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A Review on Gout

Athulya Anil*[1], Dhanya.S[2] Prasobh.Gr[3],
*[1]B Pharm student, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India. 695502.
[2]Associate Professor Department of Pharmaceutical chemistry, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India. 695502
[3]Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India. 695502

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ABSTRACT: Gout is the most common form of inflammatory arthropathi associated with excruciating pain. This condition is caused by hyper uricemia this leads to crystallization aggregation and deposition of monosodium urate crystals that accumulate in joints and soft tissues.

An overview of pharmacological therapeutics and recent knowledge on impact of lifestyle daily habits related. Acute gout is traditionally treated with NSAIDs, corticosteroids and Colchicine. The clinical picture of gout is divided into asymptomatic hyper uricemia, acute chronic tophaceous gout. Diagnosis is based on laboratory and radiological features.

KEYWORDS: Metatarsophalangeal,MSU crystals, tophi,

I.INTRODUCTION

[1] Gout is usually presents as a mono arthritis in the feet metatarsophalangeal joint of the foot and is often related to as podagra. Numerous risk factors give the development of gout have been calculated inducing hyperuricemia, genetic factors, alcohol consumption, metabolic syndrome, hypertension, obesity diuretic use and chronic renal disease. Hyper uricemia is often an important convince of renal under excretion via the kidney primarily through the proximal tubulegout or gouty arthritis, has a long and colourful history with some of the earliest descriptions dating back as far as the 5th century B.C. Historically, gout as been called "the disease of kings" due to its association with rich foods and alcohol consumption.

More recently genome wide associated studies (GWAS) have reduced genetic variants primarily involving renal urate transport that may explain certain induced property for developing hyper uricemia of gout. Among people who have gout attacks, 90% have kidneys that don't remove enough uric acid from their urine while 10% make too much uric acid in their system. 90% of gout attacks start in a single joint. Most often, it is the "bunion joint" of the big toe. Self-management of gout by patients is complex due to the impact of diet and alcohol on symptoms as well as the different classes of medications used based on whether treatment is directed towards acute versus chronic symptoms. the patients typically receive very little education on the dietary and lifestyle factors associated with gout. These deficits in patient education may contribute to medication nonadherence. In particular, patients may be unaware of the risks of gout flares with initiation of urate-lowering medications. Thus, when flares occur, patients may assume the medication is not working and therefore stop taking it. Additionally, they may be unaware or believe that medications are not to be used chronically since multiple studies have shown that the majority of patients do not use urate-lowering medications regularly.

II. ETIOLOGY

[2]Gout is caused by altered purine metabolism leading to hyperuricemia. When the local solubility limits of uric acid are exceeded, monosodium urate crystals deposition in the joints kidneys and soft tissues causes clinical manifestation including arthritis soft tissue masses nephrolithiasis and urate nephropathy
Gout is often by

- Purine diet
- Alcohol use
- Diuretic therapy
- Reduced renal clearance
- Genetic factors
- Obesity
- Chronic kidney disease
- Metabolic syndrome and hypertension

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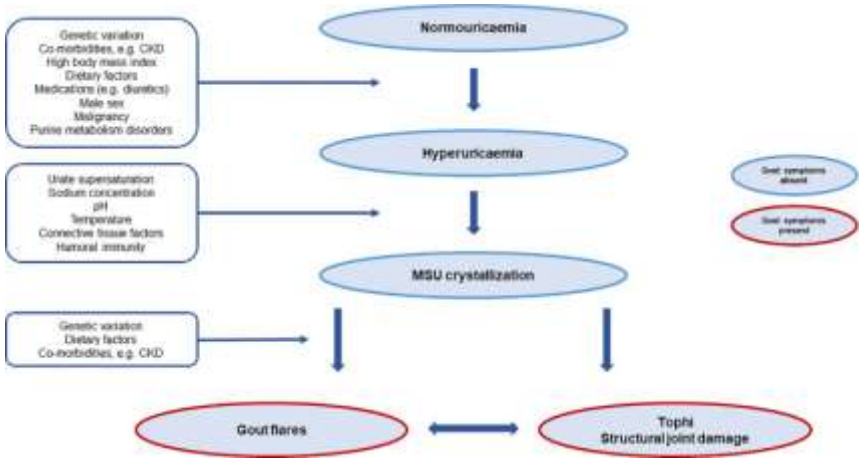
III.EPIDEMIOLOGY

[3] Current dietary and life style choices have also contributed to increased rates of comorbidities associated with hyper uricemia and gout. Clinical manifestation includes excruciatingly painful acute attacks of gout arthritis formation of tophaceous MSU crystals deposit in joints and other body tissues, chronic joint damages, renal stone formation and potential renal insufficient

Epidemiological studies have confirmed dietary factors (animal purines, alcohol and fructose) obesity, metabolic syndrome hypertension, chronic kidney disease are clinically relevant risk factors for hyperuricemia and gout. Almost all studies reported that alcohol intake increased the risk of developing incident or prevalent gout. Alcohol use measured as grams per day or drinks per day was associated with higher risk of gout. This risk varies substantially according to type of alcoholic beverage: beer confers a larger risk than spirits, whereas moderate wine drinking does not increase the risk.

IV. PATHOPHYSIOLOGY

[8] The clinical features of gout occur in response to monosodium urate (MSU) crystals. Gout should be considered a chronic disease of MSU crystal deposition. A number of pathophysiological checkpoints are required for development of gout. First, elevated urate concentrations are required: urate overproduction and underexcretion contribute to total urate balance. Overproduction occurs due to alterations in the purine synthesis and degradation pathways. Renal underexcretion is an important cause of elevated serum urate concentrations (hyperuricemia), and occurs through alterations in the urate transporters within the renal tubule (collectively known as the urate transportasome). Gut underexcretion (extrarenal urate underexcretion) also contributes to development of hyperuricemia. The next checkpoint is MSU crystal formation. In some individuals with evidence of MSU crystal deposition, symptomatic gout develops. The acute inflammatory response to MSU crystals represents a self-limiting sterile acute auto-inflammatory response which is mediated by the innate immune system activation. Interleukin 1 beta is the key cytokine that contributes to the acute inflammatory response to MSU crystals. In some patients, advanced gout may occur with structural joint damage. Joint damage in gout is mediated both by direct effects of MSU crystals on joint tissue and by indirect effects of joint inflammation. In addition to their central role in pathogenesis of gout, MSU crystals have a physiological role, particularly as an adjuvant or ‘danger signal’ in immune surveillance.



V. DIAGNOSIS

Acute attack of gout has rapid onset with pain being maximal at 6-24 hours Onset and spontaneously resolving with several days or weeks. First attack usually in single joint in the lower limb commonly the first metatarsophalangeal joints. Demonstrating the presence of monosodium urate crystals in joint fluid has been the gold standard test. Radiological and laboratory criteria are helpful

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Clinical Diagnosis:Acute gout is characterized by rapid onset and build-up and pain. The speed of the onset of pain and swelling is relevant to making the diagnosis. The exquisite pain in acute gout is associated with warmth, redness, and swelling of the affected joint Systemic symptoms and signs of fatigue, fever, and chills may occur

Laboratory Diagnosis:Definite diagnosis of gout is the presence of MSU crystals in aspirated joint fluid or tophus. MSU crystals are needle shaped approximately 2-20mm long. They exhibit strong negative birefringence under polarized light. They appear yellow when they are parallel to the axis of the slow vibration of the compensator and blue when lying perpendicular to the same axis
MSU crystals can be observed in more than 95% of patient with acute gouty arthritis.

In some asymptomatic patients MSU crystals are also detected in joints in which there is no inflammation and this is thought to confirm the diagnosis. SF leukocyte counts are elevated from 2000 to 100000/mL in patients with acute gout.

Radiology: Radiographic abnormalities are not sufficiently sensitive and specific for the diagnosis of gout. Only 45% of patients with gout manifest radiographic bone changes. The radiographic changes indicate the chronicity of the disease process. Computed Tomography (CT) scans reveals MSU deposit in vitro as well as with in the knee joint Magnetic Resonance Imaging (MRI). MRI is a useful method of determining the extent of disease in tophaceous gout and may provide information regarding the patterns of deposition and spread of MSU crystals. Ultrasound, Plain radiography, MRI and scintigraphic findings on bone scan provide helpful diagnostic clues but are not useful in making a definite diagnosis of gout.

VI CLASSIFICATION

Acute gout
- NSAIDs
- Corticosteroids
- Colchicine

Chronic gout
- Inhibit uric acid synthesis: Allopurinol, Febuxostat (Uricostatic)
- uric acid excretion: Probenecid, Sulphinpyrazol (Uricosuric Agents)

VII.MANAGEMENT OF AN ACUTE GOUT

[4]Drugs used in the management of acute attack including NSAIDs, Colchicine and corticosteroids.
NSAIDs are recommend first- line agents, but in a number of patients their use is contraindicated and a second line agents is indicated where the pain is not adequately controlled by treatment, paracetamol and weak opioid analgesics
For example, codeine or dihydrocodeine may be added to the regimen to provide additional relief.
NON- STEROIDAL ANTI-INFLAMMATORY DRUGS
[5] The usual treatment period is 1-2 weeks NSAIDs act by direct inhibition of cyclooxygenase-1 (cox-1) and Cyclo- oxygenase -2 (cox-2) via blockade of the cyclooxygenase enzyme site.
The subsequent inhibition of prostaglandin production reduces inflammation, but also result in additional activities on platelet aggregation, renal homeostasis and gastric mucosal integrity.
Indomethacin was considered the NSAID of choice in gout largely because it was one of the first NSAIDs shown to be effective in the management of gout.
Azapropazone (1200-1800 mg/daily) has been shown to have both anti- inflammatory and Uricosuric effect during an acute attack.
Unfortunately use is associated with a higher risk of upper gastro- intestinal side effects when compared to other high dose of NSAIDs (diclofenac, ibuprofen, naproxen indomethacin and ketoprofen) and this Significantly restricts it's use.
NSAIDs should be avoided in patient with heart failure, renal insufficiency and a history of gastric ulceration.
When proscribing an NSAID, the need of gastric protection should be considered in patient at increased risk of a peptic ulcer, bleed or perforation
COLCHICINE
[12] Colchicine is an alkaloid derived from the autumn crocus (colchicum autumnale).
Colchicine has a slower on set of action than NSAIDs but it is recommended in patient where NSAIDs are contraindicated. Although the mode of action of colchine in gout is not fully understand it is thought to arrest microtubule assembly in neutrophils and inhibit many cellular functions.
Colchicine blocks the release of a crystal- derived chemotactic factor from neutrophil lysosomes, blocks neutrophil adhesion to endothelium by modulating the distribution of adhesion molecules

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on the endothelial cells and inhibits monosodium urate crystals induced production of superoxide anions from neutrophils. Patients were given 1mg of colchine followed by 500 cg.
Every 2h until the attack stopped or they felt too Ill to taking continue taking colchicine.
The current dose of colchine licensed for the management of an acute gout is 1 mg initially.
A maximum of 6mg should be given per course and treatment should not be repeated within 3 days.
Common side effects associated with colchine are abdominal cramps, nausea, vomiting and rarely bone marrow suppression, neuropathy and myopathy.
Side effects are more common in patient with hepatic and renal impairment.
Colchicine is metabolised by CYP34 and excreted by p-glycoprotein toxicity can be caused by drugs that interact with its metabolism and clearance, and this includes macrolides cyclosporine and protease inhibitors.

CORTICOSTEROIDS
Corticosteroids is usually considered where use of an NSAID or colchine is contraindicated or in refractory cases. This given may be intravenously, intramuscularly or direct in to joints are affected.
An intra articular injection is highly effective in treating an attack.
Common doses of intra articular steroids are 80mg of methylprednisolone acetanoide for large joint such as knee 40 mg of triamcinolone acetanoide for a smaller joint such as wrist or elbow
Corticosteroids have fewer adverse events than other acute treatments when used short terms particularly in the elderly.

VIII.MANAGEMENT OF CHRONIC GOUT

[11]The aim of prophylactic gout treatment is maintaining the serum urate level. The serum urate level below the saturation points of monosodium urate level below the saturation point of monosodium urate level below the saturation point of monosodium urate (300 mol/L). If the serum urate is maintained below this level, crystal deposits and gout is controlled.

Drugs that lower serum uric acid can be classified into three groups according to their pharmacological mode of action

- Uricostatic agents
- Uricosuric agents
- Uricolytics

URICOSTATIC AGENTS
Uricosuric agents lower uric acid levels by inhibiting renal tubular reabsorption of uric acid, thereby increasing net renal excretion of uric acid. These agents increase the risk of renal stones, with about a 9-10% risk for probenecid.

ALLOPURINOL
Allopurinol is the prophylactic agent of choice in the management of recurrent gout in order to become pharmacologically active, allopurinol must be metabolized by the liver to oxypurinol. Both allopurinol and oxypurinol are renally excreted starting dose is 100 mg /day this is gradually increased in 100 mg increments every 2-3 weeks until the optimal serum urate level or the maximum dose is reached. The maximum recommends
Daily dose in patients with normal renal function is 900 mg/daily.

FEBUXOSTAT
Febuxostat is more selective and potent inhibitors of xanthine oxidase than allopurinol and has No effect on other involved purine or pyrimidine metabolism.
Febuxostat is more effective than fixed dose allopurinol starting dose of Febuxostat is 80mg once daily.

URICOSURIC AGENTS
Uricosuric agents increase uric acid excretion primarily by inhibiting post- secretory tubular absorption of uric acid from filtered urate in the kidney.

SULPHINPYRAZONE
Sulphinpyrazone is effective in reducing the frequency of gout attack, tophi and plasma urate levels at doses of 200-800mg/day. Inhibit URAT-1 transport resulting in reduced urate reabsorption Sulphinpyrazone inhibits prostaglandin synthesis resulting in a similar adverse effect profile to NSAIDs

PROBENECID
Probenecid mono therapy is less effective than the other agents and generally not recommend.
Doses of 0.5-2.0g/day have been used.

URICOLYTICS
Uricolytics drug convert uric acid to allantoin through the actions of the enzyme urate oxidase

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(uricase). Allantoin is more soluble than uric acid and readily excreted by the kidney. Uricolytics are indicated for hyperuricemia associated with tumour lysis syndrome and are not indicated for other forms of hyperuricemia

IX.STAGES OF GOUT

Gout is a complex form of arthritis that affects the joints, causing pain and swelling. Weight, diet, age, and certain medical conditions can all affect your risk of getting gout.

But the disease actually progresses through four stages, from the silent build-up of uric acid in the blood to chronic arthritis.

ACUTE GOUT ATTACK

By this stage, sodium urate crystals have been accumulating in the joints and formed deposits that cause pain, swelling and redness. The symptoms usually develop rapidly and pain becomes most intense within just 6 to 24 hours of onset. This is referred to as a "gout attack." Symptoms can last for between three and ten days, after which point the joint starts to feel normal again and pain subsides.

ASYMPTOMATIC HYPERURICEMIA

During this stage, the blood level of uric acid is raised but the patient does not present with symptoms. Treatment is not usually required at this stage.

INTERCRITICAL GOUT

This refers to the time period between gout attacks where the patient is free of symptoms and joint function appears to be normal. However, the uric acid crystals continue to deposit in the joints and accumulate quietly, which eventually leads to another attack unless the uric acid level is reduced to below 6.0 mg/dL.

CHRONIC TOPHACEOUS GOUT

This is the final stage of gout, which is a form of chronic arthritis characterized by permanent damage to the cartilage and bone in the joint. In the majority of cases, this stage of gout can be prevented if patients follow any treatment plans or lifestyle changes recommended to them by their GP.

X.RISK FACTORS

[7] Hyper uricemia is one of the main risk factors for gout and occurs in about 15-20% of the population

GENETICS

Genetic basis for this is not fully understood.

A polymorphism of the SLC22A12 gene which encodes for URAT-1 had been associated with under excretion of uric acid and hyperuricemia in German Caucasian. While in a Japanese cohort another mutation of the SLC22A12 gene had to been shown to be protective for the development of gout.

RENAL DISEASE

Hyperuricemia is associated with the kidney disease, but kidney damage may arise secondary to gout as a consequence of the deposition of urate crystals in the tubules of the kidney. Progressive renal failure directly due to gout.

CO- MORBIDITIES

Gout associated with a number of comorbidities, including hypertension, cardiovascular disease, renal impairment, diabetes, obesity, hyperlipidaemia and frequently in a combination known as the metabolic syndrome.

DIET

Gout has been often associated with a rich lifestyle and excess in diet. Gout is higher in people who consumes large quantities of red meat. There is also an increased risk associated with seafood consumption. Consumption of soft drinks sweetened with sugar has also been linked to an increase in the number of gout cases. The mechanism of action thought to be an increase in uric acid level caused by an increase in adenine nucleotides degradation. Vitamin C shows modest uricosuric effect.

ALCOHOL

Uric acid is the end product of purine metabolism in detects plasma urate is divided from the breakdown of cellular nucleotides synthesized de Novo and dietary purine intake. A proportion of the purine bases from cellular breakdown are recycled via the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and adenine phosphoribosyl transferase (APRT) xanthine oxidase catalase the oxidation of hypoxanthine to xanthine and xanthine to uric acid.

MEDICATION

A number of drugs are associated with increased uric acid levels. The use of both loop and thiazide diuretics is the most common modifiable risk factor for secondary gout, especially in the elderly. Loop and thiazide diuretics may precipitate an attack via volume depletion and reduced renal tubular secretion of uric acid. Aspirin has a bimodal effect low doses inhibit uric acid excretion and increase urate levels. ‘

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XI.COMPLICATIONS OF GOUT

TOPHI

[6] Tophi are clumps of urate crystals that harden under your skin. They can form on most joints and cartilage including your fingers, hands, feet, and/or ankles. Tophi also commonly form on the ears. Tophi may not cause pain, but can damage your joints, bones, and cartilage if left untreated.

JOINT DAMAGE AND DEFORMITY

[10] When you have chronic gout, you have swelling in your joints regularly. Chronic inflammation and tophi can lead to permanent joint damage, deformity, and stiffness. In the worst cases of chronic gout, you may need surgery to fix joint damage, or replace joints.

KIDNEY STONES

You are at risk for getting kidney stones when you have gout, since urate crystals can build up in your urinary tract and form stones.

Kidney disease and kidney failure

Kidney stones made from urate crystals can build up in your kidneys, and can cause damage and scars. This kidney damage from urate crystals is thought to lead to kidney disease over time, especially if gout is left untreated.

PSYCHOLOGICAL AND EMOTIONAL PROBLEMS

Chronic gout causes chronic and sometimes constant pain. Gout may affect your ability to walk, work, and carry out normal tasks. Living with pain can be emotionally distressing. Talk to your doctor about the impact gout has on your emotional health, and ask for suggestions about ways to cope with it.

Insomnia

- Fatigue
- Increased stress
- Mood swings

The pain of a gout attack can also interfere with walking, household chores, and other everyday activities. In addition, the joint damage caused by repeated gout attacks can cause permanent disability.

XIIPATIENT COUNSELLING

Foods with purine are best avoided

Gout is caused by hyperuricemia, an uncontrolled metabolic disorder that leads to the deposition of monosodium urate crystals in cell tissue and too much uric acid in the blood. Uric acid is the metabolic product resulting from the metabolism of purines that are naturally found in many foods so food with purin is avoid

Avoid alcohol

Excessive alcohol intake is one of the most common risk factors for patients with gout because it interferes with uric acid clearance. Decreasing alcohol consumption is generally seen as one of the main lifestyle changes that will help alleviate gout pain, so clinicians should be sure to recommend it to patients. If a patient must consume alcohol, then the best option is wine, according to clinical guidelines. Beer, on the other hand, is specifically cited as an alcohol to avoid because it increases patients' uric acid levels and reduces the body's ability to clear the substance from its system.

Lifestyle Modification

The goal of lifestyle modification is to help prevent both gouty attacks and complications, together with its comorbidities is a part of long-term management of gout.

ALLOPURINOL SIDE EFFECTS

- [9] Allopurinol may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:
- Upset stomach
- Diarrhoea
- Drowsiness
- Some side effects can be serious. The following symptoms are uncommon, but if you experience any of them, call your doctor immediately:
- Skin rash
- Painful urination
- Blood in the urine
- Irritation of the eyes
- Swelling of the lips or mouth
- Fever, sore throat, chills, and other signs of infection
- Loss of appetite

XIII.CONCLUSION

Prevalence of chronic gout is expected to continue to rise due to obesity, a generally aging population, and the increasing incidence in associated comorbidities.

Gout is an increasingly prevalent condition worldwide and creates heavy economic burden. Available treatments are generally effective; however, they are not devoid of adverse events.

Well designed and long term, controlled clinical trials evaluating the comparative efficacy and tolerability of

treatments for gout are needed. Management includes the patient education, diet and lifestyle changes, as well as cession of hyperuricemia drugs. The risk of gout increases with the degree of duration of hyperuricemia.

In patient with persistent hyperuricemia, regular modification should lower the serum urate concentration to an optimal level The acute phase of gout is self-limited and characterized by recurrent attacks of synovitis (articular inflammation) that present with pain, erythema, and swelling, most frequently in the large toe but other joints, tendons, bursae or other areas may be involved. Knowledge deficits about dietary triggers and chronic medications were common, but worse in those with active gout. More attention is needed on patient education on gout and selfmanagement training.

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