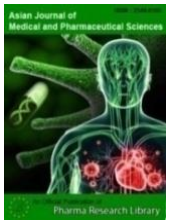

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A Study on Global Epidemiology, Pharmacological and Non Pharmacological Treatment Strategies for Prevention and Management of Gout

Sk. Mahaboob Ali[1], R.Gautham Chakra*[2], Syed Mehanaz Rafayee[3], Kotha Seleena Susan[3], Gundala Gresi[3], Pothuraju Lakshmi Devi[3], Chakali Manohar[3]

[1]Assistant Professor, Department of Pharmaceutics, Saastra College of Pharmacy and Research Center, Totapalli Gudur (M), Varigonda(V), Nellore-524311, Andhra Pradesh, India
[2]Assistant Professor, Department of Pharmacy Practice, Saastra College of Pharmaceutical Education and Research, Totapalli Gudur (M), Varigonda(V), Nellore-524311, Andhra Pradesh, India
[3]Pharm.D student, Saastra College of Pharmaceutical Education and Research, Totapalli Gudur (M), Varigonda(V), Nellore-524311, Andhra Pradesh, India

A B S T R A C T

Gout is a systemic disease that results from the deposition of monosodium urate crystals (MSU) in tissues. Increased serum uric acid (SUA) above a specific threshold is a requirement for the formation of uric acid crystals. Despite the fact that hyperuricemia is the main pathogenic defect in gout, many people with hyperuricemia do not develop gout or even form UA crystals. In fact, only 5% of people with hyperuriceamia above 9 mg/dL develop gout. Accordingly, it is thought that other factors such as genetic predisposition share in the incidence of gout. The general prevalence of gout is 1–4% of the general population. In western countries, it occurs in 3–6% in men and 1–2% in women. In some countries, prevalence may increase up to 10%. Prevalence rises up to 10% in men and 6% in women more than 80 years old. Diagnosis of gout can be made using several validated clinical prediction rules. Arthrocentesis should be performed when suspicion for an underlying septic joint is present; synovial fluid or tophus analysis should be performed if the diagnosis is uncertain. Colchicine, nonsteroidal anti-inflammatory drugs, and corticosteroids relieve pain in adults with acute gout episodes. Indications for long-term urate-lowering therapy include chronic kidney disease, two or more flare-ups per year, urolithiasis, the presence of tophus, chronic gouty arthritis, and joint damage. Allopurinol and febuxostat are used to prevent flare-ups, although febuxostat is associated with an increase in all-cause and cardiovascular mortality and is therefore not routinely recommended. Gout prevention involves a combination of dietary and lifestyle changes and, for some, medication. The prevention strategies include limiting high-purine foods and alcohol, staying hydrated, maintaining a healthy weight, and regular moderate exercise.

Keywords: Gout, serum uric acid, hyperuriceamia, allopurinol and febuxostat, high-purine foods.

A R T I C L E I N F O

Corresponding Author
Dr. R. Gautham Chakra
Assistant Professor, Department of Pharmacy Practice
Saastra College of Pharmaceutical Education &Research
Nellore-524311, Andhra Pradesh, India

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E-Mail ID: gauthamrowdhra05@gmail.com | Mobile no: 7674016126 | ORCID: https://orcid.org/0009-0007-7688-1413

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C O N T E N T S

1. Introduction

Gout is biochemically characterized by the saturation of urate in the extracellular fluid, typically reflected by hyperuricemia, with plasma or serum urate concentrations exceeding 6.8mg/dL (approximately 400 µmol/L); this level

is the approximate limit of urate solubility in the blood. The clinical manifestations of gout may include[1-5]:

- Acute gout flare (recurrent flares of inflammatory arthritis)
- Chronic gouty arthropathy
- Accumulation of urate crystals in the form of tophaceous deposits
- Uric acid nephrolithiasis
- Chronic nephropathy

Etiology

The etiology of gout is usually multifactorial, involving a combination of genetic predisposition, medical comorbidities, and dietary influences. In rare cases, a single-gene defect may underlie the development of gout, often in association with additional medical complications. Irrespective of the precipitating factors, the common pathogenic outcome is sustained hyperuricemia, which can manifest as clinical gout in susceptible individuals.

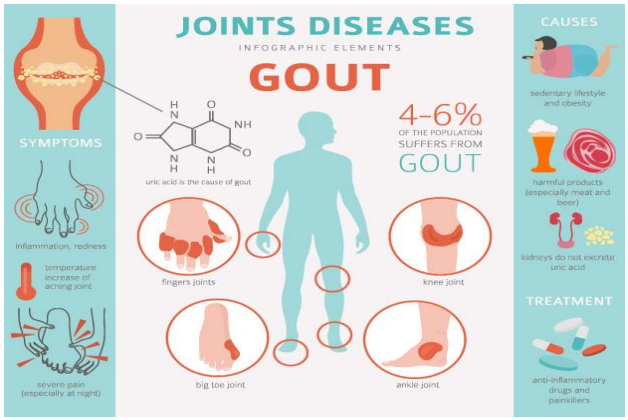

Fig.1: Gout

Genes

The heritability of hyperuricemia is estimated at approximately 73%, and 40% to 50% of individuals with gout have a positive family history of the disease.

Risk Factors

The final step of purine metabolism is the conversion of hypoxanthine to xanthine, followed by the conversion of xanthine to uric acid by xanthine oxidase. This process is then completed by the transformation of uric acid to allantoin by uricase. Allantoin has a much higher solubility than uric acid. Humans, other primates, giraffes, and Dalmatians possess gene mutations that result in the absence of uricase production, a genetic mutation resulting in the inactivation of the uricase gene occurred about 25 million years ago. Simultaneously, there was an increase in URAT1 activity, responsible for uric acid excretion.

About 20 million years ago, humans and other primates lost the ability to produce vitamin C, leading to the emergence of the antioxidant theory in which uric acid replaced ascorbic acid as the main antioxidant. One unique aspect of this evolutionary process is the development of hyperuricemia in humans, making them the only known mammals to develop spontaneous gout. Hyperuricemia is the leading cause of gout, a condition characterized by the accumulation of uric acid crystals in joints, resulting in inflammation and pain. Research has shown that individuals with higher serum urate levels face an increased risk of developing gout and experiencing more frequent flare-ups over time[6-13].

Hyperuricemia, while a significant risk factor, does not singularly account for the development of gout only a minority of individuals with elevated uric acid levels develop the condition. To assess the impact of diet on uric acid levels, examining the lower physiological uric acid range in species that do not produce uricase becomes essential. Dietary sources that can contribute to hyperuricemia and gout include the consumption of animal products such as seafood (eg, shrimp and lobster), organs (eg, liver and kidney), and red meat (eg, pork and beef). Additionally, beverages like alcohol, sweetened beverages, sodas, and those containing high-fructose corn syrup may also contribute to the onset of this disease.

Obstructive sleep apnea (OSA) is pathophysiologically linked to hyperuricemia through intermittent hypoxia, which increases purine nucleotide turnover and uric acid production, and through impaired renal uric acid excretion due to hypoxemia-induced renal dysfunction.

Epidemiological studies have reported a rising burden of gout, primarily attributed to lifestyle changes like increased protein consumption and a sedentary lifestyle. These shifts in habits highlight the complex relationship between modern lifestyle patterns and the prevalence of gout in contemporary society.

Additional factors linked to gout and hyperuricemia include older age, male sex, obesity, a purine-rich diet, alcohol, certain medications, comorbid diseases, and genetic predisposition. Medications such as diuretics, low-dose aspirin, ethambutol, pyrazinamide, and cyclosporine have been identified as potential contributors to elevated uric acid levels and gout development.

Triggers

Any condition leading to changes in extracellular urate concentration has the potential to trigger a gout flare-up. These conditions include various factors such as stress (mainly due to medical illnesses like cardiovascular illnesses, recent surgical procedure, trauma, dehydration, or starvation), dietary choices (such as the consumption of high-purine foods like organ meats or seafood, as well as alcoholic beverages like beer, wine, and spirits), and drugs (including aspirin, diuretics, or even allopurinol).

Dietary Factors That May Lower Serum Uric Acid

Certain dietary practices have been shown to lower serum uric acid and reduce the risk of incident gout. Higher consumption of meat and seafood is associated with an increased incidence of gout in men. Conversely, increased intake of dairy products is associated with decreased incidence of gout in men[14-21].

2. Epidemiology

Epidemiological estimates depend on the definition of the disease. A definitive diagnosis of gout is accepted in the

presence of monosodium urate monohydrate crystals in the joint fluid or the identification of tophus. However, given the impracticality of identifying gout through these criteria alone, various case definitions have been devised, including self-reports, the Rome criteria, the New York criteria, the American College of Rheumatology (ACR) criteria, and the 2015 ACR/European League Against Rheumatism (EULAR) criteria. The 2015 ACR/EULAR criteria have a sensitivity of 92% and specificity of 89%, surpassing the accuracy of all previous definitions and ensuring a more precise and reliable diagnosis of gout in epidemiological studies.

In men, serum urate levels typically range from 5 to 6 mg/dL and are usually attained during puberty, with a slight increase in levels due to age alone. Conversely, women exhibit lower serum urate concentrations, averaging 1.0 to 1.5 mg/dL, compared to men of corresponding ages, a difference likely influenced by renal uric acid clearance under the influence of estrogen. Following menopause, urate concentrations in women rise to levels comparable to those in adult men.

The prevalence of gout can vary by age, sex, and country of origin. Generally, the prevalence of gout is 1% to 4%. Older age and male sex are 2 common risk factors recognized globally. In Western nations, the prevalence of gout is significantly higher in men (3%-6%) compared to women (1%-2%), with a notable 2- to 6-fold difference. The prevalence of gout rises with age but plateaus after 70 years.

Comorbidities

Gout is associated with health risks, including obesity, hypertension (HTN), chronic kidney disease (CKD), diabetes mellitus (DM), hyperlipidemia (HLD), and metabolic syndrome. A study conducted in Olmsted County, MN, highlighted the increased prevalence of various comorbidities in gout patients compared to the general population. The prevalence of obesity (defined as BMI >35 kg/m2) was 29% in gout patients versus 10% in the general population, HTN was 69% versus 54%, CKD was 28% versus 11%, DM was 25% versus 6%, HLD was 61% versus 21%. Gaining weight during adulthood has been consistently associated with a heightened risk of developing gout. Other gout-related comorbidities include HLD, hypothyroidism, anemia, psoriasis, chronic pulmonary disease, osteoarthritis, and depression. Due to increased cell turnover in the epidermis, psoriasis leads to elevated uric acid production. At the same time, patients with CKD experience reduced urate excretion, resulting in hyperuricemia and an increased risk of incident gout.

3. Pathophysiology

Gout is an inflammatory arthritis triggered by the deposition of MSU crystals, the end product of human purine metabolism, in joints, soft tissues, and bones. This condition may manifest in many forms, including acute gout flare (acute arthritis), chronic gouty arthritis (chronic arthritis), tophaceous gout (formation of tophi), renal functional impairment, and urolithiasis.

The pathophysiology of gout involves a series of complex and interacting processes as follows:

- Various genetic and metabolic factors contribute to hyperuricemia in the bloodstream.
- Metabolic, physiologic, and other characteristics contribute to MSU crystal formation.
- Soluble inflammatory factors, cellular elements, and innate immune processes, along with the characteristics of MSU crystals, promote an acute inflammatory response.
- Immune mechanisms come into play to mediate the resolution of acute inflammation induced by MSU crystals.
- Chronic inflammatory processes coupled with the effects of immune cells and crystals on osteoblasts, chondrocytes, and osteoclasts contribute to cartilage attrition, bone erosion, joint injury, and the formation of tophi.

Uric Acid Physiology

Uric acid is the final product of purine metabolism in humans and higher primate species, resulting from a mutation that silences the gene encoding the enzyme uricase. Traditionally, it was believed that uric acid played a crucial role as a natural antioxidant in the human body, primarily responsible for eliminating reactive oxygen species. However, recent studies revealed that uric acid is not a significant factor in controlling oxidative stress. Instead, it is thought to be involved in immune surveillance and the regulation of blood pressure and intravascular volume.[22] Uric acid is a weak organic acid that predominantly exists in its ionized form, MSU, at pH 7.4. This form is less soluble due to the high sodium concentration. In acidic environments, such as urine, uric acid exists in its nonionized form, which is even less soluble within the physiological range. Consequently, uric acid crystals and stones can form in the urinary tract, distinguishing them from MSU associated with gout. Most urate in the body is produced endogenously in the liver, with a minor contribution from the small intestines. Renal excretion is pivotal in managing the body's urate pool under steady-state conditions since the glomerulus filters nearly all urate. In a hyperuricemic state, the urate pool expands.

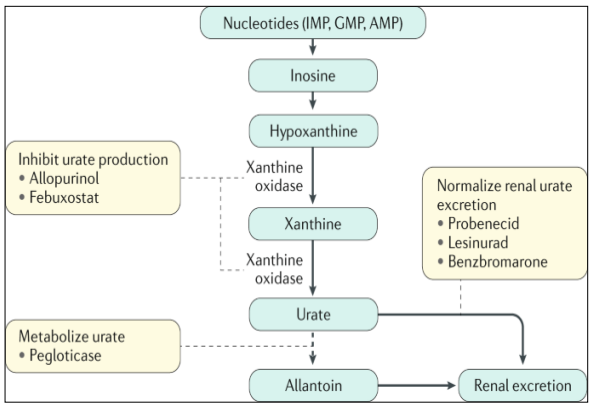

Fig.2: Uric Acid Physiology

In men, the normal urate range is 800 to 1000 mg; in women, it ranges from 500 to 1000 mg. Urate turnover

ranges from 500 to 1000 mg daily. During male puberty, serum urate concentrations increase to reach the adult range, whereas urate levels remain low in females of reproductive age. This disparity is attributed to estrogen's influence on renal urate transporters, leading to reduced renal urate reabsorption and increased clearance in women. However, in menopausal and postmenopausal women, urate levels approach those of adult males and may be influenced by hormone replacement therapies.

Hyperuricemia

Hyperuricemia plays a pivotal role in the development of gout as it facilitates the nucleation and growth of MSU crystals by reducing urate solubility. Several factors contribute to hyperuricemia in humans, including the genetic absence of uricase, the reabsorption of approximately 90% of filtered uric acid, and the limited solubility of MSU and urate in body fluids. An imbalance in the production and excretion of uric acid leads to elevated serum uric acid levels. Hyperuricemia can occur as either primary (idiopathic) or secondary. Overproduction of uric acid is observed in several diseases, toxic states, and due to certain medications. Examples include acute leukemia, tumor lysis syndrome, and psoriasis.

Purine Metabolism

Purines consist of 9-carbon purine nuclei that form fused pyrimidine and imidazole rings. Purines perform essential functions in all living cells through purine-based nucleic acids, including adenine, guanine, and hypoxanthine. The contribution of dietary purines to the urate pool is significant. Removing purines from the diet of normal individuals for 10 days reduces urate levels by 25% and urinary uric acid excretion by 50%. However, implementing severely purine-restricted diets is impractical. Conversely, diets high in fructose, meat, alcohol, and fish are associated with an increased risk of hyperuricemia.

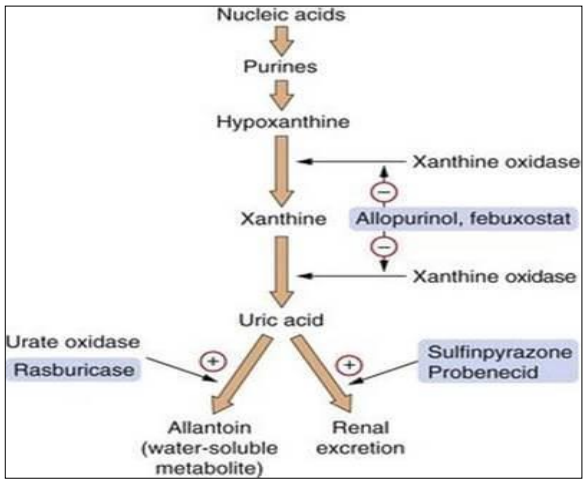

Fig.3: Hyperuricemia

The endogenous pathway of purine production, known as de novo purine synthesis, involves the conversion of ribose-5-phosphate from 5-phosphoribosyl 1-pyrophosphate (PRPP) into nucleotide inosine monophosphate through 10 key steps. This energy-intensive process prompts energy conservation through the interconversion and salvage of purine nucleotides. Urate precursors of purine degradation are hypoxanthine and guanine, most of which are salvaged. Unused guanine is deaminated to become xanthine, while hypoxanthine is oxidized to xanthine by xanthine. Xanthine oxidase is a flavoprotein containing molybdenum-pterin and iron sulfide clusters. It operates in 2 forms: as an oxidase, utilizing oxygen to convert hypoxanthine to xanthine and then to urate, and as a dehydrogenase, using nicotinamide adenine dinucleotide (NAD+). Inhibiting xanthine oxidase is the primary target for lowering urate levels in patients with gout oxidase[23-27].

The primary regulatory steps in purine synthesis include:

1. The synthesis of PRPP in the PRPP synthetase pathway.
2. The utilization of PRPP in the first step of de novo purine synthesis.

The pathway is regulated through inhibition by purine nucleotide products of purine synthesis and activation by increased PRPP. This antagonistic control mechanism is disrupted in 2 rare X-linked disorders: deficiency of the salvage enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and overactivity of PRPP synthetase (PRS1). Conditions such as excessive adenosine triphosphate (ATP) depletion during tissue hypoxia or acute alcohol intoxication can lead to decreased concentrations of inhibitory nucleotides and excess urate production.

Renal Uric Acid Secretion

In adults, only 5% to 10% of uric acid is cleared compared to creatinine clearance, despite 100% uric acid filtration at the glomerulus. This is because 90% of the filtered uric acid is reabsorbed in the renal tubules. Consequently, individuals with hyperuricemia resulting from impaired renal excretion may exhibit normal urinary urate levels due to impaired uric acid clearance. Through genomic and molecular studies, researchers have identified several renal uric acid clearance transporters. Among these, glucose transporter 9 (GLUT9), urate anion transporter 1 (URAT1) have a significant impact on serum urate levels.

Glucose Transporter 9 (GLUT9)

GLUT9, a product of the *SLC2A9* gene, functions as a voltage-driven urate transporter responsible for mediating uric acid reabsorption from tubular cells. GLUT9 exists in 2 isoforms: GLUT9L, located on the basolateral side of the proximal renal tubular epithelium, and GLUT9S, located on the apical side. This transporter is also expressed in the hepatocytes, regulates serum urate concentrations through its dual effects in the kidney and the liver. Additionally, GLUT9 facilitates the transfer of glucose and fructose, which could explain the dietary influence of these substances on hyperuricemia. Studies involving mice with a GLUT9 knockout had moderate hyperuricemia, massive hyperuricosuria, and early-onset nephropathy.

URAT1

URAT1, encoded by the SLC22A12 gene, is highly specific for uric acid and influences renal uric acid transport by mediating the exchange of various anions. Mutations in SLC22A12 can lead to hypouricemia, hyperuricosuria, and exercise-induced renal functional impairment. Uricosuric drugs, such as probenecid, benzbromarone, and lesinurad, inhibit URAT1 and increase uric acid excretion. Other urate

transporters include ABCG2, NPT1, NPT4, and multidrug resistance protein 4 (MRP4).

Autosomal Dominant Tubulointerstitial Kidney Disease

Tubulointerstitial kidney disease, caused by pathogenic variants in the UMOD gene, is characterized by early-onset hyperuricemia (with or without gout), hypertension, and progressive tubulointerstitial inflammation and fibrosis. This condition leads to end-stage renal disease by the age of 40. Previously known as familial juvenile hyperuricemia nephropathy and medullary cystic kidney disease, most affected patients exhibit a mutation in uromodulin, which encodes the Tamm-Horsfall protein. Uromodulin maintains the integrity of the ascending loop of Henle by forming a gel-like lattice that coats the luminal side of the tubule. Defects in the lattice alter solute fluxes, reducing Na and Cl reabsorption, decreasing extracellular volume, and compensatory enhancement of sodium-dependent urate transport in the proximal tubule.

Extrarenal Urate Excretion

In the intestines, urate excretion is facilitated by the ABCG2 transporter. Studies involving reduced ABCG2 knockout mice have revealed that decreased intestinal urate excretion leads to increased serum urate levels. Consequently, hyperuricemia resulting from urate overproduction can be classified as a renal overload type consisting of extrarenalunderexcretion and genuine urate overproduction subtypes.

Urate Crystal Formation

The formation of MSU crystals requires sustained supersaturated urate concentrations. Factors such as the presence of particulate seeds, local cation concentrations, pH, temperature, and dehydration influence crystal formation (see **Table.** Factors Influencing Urate Crystal Formation).Immunoglobulin (Ig) G may also facilitate crystal formation and growth in patients with gout. MSU crystals tend to form in the first metatarsophalangeal joint, midfoot, and Achilles tendon. Emerging evidence indicates a connection between osteoarthritis (OA) and sites of MSU crystal deposition. In osteoarthritic joints, cartilage degradation products, such as chondroitin sulfate, lower urate solubility, thereby promoting nucleation and crystal growth.

Inflammatory Response:

Histopathologic and imaging studies have shown the presence of urate crystals within joints for prolonged periods without causing overt inflammatory reactions. Heavily crystal-laden fluids (urate milk) are sometimes found in uninflamed joints and bursae. The dense urate crystal mass in tophi sometimes reaches massive dimensions, accompanied by minor inflammation and symptoms, until it exerts critical compression on surrounding tissues. The initiation of inflammation in gout typically involves microcrystals that are usually shed from preexisting synovial tophi. This is supported by observing acute gout flares, characterized by rapid changes in urate concentrations. The initiation of inflammation depends on multiple factors, including crystal size, the proteins and molecules coating them, and the recruitment of inflammatory cells. MSU crystal surfaces can bind to various proteins, including IgG, lipoproteins, and lipids. In patients with asymptomatic tophi, synovial fluid macrophages frequently contain MSU microcrystals, suggesting active engagement with phagocytes without apparent inflammation. Synovial macrophages and blood monocytes mount a vigorous response to MSU crystals compared to well-differentiated macrophages due to the release of TGF-b1.

1. Activation of phagocytes leads to lysosomal fusion, respiratory burst, and the release of lysosomal enzymes and inflammatory mediators, including TNF-alpha and IL-8.
2. The predominant pathway of cytosolic protein complex activation involves the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome. MSU crystals activate macrophages and monocytes via toll-like receptors (TLR) 2 and 4, resulting in signal transduction by My88, interleukin-1 receptor-associated kinase 1 (IRAK1), and IRAK4. This activation triggers the nuclear factor-kB, which in turn activates the NLRP3 inflammasome. The activated NLRP3 inflammasome subsequently recruits caspase-1, which processes pro-interleukin-1β (IL-1β) into its active form, IL-1β. IL-1β plays a crucial role in the inflammatory response to gout by promoting vasodilation, recruiting monocytes, and initiating and amplifying the inflammatory cascade. Additionally, IL-1β secretion can result in the breakdown of bone and cartilage. Other cytokines, such as TNF-alpha, IL-6, CXCL8, and cyclooxygenase 2 (COX-2), are also involved in the inflammatory response[28-29].

Lab test:

Synovial Fluid Analysis

Monosodium urate crystal identification remains the gold standard for diagnosing gout. Gout flares are characterized by the presence of MSU crystals in synovial fluid from affected joints or bursae, visualized using compensated polarized light microscopy. The crystals are often intracellular, indicating active phagocytosis. This technique can also identify uric acid crystals from tophaceous deposits and joints during the intercritical period.

Laboratory Study

The examination typically reveals elevations in the WBC count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels during acute gouty arthritis. These features are nonspecific and do not confirm or differentiate the diagnosis from septic arthritis.

Imaging

Although not routinely used, ultrasonography and dual-energy CT (DECT) can assist in diagnosing gout. On ultrasound, MSU deposition appears as a hyperechoic enhancement over the cartilage, known as the double contour sign. DECT can identify urate deposits based on the beam attenuation after exposure to 2 different X-ray spectra. In a pooled analysis, the ultrasound double contour sign had a sensitivity of 83% and a specificity of 76%, while DECT had a sensitivity of 87% and a specificity of 84% for diagnosing gout.

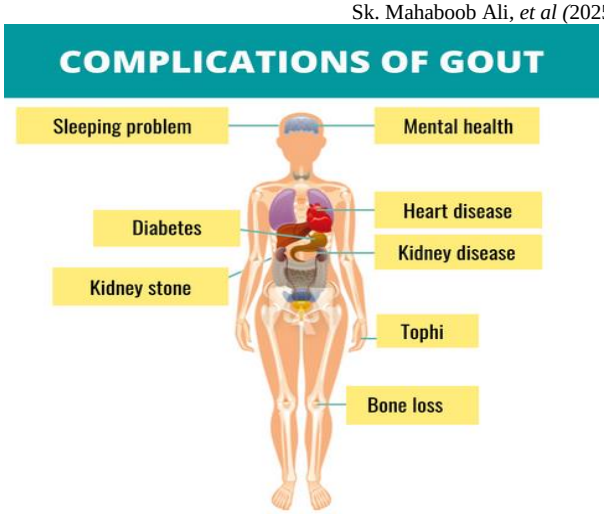

Fig.4: Gout complications

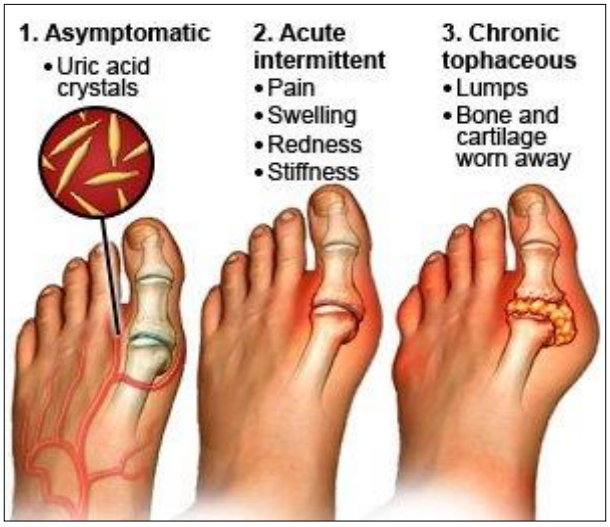

Fig.5: Gout symptoms

4. Treatment and Management

Specific goals guide the treatment of gout. During acute flares, the primary objective is to alleviate inflammation and symptoms. In the long term, the goal shifts toward reducing serum urate levels to suppress flare-ups and regression of tophi.

General Principles of Therapy

- Early on, introducing treatment for a gout flare leads to a more rapid resolution of symptoms.
- The duration of gout flare therapy ranges from a few days to several weeks, depending on when treatment is initiated.
- Anti-inflammatory gout flare prophylaxis should generally be continued during the early months (up to 6 months) of ULT.
- For patients receiving urate-lowering therapy (ULT) at the time of a gout flare, the medication should be continued without interruption, as there is no benefit to temporary discontinuation.
- The presence of tophi indicates the initiation of long-term ULT either during or following the resolution of a gout flare to reverse or prevent joint damage and chronic gouty arthritis.

Acute Gout Flare

The management of acute flares of gouty arthritis aims to decrease inflammation and resulting pain. Treatment should commence within the first 24 hours of onset to reduce the severity and duration of the flare-up if possible. Nonpharmacological management, such as rest with topical application of ice packs can be combined with medications that reduce inflammation. First-line treatments for gout flares are nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or systemic glucocorticoids[30-31].

NSAIDs

NSAIDs are most effective when therapy is initiated within 48 hours of the onset of gout symptoms. Indomethacin and naproxen are the more potent NSAIDs for gout, although many other commonly used NSAIDs exist. NSAID names and dosing are as follows:

- Indomethacin 50 mg 3 times daily
- Naproxen 500 mg twice daily
- Naproxen 500 mg twice daily
- Ibuprofen 800 mg 3 times daily
- Diclofenac 50 mg 2 to 3 times daily
- Celecoxib 200 mg twice daily

Oral Glucocorticoids

Glucocorticoids are recommended for gout patients with contraindications to NSAIDs and colchicine, and they are also preferred for patients with renal insufficiency. The initial dose for a gout flare is:

- Prednisolone or prednisone 30 to 40 mg once daily or divided into twice-daily doses until resolution begins. Taper the dose over the next 5 to 10 days.

Parenteral Glucocorticoids

Intravenous or intramuscular glucocorticoids are recommended for patients who are not candidates for intraarticular glucocorticoid injection or who are unable to take oral medications. A typical methylprednisolone dose is 20 mg intravenously twice daily, with a stepwise reduction and rapid transition to oral prednisone when improvement begins. Adrenocorticotropic hormone (ACTH) is also efficacious for treating gout flare, but limited availability and high cost restrict its use.

Colchicine

Colchicine acts by binding tightly to unpolymerised tubulin and forms a colchicine-tubulin complex that regulates microtubule and cytoskeletal function. This regulation extends to various cellular processes, including cell proliferation, gene expression, signal transduction, chemotaxis, and the secretion of granule contents by neutrophils. Furthermore, colchicine decreases neutrophil adhesion by suppressing the redistribution of E-selectin in the endothelial membrane.

Prophylaxis for Acute Gout

The subclinical joint inflammation in gout justifies colchicine prophylaxis, as acute gout flares are ULT's most common adverse effect. For prophylaxis, low-dose colchicine therapy is the first choice. It is commenced 1 or 2 weeks before using urate-lowering drugs and continues for up to 6 months after normalizing uric acid levels or until the clinically visible tophi are resolved[32-35].

Interleukin-1 Inhibition

IL-1 antagonists have shown efficacy in refractory cases of gouty arthritis. Anakinra, a soluble IL1 receptor antagonist, is administered at 100 mg/day subcutaneously for 3 days.

Xanthine oxidase inhibitors (XOI)

XOIs work by inhibiting uric acid synthesis. This class includes allopurinol and febuxostat. Allopurinol is the recommended first-line pharmacological ULT in gout.

Allopurinol

Allopurinol is converted to its active metabolite, oxypurinol, in the liver and has a half-life of approximately 24 hours. The initial allopurinol dose is 100 mg daily in patients with a CrCl greater than 60 mL/min and is titrated upward by 100 mg every 2 to 4 weeks.

A daily dose of 300 mg of allopurinol reduces serum urate levels in 33% of the population. Allopurinol can be increased above 300 mg daily to achieve the target serum uric acid.

Febuxostat

Febuxostat is a selective XOI that occupies the access channel to the molybdenum-pterin active site of the enzyme. Renal elimination plays a minor role in the pharmacokinetics of febuxostat. FDA approval for febuxostat in treating patients with gout and hyperuricemia includes initial daily doses of 40 mg. If the urate levels do not normalize within 2 weeks, the dosage is increased to 80 mg daily. Studies have demonstrated the superior effectiveness of febuxostat over allopurinol (maximum dose of 300 mg daily).

Uricosuric Drugs

The uricosuric agents work by increasing renal urate clearance. Patients with low or normal urinary uric acid excretion in the presence of hyperuricemia are potential candidates for uricosuric therapy.

Drugs in this class include probenecid and lesinurad (withdrawn from the US market). These agents inhibit URAT1 at the apical membrane of renal proximal tubular epithelial cells. However, they are ineffective as monotherapy in patients with low creatinine clearance (<30 mL/min) and contraindicated in patients with a history of nephrolithiasis.

UricasePegloticase (urate oxidase)

Uricase is present in nonprimates and lower primates. Pegloticase, a pegylated recombinant form of uricase, is a potent agent that rapidly reduces serum urate levels by directly degrading uric acid into highly soluble allantoin. Polyethylene glycol (PEG) molecules are attached to the recombinant porcine-baboon uricase in a process known as PEGylation.

Investigational and emerging therapies for gout

Tigulixostat: A new drug currently in Phase 3 clinical trials, being tested for its safety and efficacy compared to allopurinol36.

URAT-1 inhibitors: These are drugs being developed to block a specific protein in the kidney that is crucial for uric acid regulation.

Nanoparticle drug delivery: This is an advanced approach that uses nanoparticles to deliver drugs more precisely to the affected joints, potentially increasing effectiveness and reducing side effects.

Other advanced approaches

- **IL-1 antagonists:** These drugs can be used to rapidly stop acute attacks, especially for those who can't take NSAIDs, colchicine, or corticosteroids.
- **Advanced diagnostics:**
- New diagnostic tools like ultrasound and MRI can help visualize tophi and monitor their dissolution[37-39].
- **IV uricase:** This can be used for patients with severe tophaceous gout to help dissolve urate deposits, with the goal of allowing maintenance with other drugs later.

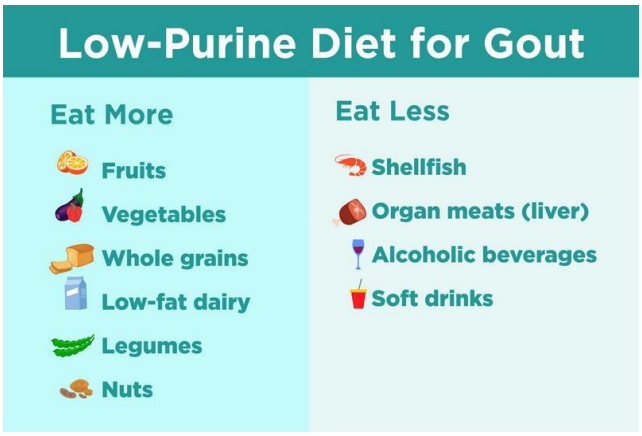

Fig.6: Diet therapy for gout

5. Conclusion

Several comorbidities, diet, medications and alcohol intake increase the risk for incident gout and/or gout flares in patients with known gout. Studies focused on primary and secondary prevention of gout were scarce. Primary and secondary prevention studies are needed to identify whether prevention of gout is achievable. Risk factors should be often taken into consideration in the medical management of patients with gout, since several risk factors (alcohol, obesity, thiazide diuretics etc.) are potentially modifiable, of which at least some are amenable to behavioral and other interventions. The healthcare providers must follow treatment guidelines and strictly implemented in clinical practice to standardise high-quality care and optimise the patient outcomes.

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