Review Article

Gout-Reasons and Remedies

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ABSTRACT

Gout has been known since antiquity historically, it has been referred to as the King of diseases and Disease of King or Rich man's disease. Gout also known as "Podagra" which it involves the great toe. It has increased frequency in recent decades, affecting 1-2% of the western population at some point of their life time. It has increased by double between 1990 and 2010. This increase believes to be due to increasing risk factors in the population, such as metabolic syndrome, longer life expectancy change in diet and hypertension. Gout is an inflammatory response to monosodium urate (MSU). Monohydrate crystals formed secondary to hyperuricaemia. Commonly occurs in fourth decade of life. Major clinical manifestations are acute synovitis, chronic erosive and deforming arthritis, tophi, nephrolithiasis and interstitial nephritis. Hyperuricaemia is primary or secondary is associated with obesity, metabolic syndrome, dislipemia and diabetes, as been found recently. Most frequent presentation is arthritis of first metatarsophalangeal joint. Articular gout may be acute or chronic. Hyperuricaemia also predisposed to renal stones, uric acid nephropathy, cerbrovascular and cardiovascular diseases. Diagnosis is confirmed by visualization of needle like and negatively birefringent bypolarized light microscopy and demonstration of monosodium urate crystals (MSU) in all synovial fluid. Asymptomatic hyperuricaemia though benign entity may have serious repurcushions in long term. Treatment of gout is reduction of inflammation with colichicine, NSAID, glucocorticoids, ACTH, anakinra and rilonacept. Chronic gout is managed by dietary modifications like increasing consumption of dietary products, Vitamin C, calcium, coffee and reducing high purine diet. Uricostatic drugs like allopurinol, flebuxostat, uricosuric drugs like probenecid and benzbromarone or uricases lilke rasburicase and pegloticase are being increasingly used for chronic gout.

Keywords: Gout, uric acid, hyperuricaemia, inflammatory response, monosodium urate (MSU), serum uric acid (SUA).

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INTRODUCTION

The first documentation of the disease is from Egypt in 2,600 BC in a description of arthritis of the big toe. The Greek Physician Hippocrates around 400BC commented on it in his Aphorisms, noting its absence in premenopausal women [(1, 2)]. Gout is rare in most of the animals due to their ability to produce uricase, which breaks down uric acid [(3)]. Humans and other great apes do not have this ability, Hence gout is common [(4)].

Gout is an inflammatory response to the monosodium urate monohydrate (MSUM) crystals formed secondary to hyperuricaemia. The major clinical manifestations are acute synovitis, chronic erosive and deforming arthritis, tophi, nephrolithiasis, interstitial nephritis and hypertension. The epidemiology of hyperuricaemia is different from that of gout. Mean uric acid (urate) concentrations are age and sex-related. Prepubertally, in males the mean concentration is around 3.5 mg/dl, with a steep rise to 5.2 mg/dl at puberty. In females the rise is appreciated only after menopause (up to 4.7mg/dl). Hyperuricaemia has been defined as a serum or plasma urate concentration greater than 7.0 mg/dl in males and 6.0 mg/dl in females [(5)] estimated in fasting samples. Serum Uric Acid (SUA) is usually raised (>10 mg/dL) but it should be noted that up to 40% patients may have normal or low SUA level during the acute attack as the stress- induced liberation of ACTH and disease induced secretion of cytokines are uricosuric.

The prevalence of hyperuricaemia varies amongst communities. Only about a tenth of patients of hyperuricaemia exhibit gout. The incidence of gout varies in populations from 0.2 to 3.5 per 1000, with an overall prevalence of 2.0 to 26 per 1000. Gout is rare in children and premenopausal females. The peak age of onset in males is between 40 and 50 years [(30)].

EPIDEMIOLOGY

Incidence of gout in India is not very 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. Occurance of first attack of gout is observed 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 [7]. Globally, the incidence and prevalence of gout has doubled over the last two decades [8].

Another Indian study by Mishra etal 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 greater prevalence of obesity [9].

- A family history of gout or hyperuricemia is found in as many as 80% of patients.
- The condition is about five times more common in men than in women in this age group. The age of onset of first attack is about a decade later then in man and involvement is more in upper extremity.
- An increasing prevalence of the disease is closely linked with hypertension and the use of diuretic agents.
- Transplant patients and patients on cyclosporine therapy are at increased risk for the disease.
- The syndrome of gout may precede the myeloproliferative disorder.
- Acute gout most commonly affects the first metatarsal joint of the foot, but almost any joint can be involved.
- Tophaceous gout occurs in less than 10%, of patients, and the highest incidence of attacks is reported in the spring.
- Acute attacks may be provoked by trauma, surgery, infection, starvation, and alcoholic or dietary indiscretions. Acute attacks have been known to follow a game of golf, a long walk, or a hunting trip.

Table 1: Etiology of hyperuricemia

Increased production (10%) :	
Primary (Inherited enzyme defect <5%)	
• Hypoxanthine-guanine phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome)	
• Glucose-6-Phosphatease deficiency	
• Phosphoribosyl pyrophosphate synthetase (PPP) overactivity	
Secondary (>95%):	
• Myelo and lymphoproliferative disorder	
• Chronic hemolytic anemia	
• Exfoliative psoriasis	
• Carcinomatosis and tumour lysis syndrome	
• High purine diet	
• Alcohol	
Decreased excretion (90%)	
Idiopathic :	In about 90%
Renal :	Chronic renal failure, polycystic kidney disease, lead nephropathy
Endocrine:	Hypothyrodism, hyperparathyroidsim,
Metabolic :	Diabetes insipidus
/ Metabolic syndrome:	
Drugs :	Lactic acidosis, ketoacidosis, starvation, severe dehydration
Miscellaneous:	Obesity, dyslipidemia, hypertention, diuretics, low dose aspirin, pyrazinamide, ethambutol, cyclosporine
	Sarcoidosis, toxemia of pregnancy, Down syndrome.

PATHOLOGY

Uric acid is the end product of purine degradation in humans because of lack of the enzyme uricase, which converts uric acid to allantoin, a more soluble excretory product. Hyperuricemia results from several causes, including over activity of phosphoribosylpyrophosphate sythetase, an enzyme responsible for converting purine nucleotides to uric acid; enzyme deficiencies, such as glucose-6 phosphatase deficiency (glycogen storage disease) and hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan Syndrome); and renal disease with failure of secretion of urate by the renal tubules .

Uric acid salts, most notably monosodium urate (MSU), form in the presence of elevated uric acid levels and may be complexes with proteins in body fluids. Precipitation occurs beyond their solubility products or when they are perturbed. MSU crystals also may be found in the synovial fluid of asymptomatic patients. The increase in gout attacks in the peripheral joints in cold weather and with a lower body temperature. Acute attacks of gouty arthritis occur when intrarticular monosodium urate crystals are phagocytized by white blood cells that they release inflammatory mediators.

Uric acid is the most abundant natural antioxidant in the human body, and possibly provides protection against oxidant induced neurological and cardiovascular degenerative processes.

Thiazide diuretics, alcohol, low-dose salicylates, and cyclosporine decreases the renal excretion of uric acid and promote the development of gout. Amiloride, ethacrynic acid, cyclosporine, levodopa, furosemide, ethambutol, aspirin (low dose), pyrazinamide, bumetanide, nicotinic acid, cytotoxic drugs etc [14] may trigger an acute attack of gout.

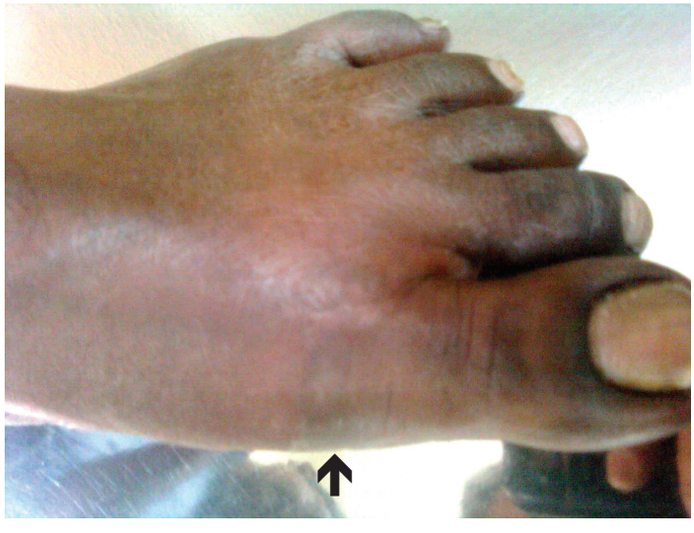

Fig 1: Gout (Podagra)

Genetic: The link with hyperlipidemia may be related to genetic factors [15].

Dyslipidemia: Hyperurcemia is found in 80% of patients with hypertriglyceridemia [14].

HIV: In most of patients with HIV disease though gouty arthritis is not uncommon. The prevalence of hyperuricemia is more in HIV infected persons than in general population (41.9% versus 2-8%) [18].

Pre-eclampia: In hypertensive pregnant patients, high serum uric acid level > 5.5 mg/dL may indicate an increased likelihood of pre-eclampsia. Hyperuricemia results from contracted plasma volume and local relase of angiotension II by the kidneys [17].

CLINICAL SPECTRUM

ASYMPTOMATIC HYPERURICAEMIA

Hyperuricaemia can be due to underexcretion or over production of urate or both. The majority of patients with primary gout are underexerters. Elevated uric acid levels are found in susceptible individuals many years before the onset of symptoms. Hyperuricemia is believed to begin at puberty in males and menopause in females [27-28].

ACUTE GOUT

Classically, gout presents in the early hours of the morning as an acute monoarthritis affecting the lower extremity, often the first meta-tarsophalangeal joint (70% of attacks are in this joint), in some, ankle or knee. The affected joint is warm, tender and swollen, and in most cases the overlying skin is erythematous. Low grade fever, general malaise and anorexia may accompany the symptoms. The pain often begins suddenly at night and can be excruciating. With chronic disease, any joint in the body may be involved. Avascular necrosis has been reported in association with gout, but the association may be fortuitous and coincidental [19].

INTERCRITICAL GOUT

Symptom free intervals between attacks with established gout referred to as intercritical gout during this period patients have hyperuricaemia, and synovial fluid analysis may show MSU crystals. Deposit may be in tendons, and ligaments, cartilage, bone and other soft tissues, including bursae and other synovial spaces, and are para-articular in the subcutaneous tissues. Weakening of tendons and ligaments by the presence of tophi predisposes these structures to rupture. The predilection for deposits occur around the olecranon bursa, the cartilages of the ear, and nose. Tophaceous deposits may result in carpal tunnel syndrome in the wrist, and paraplegia in the spine [19].

CHRONIC GOUT (Tophaceous Gout)

Chronic polyarthritis and/or tophi developing after a first gouty attack ranges from 3 - 42 years. With an average of 11.6 years. Tophi have been reported to occur in 12% of patients after 5 years and 55% after 20 years of untreated disease.

OTHER PRESENTATIONS OF GOUT

Gout myopathy has been observed in long-standing disease with increased signal intensity at MR imaging, but frequently associated with coexisting condition.

GOUT UROPATHY

Gout has two types of urinary syndromes, urolithiasis and chronic urate nephropathy[3] uric acid stones accounts for 5%. Acidic urine, hyperuricaemia, and low urine volume are rich factors for urolithiasis.

GOUTY NEPHROPATHY

This entity seen in chronic urate nephropathy cases. The monosodium urate crystal deposited in the distal renal tubules and the collecting ducts induce tophus formation.

LAB INVESTIGATIONS

- Demonstration of strongly negative birefringent needles and rod shaped crystals of MSU in synovial fluid under compensated polarizing light microscopy is gold standard method of diagnosis. Hyperuricemia usually constantly present but it does not confirm.
- Fasting serum uric acid levels usually raised (> 10 mg/dl). Up to 40% of patients may have normal or low SUA level during acute attack as stress induced liberation of ACTH and disease induced secretion of cytokines are uricosuric. Measurement of a single urine sample for uric acid / creatinine ratio (normal <0.5) may be useful parameter [22].
- Complete urine exam and serum creatinine
- Blood glucose and serum lipid profile. CBC and ESR to detect myeloproliferative disorder.
- Hematology: Elevated CRP, neutrophilia is marked in acute phase response. Reactive thrombocytosis may also be seen.
- X-ray: usually normal in early disease, narrowing of joint space, sclerosis and OA changes may develop in affected joints with time. Gout "erosions" (bony tophi) are less common, but punched out" with sclerotic and overhanging edges- "rat bite erosions" are seen [19].

DIFFERENTIAL DIAGNOSIS

• Septic arthritis

• Pseudogout (presence of calcium pyrophosphate crystals (positive birefringence) in joint fluid and normal serum uric acid but with radiological appearance of chondrocalcinosis.

• Chronic Rheumatiod arthritis with tophaceous arthritis.

• Radiological appearance similar to rheumatoid arthritis, sarcoidosis, multiple myeloma, hyperparathyroidism, Hand-Schiller-Christian disease [32].

• Chronic lead intoxication may result in acute gouty arthritis (saturnine gout) [30, 31].

TREATMENT OF GOUT

The therapeutic aims in gout are:

• Treating an acute attack promptly and appropriately.

• To prevent recurrence of acute gouty arthritis

• Lowering urate levels

• To prevent or reverse complications of the disease resulting from deposition of sodium urate or uric acid crystals in the joint, kidneys or other sites.

• To prevent or reverse co-morbid conditions like obesity, hypertension, hypertriglyceridemia, and renal complications.

DIET MANAGEMENT

• Reduce Alcohol intake especially beer (which is high in purines).

• Higher intake of coffee (4 cups/day) is beneficial in lowering urate level, but no such effect with tea [26].

• Higher intake of meat, seafood, soft drinks high in fructose and sweat corn syrup is associated with higher serum uric acid level.

Patients should be advised to limit consumption of the following purine-rich foods: meats, particularly organ meats (liver, kidney, etc,). Sea food, particularly shellfish, sardines, anchovies. But Vegetables and legumes; asparagus, cauliflower, spinach, beans, peas, and mushrooms can reduce serum urate by 15% and delay the need for drugs [26].

• Dairy products (milk) decrease serum urate level.

• Fruits and vegetables rich in vitamin C are beneficial as it has got a uricosuric effect.

• Maintenance of high level of hydration with 2-3 liters of water intake/day.

TREATMENT

The use of NSAID in high doses rapidly reduces the pain and swelling, initially.

• ***Naproxen:*** 750 mg immediately, then 500mg every 8-12 hours.

• ***Diclofenac:*** 75-100mg, then 50mg every 6-8 hours

• ***Indomethacin:*** 75mg, then 50mg every 6-8 hours is regarded as gold standard.

• ***Colchicine:*** 1000mg. then 500 mg every 6-12 hours this cause diarrhea

• ***Cortico steroids:*** Intra muscular and Intra-articular depot methy prednisolone.

TREATMENT OF ASYMPTOMATIC HYPERURICEMIA

No evidence based recommendation of benefits of therapy upto 11 mg/dl in males and 9 mg/dl in females, with serum uric acid except in conditions associated with tumor 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 [17].

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 the patients where the diagnosis of gout is not confirmed. It acts by inhibiting the action of neutrophils and prevents chemotaxis. It also down regulates TNF-a receptors and inhibits mast cell histamine release [18]. 3 doses of 0.5 mg/day for 4 to 5 days followed by 0.5 mg once or twice daily up to 6 months depending on renal status [35].

• **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 :** The first line option in patients with renal dysfunction where NSAIDs and colchicines are not suitable. Prednisolone in a dose of 0.5 mg/kg daily is effective in gout flares. Intravenous methylprednisolone (100-150mg) or triamcinolone (60mg) intramuscularly is equally effective. Intra articular methylprednisolone depot preparation is also effective.

• **ACTH - Dose :** 25-40 IU i.m. or s.c. in polyarticular gout.

CYTOKINE ANTAGONIST

• **Anakinra :** Soluble IL-1 receptor antagonist at dose of 100 mg/day subcutaneously for 3 days has been used with good results in refectory chronic gout [34].

• **Rilonacept:** It also known as IL-1 Trap. 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.

Dose : 320 mg s.c loading, followed by 160 mg s.c. weekly for 16 weeks.

TREATMENT OF CHRONIC GOUT

It is imperative to have prophylactic use of urate lowering drugs. Classified as : 3

1. Uricostatic : decrease production of uric acid

2. Uricosuric : increases excretion of uric acid via kidney.

3. Uricolytic-Uricase, conversion of uric acid to allantoin.

URICOSURIC DRUGS

The primary uricosuric agents, Probencecid, benzbromarone, sulfinpyrazone, losartan, high dose salicylate, fenofibrate, amlodipine and vitamin C.

Losartan: is preferred in gout with hypertension, fenofibrate in gout with dyslipidemia and sulfinpyrazone in gout with past history of cerebral infarction (sulfinpyrazone prevents platlet aggregation).

The use of losartan and fenofibrate alone or in combination with urate lowering therapies could have an extra value in the prevention and management of hyperuricaemia in patients with hypertension and dyslipidaemia [7].

Gout in Transplant Patients: Recent studies report that amlodipine may reduce cyclosprine induceed hyperuricemia [22].

URICOSTATIC DRUGS

Allopurinol : is a non-selective xanthine oxidase inhibitor. Dose 100 mg/day given once daily is used in over producers of uric acid, stone formers and patients with advanced renal failure. In renal failure, the dose is reduced much and even in patients with dialysis, the dose is 50-100mg/day. Allopurinol is purely a urate-lowering agent and it has no role in acute attack. Skin rashes are the most common side effects. Bone morrow suppression is very rare. Allopurinol may induce acute gout when it is first introduced [4].

Febuxostat : It is a selective inhibitor of xanthine oxidase. 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. Another advantage is its effectiveness in mild to moderate renal failure. Major side effects include rash, elevated liver enzymes, diarrhoea and non-specific arthralgias.

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: Pegyland uricase is now available. It is given 8 mg every 2 weeks and is effective in severe chronic tophaceous gout as well as refractory hyperuricemia due to tumour lysis [37, 38].

PHYSIOTHERAPY

In small, randomized trial of 19 patients, ice therapy on the inflamed joints for 30 minutes, 4 times daily along with drug treatment caused a significant reduction in pain as well as joint circumference as compared with a control group of 9 patients who were given the same drug regimen but without the ice therapy [12, 13].

During an acute attack of gout, use relaxation exercises to minimize pain and muscle guarding. Heat and cold therapy may be used. Ultrasound therapy and laser therapy can be preferred[11].

Surgery : Surgical intervention should be considered in specific circumstances such as nerve compression, mechanical impingement or sepsis [40].

CONCLUSION

Gouty Arthritis is a painful but readily condition experienced by many adults. The prevalence of gout in western countries is on the rise, most likely due to life choices. Hypertension, high alcohol intake, diuretics use (specifically, thiazides & loop diuretics) and obesity contribute both independently & additively to the development of gout in hyperuricemic patients. Incidence of gout is increasing in urban India. Gout, the second harmful metabolic disease after diabetes mellitus. Rising in elderly patients, may be due to high usage of diuretics declining use of estrogen replacement therapy.

Uric acid is the most abundant natural antioxidant in human body, hyperuricemia may be a true independent risk factor for coronary artery disease (CAD). Hyperuricemia is a strong marker of endothelial dysfunction and insulin resistance, and

an independent risk factor for hypertension.

Research shows Hyperuricemia to be a good predictor of ischemic cardiovascular disease and poor outcomes related to these diseases. The treatment of gout has been established, researchers are still finding potential new treatments, such as fenofibrate and potential implications for treatment, such outcomes in cardiovascular disease, gout research remains an important endeavor.

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