaemia

In most cases specific urate-lowering drugs are nt indicated. An effort should be made to determine the cause and address contributing factors like hypertension, obesity, alcoholism, hyperlipidemia and diabetes mellitus. Lifestyle advice including diet, and exercise should be offered. Losartan and fenofibrate should be considered in metabolic syndrome.

Pathophysiology of Gout

'Turning on' the acute gouty attack: Uncoated urate crystals engulfed by monocytes, or synoviocytes activate them through, toll-like receptor 2 and 4, and their adaptor protein, MyD88. These cells release TNF-α, IL-1β, IL-6, IL-8 and IL-10, which activate endothelial cell adhesion molecules (E-selectin, ICAM-1, VCAM-1). This leads to neutrophil recruitment and further inflammation.

'Turning off' the acute gouty attack: As monocytes mature into macrophages, they continue to ingest crystals but release anti-inflammatory TGF-β1. With the increased vascular permeability caused by the inflammatory response, large proteins (apolipoprotein B) enter synovial space and coat the crystals.

Management of Gout

Following classes of drugs are used in the treatment of gout:

- Uricosuric drugs: probenecid, sulfinpyrazone, benzbromarone, lesinurad, fenofibrate, losartan, vit C (500 mg twice daily), amlodipine
- Uricostatic drugs: allopurinol, oxypurinol, febuxostat, topiroxostat
- Uricolytic drugs: uricase (e.g., rasburicase or pegloticase)
- Drugs for acute gout: NSAIDs, colchicine, glucocorticoids, ACTH (IM)
- Treat-to-target drugs: IL-1 inhibitors e.g., anakinra, canakinumab and rilonacept

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Table 1: Mechanism of action of drugs used in acute gout.

Drug	Mechanism of action
Colchicine	Inhibition of E-selectin mediated polymorphonuclear (PMN) adhesion, PMN E-selectin expression, L-1 expression, IL-8 production, PMN motility and chemotaxis
NSAIDS	Inhibition of PGE2
Coricosteroids	Inhibition of PGE2 and LTB4 Stabilization of lysosomal membranes
ACTH	agonist of the leucocyte melatonin receptor-3

Table 2: List of upcoming/ under trial urate lowering drugs.

Topiroxostat (xanthine oxidase inhibitor)
Uricase (rasburicase, pegloticase)
Lesinurad / verinurad
Bucillamine (in Japan and Korea)
Arhalofenate (first ULT with anti-flare therapy)
Pralnacasan (caspase-1 inhibitor)
Levotofisopam (a benzodiazepine derivative)
Ulodesine (for chronic gout)
Tranilast (in phase II trial)

The drugs with anti-inflammatory action, viz. colchicine, NSAIDS and corticosteroids are helpful in the management of acute flare ups. On the other hand, the urate lowering drugs are useful in the long-term management. These include xanthine oxidase inhibitors like allopurinol and febuxostat; and uricosuric drugs like probenecid, sulfinpyrazone and benzbromarone. Some drugs used for other indications that have urate lowering properties include losartan (50 mg/day), fenofibrate, amlodipine (in cyclosporine induced hyperuricemia) and canagliflogin.

The goal of urate lowering therapy is to reduce the serum urate level < 6 mg/dL for acute gout and < 5 mg/dL in chronic gout.

With the usage of effective urate lowering drugs, dietary purine restriction is rarely necessary. However, beneficial results have been reported with a diet of approximately 1600 calories/day with low carbohydrate and proportionately increased proteins, unsaturated fats and high fibres. Increase in fluid intake is advisable. High amounts of meat, sea fish, fructose and alcohol should be avoided. Alcohol may both increase the production and impair the excretion of uric acid. Vitamin C at a dose of 8 g/day for 3 to 7 days reduces serum urate by as much as 3.1 mg/dL. Consuming 4-5 cups of coffee per day reduces the risk of gout by 40% in men.

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