GOUT - UPDATED

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ABSTRACT

Gout is an inflammatory response to monosodium urate monohydrate (MSUM) crystal deposition in the joints due to alteration in body urate milieu. It commonly occurs in men over 40 years of age. The incidence is rising over the last decade due to increased consumption of foods rich in purine, fructose containing and alcoholic beverages. Hyperuricemia is the biochemical precursor of gout. Most cases are due to decreased tubular secretion of uric acid. Hyperuricemia may be primary, or secondary. An association of hyperuricemia with obesity, metabolic syndrome, dyslipidemia and diabetes has been found recently. Most frequent presentation is arthritis of first metatarsophalangeal joint. Articular gout may be acute, intercritical or chronic tophaceous. Hyperuricemia also predisposes to renal stones, uric acid nephropathy and cardiovascular and cerebrovascular diseases. Diagnosis is confirmed by visualization of negatively birefringent MSU crystals in synovial fluid under polarized light microscopy or demonstration of MSU in tophi. Asymptomatic hyperuricemia, though a benign entity may have serious repercussions in the long term. Treatment of acute gout revolves around reduction of inflammation with colchicine, NSAIDs, glucocorticoids, ACTH, anakinra and rilonacept. Chronic gout is managed by dietary modifications like increasing consumption of dairy product, vitamin C, calcium, coffee and reducing high purine diet. Uricostatic drugs like allopurinol and febuxostat, uricosuric drugs like probenecid and benzbromarone, or uricases like rasburicase and pegloticase are being increasingly used for the treatment of chronic gout.

Abbreviations used:
ACR- American College of Rheumatology; CVD- cardiovascular disease; ILAR- International League of Nations Against Rheumatism, IL- Interleukin; GLUT- glucose Transporter; MTP- Metatarsophalangeal; GCSF- granulocyte colony stimulating factor; CKD-chronic kidney disease; ESRD- End stage renal disease.

INTRODUCTION:

Gout is an inflammatory response to monosodium urate monohydrate (MSUM) crystal deposition in the joints due to alteration in body urate milieu. It is the commonest crystal arthropathy occuring in men over 40 years of age, presenting usually in the form of “podagra” (acute onset pain, erythema and swelling of the first metatarsophalangeal joint).

EPIDEMIOLOGY:

Data on the exact incidence of gout in India is not clear. The ILAR COPCORD study from Bigwan village shows a prevalence of 0.1%. The prevalence is higher in urban Indian population. Moreover, due to increasing prevalence of metabolic syndrome in younger population, occurrence of first attack of gout is a decade earlier in urban Indians. A study by Mathew and Danda from Vellore showed that 15.8% of the affected patients were below the age of 30 years. Globally, the incidence and prevalence of gout has doubled over the last two decades. Another Indian study by Mishra et al showed correlation of elevated serum uric acid levels with laboratory and anthropometric parameters of metabolic syndrome, which authors opined, was due to high caloric diet, sedentary habits and
PATHOGENESIS:

Uric acid is the most abundant natural antioxidant in the human body, and possibly provides protection against oxidant-induced neurological and cardiovascular degenerative processes. Hyperuricemia is the biochemical precursor of gout which is ultimately crystal deposition-mediated inflammatory response to one or more derangements in the urate physiology. Hyperuricemia may be classified as primary or secondary, as shown in Table 1.

Renal uric acid excretion: About 90% of the uric acid filtered through the glomeruli is reabsorbed. There is a four step renal handling of uric acid.7

- Step1: 100% filtration at glomeruli
- Step2: 98-100% presecretory reabsorption at proximal convoluted tubule (PCT) by active transport
- Step3: 50% secretion of reabsorbed urate at PCT
- Step4: 40-50% post-secretory reabsorption

Finally, around 5-10% uric acid is excreted through urine, as final net absorption is 90-95%.

Urinary uric acid excretion: It is essential to identify underexcretors or overproducers. Overproducer status is determined by total excretion over 1000mg/day and underexcretor below 600mg/day on a normal purine diet. The value of 800-1000mg/day is borderline. A single urine sample for uric acid/creatinine ratio is also diagnostic of overproducer when the value is more than 0.5 (normal is < 0.5). It is expressed as:

- Urinary uric acid (mg/dl) × Serum creatinine
- Urinary creatinine (mg/dl)

URATE TRANSPORTERS: 6

There are two main renal transporters of the organic acid transporter (OAT) family:

- URAT 1 is highly specific and localized to the apical brush border of proximal tubular lumen. Probenecid and benz bromarone increase urate excretion by inhibiting URAT 1 and other OATs.
- GLUT 9 exists in two isoforms, GLUT 9L and GLUT 9S, located at the proximal tubular epithelial cells. GLUT 9 is also a transporter for glucose and fructose and thus has a role in dietary influences of glucose and fructose on hyperuricemia and gout. GLUT 9 is also inhibited by uricosuric agents like probenecid and benzbromarone.

Other transporters are:

- UAT 1 - associated with luminal secretion of urate
- ABCG 2
- NPT 1, NPT 4 - Sodium-dependent phosphate co-transporter

Endogenous regulators of urate transport are:

- Insulin
- Leptin
- Adiponectin
- Estrogen
- Uratin- hepatic effector of renal uric acid transport.

ASYMPTOMATIC HYPERURICEMIA:

It is defined as a serum urate level greater than 6.8 mg/dl, a level at which MSU remains soluble in serum at 37°C; beyond which there is supersaturation of body fluids and a possibility of deposition in various tissues. This level has been rounded off to 7.0 mg/dl in men and 6 mg/dl in women.

Asymptomatic hyperuricemia is not equivalent to gout. It is common and found in about 5 to 8% of adult males.8 It is more common in Filipinos and south east Asians.9 The risk of gouty arthritis and urolithiasis increases with duration and severity of hyperuricemia. Clinical gout develops in only about 12% of patients with urate levels between 7.0 and 7.9 mg/dl over a 14 year period.

When serum uric acid level is greater than 9.0 mg/dl, the probability of progression to clinical gout is six times.8
**ARTICULAR GOUT**

It is divided into 3 clinical stages:

1. Acute gouty arthritis- Self limiting, subsides within 7 to 10 days, may not recur for months.

2. Acute intermittent gout (intercritical gout)—may last several months to years.

3. Advanced gouty arthritis (chronic tophaceous gout).

**ATYPICAL GOUTS**

Petite gout: McCarty described a much milder variety with subtle episodic pain lasting only minutes to hours. This may recur for several years before culminating into the first classical attack of gout.

Gout in the women: Women represent about 5% of all gouty patients. However in the last two decades, there has been doubling in the incidence of gout in women. The age of onset of first attack is about a decade later than men and there is more upper extremity involvement. There is also higher incidence of co-morbidities like hypertension (73%), renal failure (50%) and pre-existing osteoarthritis (38%) and occurrence of oligoarticular and polyarticular flares.

Gout in the elderly: Usually occurs over the age of 65 years. Male and female ratio is equal. The classical podagra may be absent. It tends to be polyarticular with involvement of both upper and lower extremity. Finger involvement is commoner than typical gout. Tophi occur early. There may be associated renal insufficiency. There is usually associated diuretic overuse. Co-morbidities like obesity, hypertension and alcohol abuse are absent.

**GOUT AND KIDNEY DISEASE:**

Three types of kidney diseases occur with hyperuricemia and gout:  
- Urolithiasis- Uric acid acting as nidus for calcium oxalate stone
- Urate nephropathy- Late manifestation of severe hyperuricemia due to deposition of MSU crystals in the medullary interstitium and pyramids, leading to CRF and ESRD.
- Uric acid nephropathy- Due to precipitation of uric acid in renal tubules or collecting ducts causing obstruction. Usually seen in the setting of tumour lysis syndrome, in patients with severe dehydration and acidosis.

**HYPERURICEMIA AND CVD:**

Multiple studies have confirmed the relationship between hyperuricemia, gout, CVD and metabolic syndrome. The National Health Nutrition Examination Survey III-USA has shown that serum urate more than 6 mg/dl is an independent risk factor for CAD and serum urate more than 7 mg/dl is an independent risk factor for stroke.

**MOLECULAR BASIS OF ACUTE GOUTY ARTHRITIS:**

Mere presence of MSU crystals in the joint does not lead to acute attacks because
- Gout patients often have urate crystals in clinically uninvolved joints.
- Urate milk: high concentration of crystals in joint fluid is sometimes found in uninflamed bursae and joints.
- Urate crystals in tophi can be very large with little inflammatory response.
- Urate crystals in intercritical and chronic gout also do not elicit synovial inflammation.

**Key points of inflammatory response:**

The various steps are shown in Table 2. There are various other mediators like prostaglandin E2, thromboxane A2, causing vasodilatation, edema and further leukocyte immigration.

Resolution of attack: The self-limiting nature of gouty attacks is still ill-understood. However, due to vasodilatation, various anti-inflammatory molecules also come into play, like crystal coating by Apo B, Apo E, and TGF-β and IL-10, which inhibit further neutrophil activation. Othersystemicanti-inflammatory mediators coming into action are melancortins, ACTH and melanocyte-stimulating hormone (MSH). Apart from these, PPAR α and PPAR γ also are activated, which inhibit TNF α, IL-1, IL-6, MMPs and COX2.

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<th>Table 2: Molecular basis of the inflammatory response</th>
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<td>Microcrystal shedding</td>
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<td>Proinflammatory coating (IgG, complements)</td>
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<td>Interaction with tissue macrophages, fibroblasts, mast cells etc.</td>
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<td>Activation of membrane signalling molecules (TLR, CD-14)</td>
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<td>Release of cytokines (IL-1, TNF-α) &amp; chemokines</td>
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<td>Activation of endothelial cell adhesion molecules</td>
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<td>Emigration, attraction and activation of neutrophils</td>
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<td>Phagocytosis of crystals by neutrophils</td>
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<td>Delayed neutrophil apoptosis by CSF, IL-1, IL-6 etc.</td>
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TREATMENT

Principle goals of management are:
1. Prompt treatment of acute attack to alleviate pain and restore joint function.
3. Prevent or reverse complications due to crystal deposition in joints, kidneys or other sites.
4. Correction of co-morbidities like obesity, dyslipidemia or hypertension.

Role of diet

There are lots of taboos and misconception regarding diet in hyperuricemia and gout, most of which has been disseminated by orthopaedicians and primary care givers, and society at large.

It is the primary duty of trained physicians and rheumatologists to allay these misconceptions. The key points to remember are:

- Alcohol, especially beer and hard liquor increases the risk.
- Higher intake of meat, seafood, soft drinks high in fructose, and sweet corn syrup is associated with higher serum uric acid level.
- Higher intake of coffee (4 cups/day) is beneficial in lowering urate level, but no such effect with tea.
- Foods rich in purine should be avoided or taken in moderation viz mutton, bacon, beef, sea fish, organ meat. Purines are found in all protein food but it is not possible or advisable to eliminate it all together.
- Dairy products (milk) decreases serum urate level.
- Diuretics especially thiazides associated with higher risk of incident gout and gout flares.
- Vegetables are not associated with increased serum urate.
- Fruits and vegetables rich in vit C are beneficial as it has got a uricosuric effect.
- As gout and hyperuricemia is associated with metabolic syndrome and atherosclerosis, it is appropriate to prescribe low fat low cholesterol, weight reducing diet.
- Maintenance of high level of hydration with 2-3 liters of water intake/day.

Treatment of asymptomatic hyperuricemia: There is no evidence based recommendation of benefits of therapy upto 11mg/dl in males and 9mg/dl in females, except in conditions associated with tumour lysis syndrome to prevent acute uric acid nephropathy. In more than 70% of cases of hyperuricemia, an underlying cause like metabolic syndrome, renal and thyroid disease, alcoholism and drugs are the usual causes and needs appropriate correction.16

Treatment of acute gout: Multiple options are available and have to be individualized based on backdrop of renal, cardiac, hepatic or gastrointestinal disease.

Colchicine – It is the ideal drug in patients where the diagnosis of gout is not confirmed. It acts by inhibiting the action of neutrophils. It retards the adhesiveness and motility of neutrophils and prevents chemotaxis. It also downregulates TNF-α receptors and inhibits mast cell histamine release.21

Doses: Older regimen: 0.5mg orally hourly until one of three things occur:
1. Joint symptoms subside.
2. Nausea, vomiting or diarrhoea.
3. Total dose of 5 mg (10 doses).

EULAR regimen: Three doses of 0.5mg/day for 4 to 5 days followed by 0.5mg once or twice daily upto 6 months depending on the renal status.22

Drug interaction: Cyclosporin, macrolide antibiotics (clarithromycin, erythromycin) and statins inhibit cytochrome P-450-3E4 isoenzyme which carries out the hepatic demethylation of colchicine to inactive metabolites. Thus there is chance of drug toxicity like myopathy including rhabdomyolysis.

NSAIDs – Very effective in acute attack. All the NSAIDs are effective, but etoricoxib is the best studied COX-2 selective inhibitor. Indomethacin and etodolac have additional uricosuric properties, but indomethacin has some gastrointestinal side effects.

Glucocorticoids – They are the first line option in patients with renal dysfunction where NSAIDs and colchicine are not suitable. Prednisolone in a dose of 0.5mg/kg daily is effective in gout flares. Alternatively, short course (3 to 5 days) of intravenous methylprednisolone (100-150mg) or triamcinolone (60mg) intramuscularly is equally effective. Intra-articular methylprednisolone depot preparation is also effective. However, it is advisable to start low dose colchicine at the same time as systemic glucocorticoids to inhibit rebound gout flares after cessation of glucocorticoids.

ACTH – Dose: 25-40 IU i.m. or s.c. It is particularly effective in polyarticular gout. The peripheral effects of ACTH via phagocyte MR3 (Melanocortin Receptor 3) activation is the cause of rapidity of efficacy of the therapeutic action of ACTH.

Cytokine antagonist –

Anakinra – Soluble IL-1 receptor antagonist at a dose of 100 mg/day sub-cutaneously for 3 days has been used with good
results in refractory chronic gout. Rilonacept—Also known as IL-1 Trap, is a dimeric fusion protein consisting of the extracellular domain of human IL-1 receptor and the Fc domain of human IgG1 that binds and neutralizes IL-1. It is currently approved for use in cryopyrin associated periodic syndromes (CAPS). It is also used in patients with gout on allopurinol to reduce the number of flares. It is given s.c once a week. It has been used to treat gout flares. Many patients who cannot tolerate colchicine and NSAIDs or prednisolone can be successfully treated with rilonacept.

Dose: 320 mg s.c loading, followed by 160 mg s.c weekly.

**Treatment of chronic gout:** About 1/3rd of patients with an attack of gout have a second attack within one year. So it is imperative to have prophylactic use of urate lowering drugs. These are of 3 categories:

- Uricostatic- decrease production of uric acid.
- Uricosuric- increases excretion of uric acid via kidney.
- Uricolytic- Uricase, conversion of uric acid to allantoin.

**URICOSTATIC DRUGS:**

**Allopurinol:** It is a non-selective xanthine oxidase inhibitor, useful in both urate overproducers and underexcretors. It is better to start with a low dose of 100mg daily, 4 to 8 weeks after subsidence of acute attack. The dose is gradually escalated to 300mg/day. Some patients may need upto 800mg/day. Allopurinol undergoes hepatic conversion to the active metabolite oxypurinol, whose half life is about 24 hours. Thus, once daily dosing is to be given. The half life rises substantially with renal dysfunction as it is primarily cleared by the kidneys.

Adverse effects: Hypersensitivity reaction (2%), drug intolerance (10%) and elevated liver enzymes, and in extreme cases Steven-Johnson syndrome or TEN. Rarely there may be bone marrow suppression.

Allopurinol hypersensitivity syndrome (AHS) present as severe multiorgan disease with rash, hepatic and renal dysfunction, eosinophilia and vasculitis, granulomatous hepatitis, cholestatic jaundice and severe liver necrosis, with 20-25% mortality.

Drug interaction: Azathioprine, 6-mercaptopurine, theophylline, which are metabolised by xanthine oxidase may cause toxicity. Patients on warfarin need careful observation. Ampicillin and amoxycillin can trigger rash in about 20% of patients treated with allopurinol.

**Febuxostat:** It is a selective inhibitor of xanthine oxidase. It is a non-purine analogue, and thus does not block the other metabolites of purine and have no effect on pyrimidine metabolism. All these help to alleviate allopurinol toxicities. Usual dosage is to start with 40 mg daily and if serum urate is not normalised after 2 weeks, the dose is increased to 80 mg once daily. Various trials have established the efficacy of febuxostat 40 mg to 80 mg daily compared to 300 mg of allopurinol. Another advantage is its effectiveness in mild to moderate renal failure. Major side effects include rash, elevated liver enzymes, diarrhoea and non-specific arthralgias. There is lesser drug interaction with azathioprine, 6-mercaptopurine and theophylline.

**URICOSURIC DRUGS:**

The primary uricosuric agents, probenecid, benzbromarone and sulfinpyrazone and less potent ones like losartan, high dose salicylate, fenofibrate, amlodipine and vitamin C inhibit the urate anion exchanger URAT 1 located at the apical (brush border) membrane of renal proximal tubule.

Probenecid and benzbromarone also inhibit voltage-dependent urate anion reabsorption by GLUT 9. Probenecid is initiated with a starting dose of 250 mg twice daily, titrated upto 1000 mg twice daily. Benzbromarone is given in a dose of 50 mg daily to 100 mg twice daily. Both these drugs may promote urolithiasis and thus adequate hydration should be maintained. They are contraindicated in patients with low GFT, uric acid overproduction, and history of urolithiasis. Benzbromarone retains its efficacy at lower GFR (<60ml/min – CKD –III), but had limited availability and potential risk of fulminant hepatotoxicity.

The first-line pharmacotherapy to lower serum urate in chronic renal disease is lowering uric acid synthesis by xanthine oxidase inhibitors.

**URICOLYTIC DRUGS:**

**Uricase:** Uricase, an enzyme deficient in human and higher primates breaks down relatively insoluble uric acid to highly soluble allantoin.

**Rasburicase:** A recombinant fungal enzyme was used in tumour lysis syndrome. It has a half-life of 24 hours, and is highly immunogenic.

**Pegloticase:** Pegylated uricase is now available. It is given
CONCLUSION:
There is an increasing prevalence of gout and hyperuricemia worldwide due to increasing access to high caloric foods and greater prevalence of obesity, increasing life expectancy and use of predisposing medications like diuretics and fructose in beverages.

Asymptomatic hyperuricemia needs individualized approach. Appropriate diagnosis and treatment of acute gout should be followed by aggressive treatment of hyperuricemia and other risk factors. Acute flare of gout is better managed with low dose colchicines and NSAIDs.

Both allopurinol and febuxostat are effective in the treatment of chronic hyperuricemia. Febuxostat has some advantages over allopurinol, being a non-purine xanthine oxidase inhibitor with lesser side effects and drug interaction.

REFERENCES