AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A Short Duration Study Of Febuxostat- The Clinical Improvement, Side Effects and Serum Uric Acid Levels In Gouty Arthritis Patients - A Prospective Study

Ravi Prakash Degala[*1], N.Suvarna Jyothi[2], L.Chandrika [3], M.S.S.S.S.Kalyani[3], G.Anupama[3] D.Jenny[3]

1.Associate Professor, Department of Pharmacy Practice, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India

2.Professor and Principal, Department of Pharmacology, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India

3. Pharm D Scholar, Department of Pharmacy Practice, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India

ABSTRACT

Febuxostat is a novel, potent, non-purine selective xanthine oxidase inhibitor, which in clinical trials demonstrated superior ability to lower and maintain serum urate levels below 5 mg/dL compared with conventionally used doses of allopurinol. Febuxostat was well tolerated in long term treatment in patients with hyperuricemia including those experiencing hypersensitity/intolerance to allopurinol. Dose adjustment appears unnecessary in patients with mild to moderate renal or liver insufficiency or advanced age. The most common adverse reactions reported were abnormal liver function tests, headache, and gastrointestinal symptoms, which were usually mild and transient. However, whether hepatotoxicity becomes a limitation in the use of febuxostat needs to be determined in further studies. An increased frequency of gout flares occurs for a prolonged period after treatment initiation, as with any aggressive lowering of serum urate, and prolonged prophylaxis with colchicine or NSAIDs is usually required. Febuxostat has been granted marketing authorization by the European Commission in early 2008 for the treatment of chronic hyperuricemia and gout. Febuxostat is the first major treatment alternative for gout in more than 40 years and is a promising alternative to allopurinol, although continued long-term surveillance on safety and efficacy is required.

Keywords: Short duration study, Febuxostat, clinical improvements, serum acid levels, gouty arthritis patients.

*Corresponding Author Email: raviprakashdegala@gmail.com

Received 20 April 2025, Accepted 16 May 2025

Please cite this article as: Degala RP *et al*., A Short Duration Study Of Febuxostat- The Clinical Improvement, Side Effects and Serum Uric Acid Levels In Gouty Arthritis Patients - A Prospective Study. American Journal of PharmTech Research 2025.

INTRODUCTION

Skeletal System:

Cells, provides The skeletal system is body's support structure. It gives body shape, allows movement, makes blood protection for organs and stores minerals. The skeletal system is also called the musculoskeletal system. It is made of cartilage and bones. The human body has roughly 270 bones at birth. As a result of some bones being fused, it falls to 206 bones by adulthood. The skeletal system gives body shape and holds organs in place. In the simplest terms, the skeletal system is body's most important support structure. But it's more than just skeleton and bones. The skeletal system also includes connective tissue that helps to stay supported and safe while moving and still. It includes muscles that help to move and creates new blood cells that keep healthy.

TREATMENT OF SKELETAL SYSTEM:

Medication:

Over-the-counter (OTC) medicines like acetaminophen relieve pain and reduce swelling. The provider might prescribe corticosteroids or specific medications to treat an autoimmune disease.

Immobilization:

It's common to need a brace, splint, sling or cast after an injury. It'll hold injured body arts in a stable position while recover. The provider will tell which type of immobilization need and how long to wear it for.

Physical therapy:

A physical therapist will help to strengthen muscles and increase flexibility, especially after an injury.

Arthroplasty (joint replacement):

Some people need partial or total joint replacements. Hips and knees are some of the most commonly replaced joints. The provider or surgeon will tell what to expect.

GOUTY ARTHRITIS:

Definition: GOUT is the most common inflammatory and metabolic joint disorder which is caused by the deposition of monosodium urate crystals in joints and soft tissues following chronic hyperuricaemia.

Chronic hyperuricaemia is associated with disorders of purine metabolism due to under excretion or overproduction of uric acid, the final metabolite of endogenous and dietary purine metabolism.

GOUT is known as "disease of kings" and "rich man's disease". GOUT [also known as podagra when it involves the big toe].

It is a medical condition usually characterized by recurrent attacks of acute inflammatory arthritis- red , tender , hot , swollen joints.

Gout is a picturesque presentation of uric acid disturbance. It is the most well understood and described type of arthritis. Its epidemiology is studied. New insights into the pathophysiology of hyperuricemia and gouty arthritis; acute and chronic allow for an even better understanding of the disease. The role of genetic predisposition is becoming more evident. The clinical picture of gout is divided into asymptomatic hyperuricemia, acute gouty arthritis, intercritical period, and chronic tophaceous gout. Diagnosis is based on laboratory and radiological features. The gold standard of diagnosis is identification of characteristic MSU crystals in the synovial fluid using polarized light microscopy. Imaging modalities include conventional radiography, ultrasonography, conventional CT, Dual-Energy CT, Magnetic Resonance Imaging, nuclear scintigraphy, and positron emission tomography. There is remarkable progress in the application of ultrasonography and Dual-Energy CT which is bound to influence the diagnosis, staging, follow-up, and clinical research in the field. Management of gout includes management of flares, chronic gout and prevention of flares, as well as management of comorbidities. Newer drugs in the pharmacological armamentarium are proving successful and supplement older ones. Other important points in its management include patient education, diet and life style changes, as well as cessation of hyperuricemic drugs.

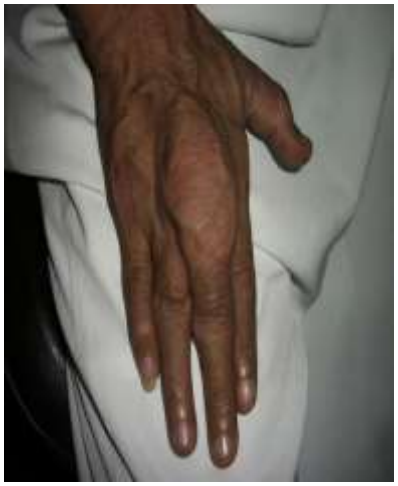


Figure 1

GOUT is a kind of arthritis that occurs when uric acid builds up in blood and causes joint inflammation.

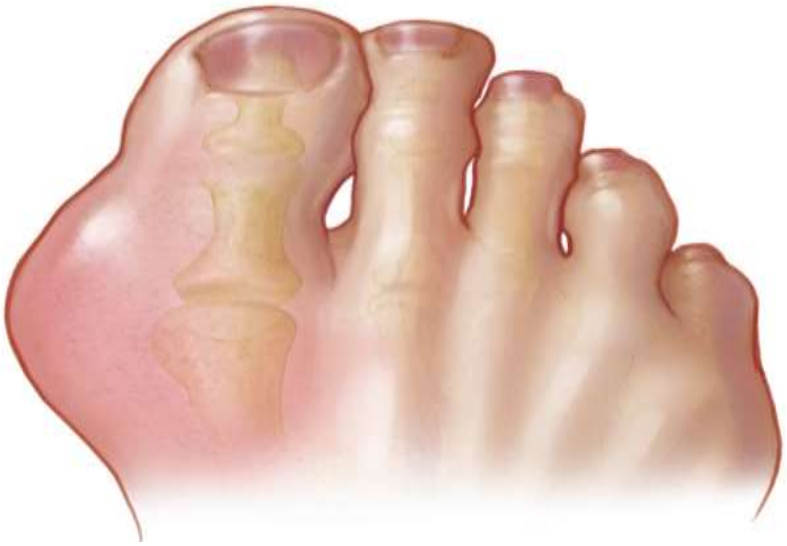


Figure 2:

The signs and symptoms of gout almost always occur suddenly, and often at night. They include:

Intense joint pain. Gout usually affects the big toe, but it can occur in any joint. Other commonly affected joints include the ankles, knees, elbows, wrists and fingers. The pain is likely to be most severe within the first four to 12 hours after it begins.

Lingering discomfort. After the most severe pain subsides, some joint discomfort may last from a few days to a few weeks. Later attacks are likely to last longer and affect more joints.

Inflammation and redness. The affected joint or joints become swollen, tender, warm and red.

Limited range of motion. As gout progresses, you may not be able to move the joints

Epidemiology:

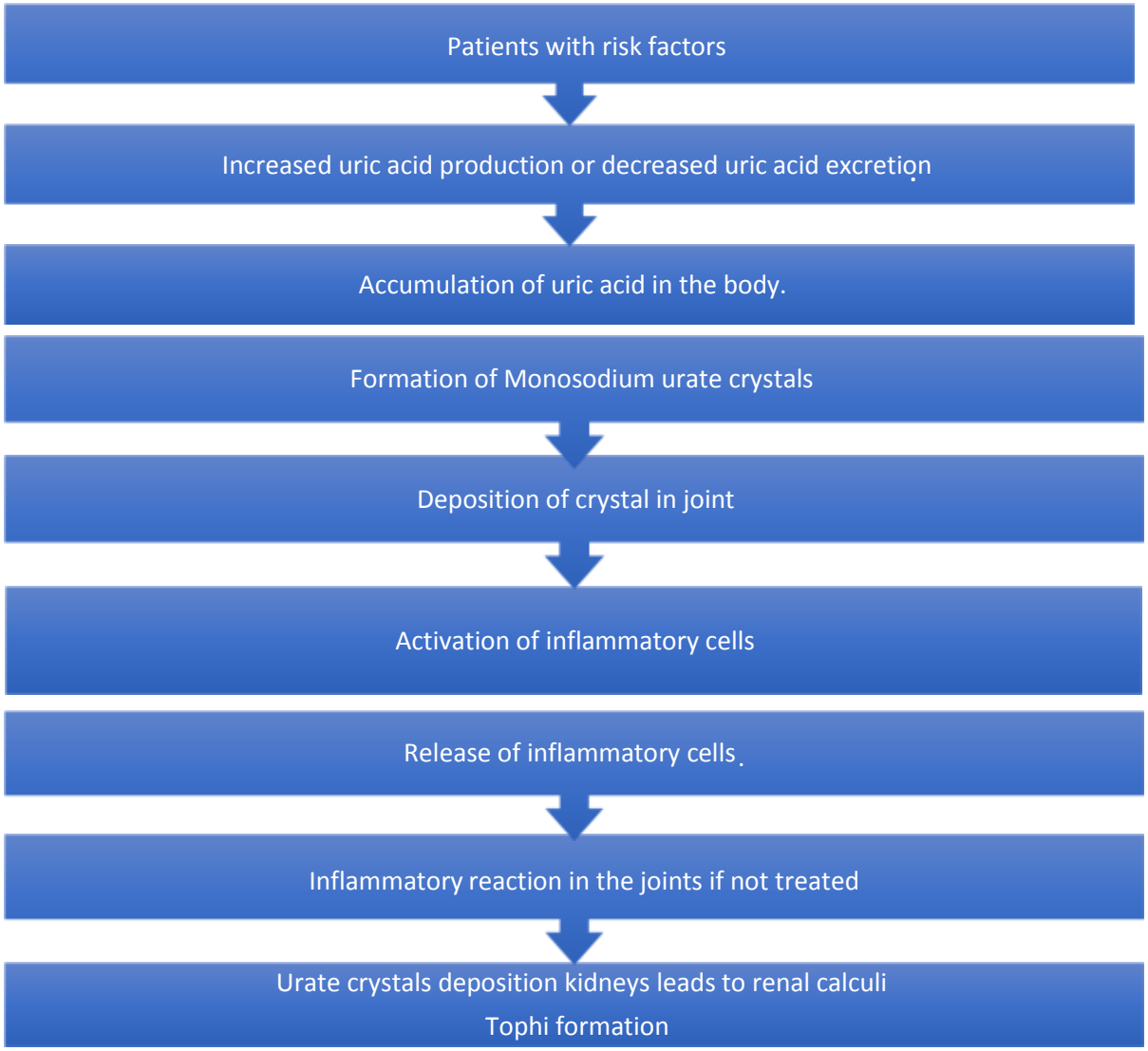
GOUT is one of the oldest recognized disease and was identified by the Egyptians in 2460 B.C.GOUT affects 1-2% of adults in developed countries and in recent decades there has been a great significant rise in its prevalence and incidence. The USA has seen a doubling in the number of cases with rate of gout increasing to 4.1%in order males. GOUT is predominantly a disease of men with male to female ratio of 36:1. In women ,it tends to develop after menopause when levels of Oestrogen , a known uricosuric fall.

The prevalence of gout can vary by age, sex, and country of origin. In general, the prevalence of gout is 1 to 4%. Older age and male sex are two common risk factors noted globally. In Western nations, the prevalence of gout in men (3 to 6%) is 2 to 6 fold higher than in women (1 to 2%). Prevalence increases with age but plateaus after 70 years of age.

Etiology:

Although environmental factors are clearly implicated in the development of gout, inheritance also plat an important role.

- In recent years, research into genetic background of gout has identified several renal , urate transporters including URAT-1&GLUT -9 and the genes encoding for them.
- Eg:SLC22A12 & SLC2A9 respectively.
- Polymorphism in these genes are associated with increased hyperuricaemia and gout.



Pathogenesis of hyperuricemia:

Urate is the ionized form of uric acid present in the body. Uric acid is a weak acid with pH of 5.8. Urate crystals deposition in tissues starts to occur when serum uric acid level rises above the normal threshold. Pathological threshold of hyperuricemia is defined as 6.8 mg/dL .

Factors affecting SUA levels include age and gender. SUA is low in children. After puberty, SUA levels start to increase to reach their normal levels. In men, levels are higher than in women. However, SUA levels in postmenopausal women increase to reach men's levels. This explains why gout is usually a disease of middle aged and older men, and postmenopausal women. Rarely, it may happen in children and young adults in some rare inborn errors of purine metabolism. These

enzymatic defects result in increased SUA with consequent production of UA crystals in kidneys and joints.

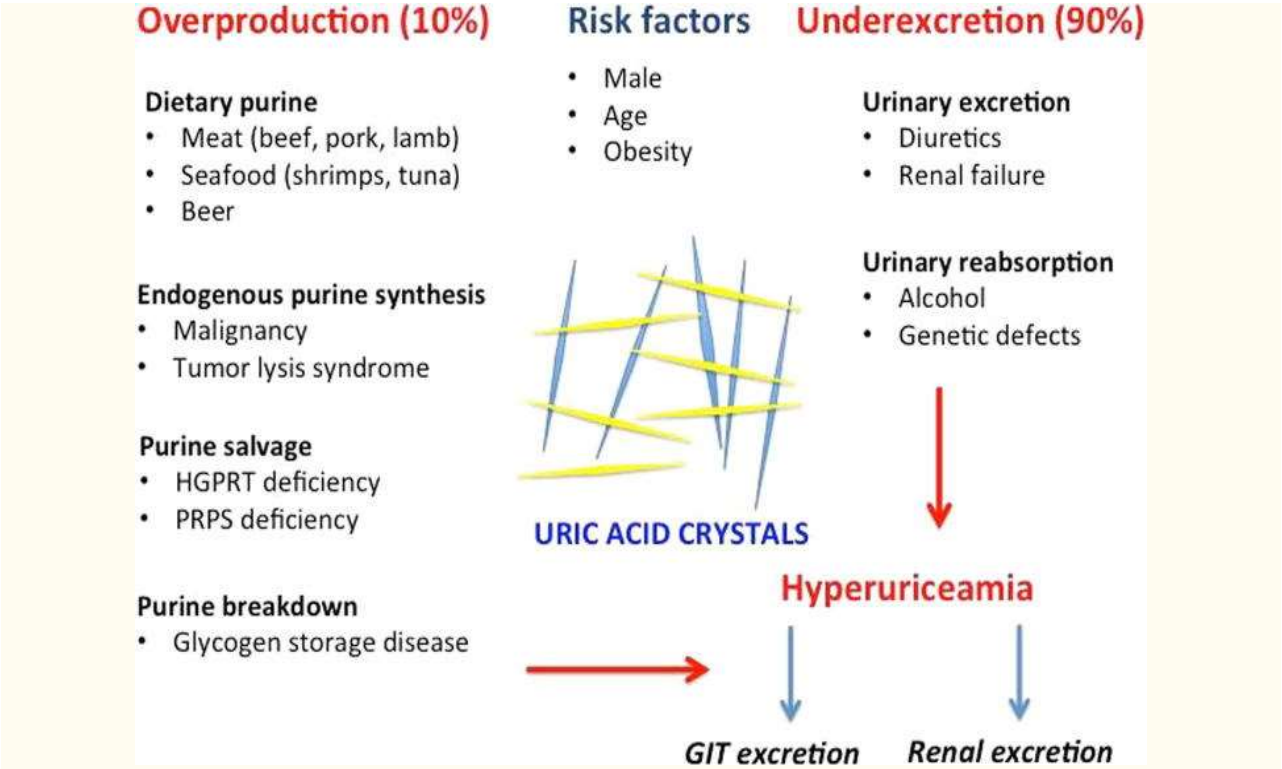


Figure 3: Pathogenesis of hyperuriceamia (perceived and designed by Dr. EL-Shahaly).

Overproduction of uric acid

Deficiency of enzymes involved in purine metabolism leads to overproduction of UA. For example, Lesch-Nyhan syndrome is an inborn error of metabolism resulting from deficiency of an enzyme involved in UA metabolism named hypoxanthine–guanine phosphoribosyl transferase. It is a genetic X-linked recessive disorder with varying degrees of severity according to the type of mutation. The clinical picture of this disease involves neurological abnormalities such as dystonia, chorea, cognitive dysfunction, compulsive injurious behavior, self-mutilation and articular manifestations (early onset gout) in addition to renal stones. If left untreated, it may lead to tophi formation and renal failure.

Another enzymatic abnormality that causes gout in the young is the superactivity of phosphoribosyl pyrophosphate synthetase. It is an X-linked dominant inherited disorder. The syndrome has two clinical forms, a severe early onset form in children and a mild late juvenile or early adult onset form. Clinical picture includes neurological abnormalities such as sensorineural hearing loss, hypotonia and ataxia in the severe form. The mild form manifests as uric acid renal stones and arthritis. However, these enzymatic disorders constitute only less than 10% of cases of overproduction of urates

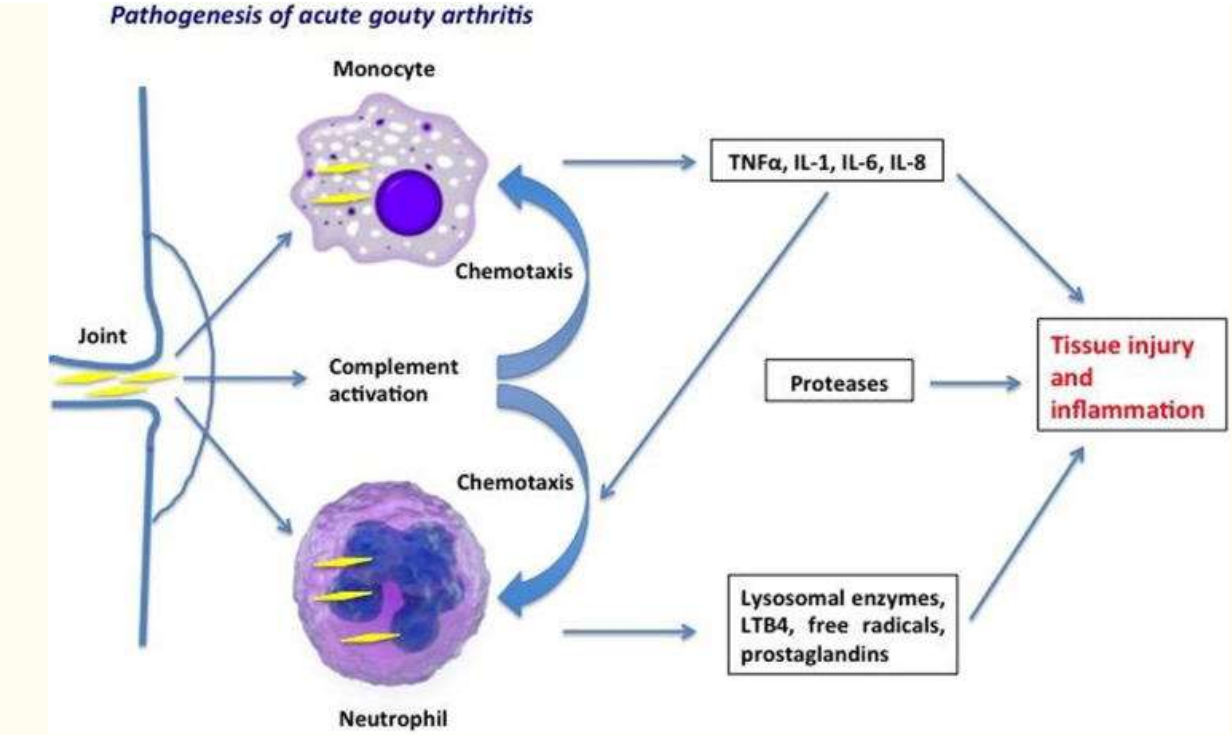


Figure 5: Pathogenesis of acute gouty inflammation (perceived and designed by Dr. EL-Shahaly).

Pathogenesis of chronic gout

Chronicity is a feature of gout. It results from chronic inflammation that follows recurrent attacks of gout. Chronic gout manifests by chronic synovitis, bony erosions, cartilage damage and tophi formation. This can be explained by different mechanisms. Presence of urate crystals in the synovium leads to stimulation of chondrocytes to produce inflammatory cytokines, nitric oxide and matrix metalloproteases resulting in cartilage damage.

On the bone level, IL-1β and activation of receptor for nuclear factor κ B (RANK) and RANK ligand (RANK-RANKL) pathway are key players in osteoclastogensis and the formation of bone erosions. Gouty erosions are characterized by having overhanging edges and partial preservation of joint space. Furthermore, osteoblasts release pro-inflammatory cytokines leading to erosions and bone destruction in addition to compromising their own bone formation function. In the intercritical phase, there is persistent low-grade inflammation in affected joints. The same cytokines responsible for the acute flare up can be found at lower concentrations in between attacks. Although chronicity may result even with the use of uric acid lowering drugs and appropriate management of acute flare ups, yet its incidence is lower compared to patients with recurrent inappropriately treated attacks. Chronicity can be decreased by long-term use of low dose anti-inflammatory agents such as colchicine and lowering SUA to safe levels (<6 mg/dL) . Increased uric acid excretion in urine is usually calculated by the fractional excretion of urate

compared to creatinine clearance. Both urine and blood samples are taken at the same time. The formula to calculate this parameter is [urine UA × serum Cr/serum UA x urine Cr]. The normal fractional excretion of uric acid is 7–10%. When it decreases, this reflects a reduction of uric acid excretion resulting in increased serum urate level .Interestingly, it appears that levels of SUA actually decrease during the acute attack of gout. Furthermore, precipitation of an attack is common following the introduction of allopurinol or febuxostat without the prophylactic use of NSAID or colchicine. Also, states with increased excretion of SUA such as during surgery can trigger an acute gouty attack. Accordingly, it is assumed that sudden reduction of SUA precipitates acute gout.

Although hyperuriceamia is the main cause of gout, uric acid itself is an *anti*-oxidant that has a protective role on vascular endothelium. So, the presence of uric acid is essential for vascular integrity and homeostasis of human body's functions. On the other hand, some studies found that allopurinol, a xanthine oxidase inhibitor used for treatment of hyperuriceamia and gout, has protective effects on vascular endothelial cells reducing cardiovascular risk. What determines whether presence of uric acid is beneficial or not is the type of tissue affected, whether it is intracellular or extracellular and its concentration.

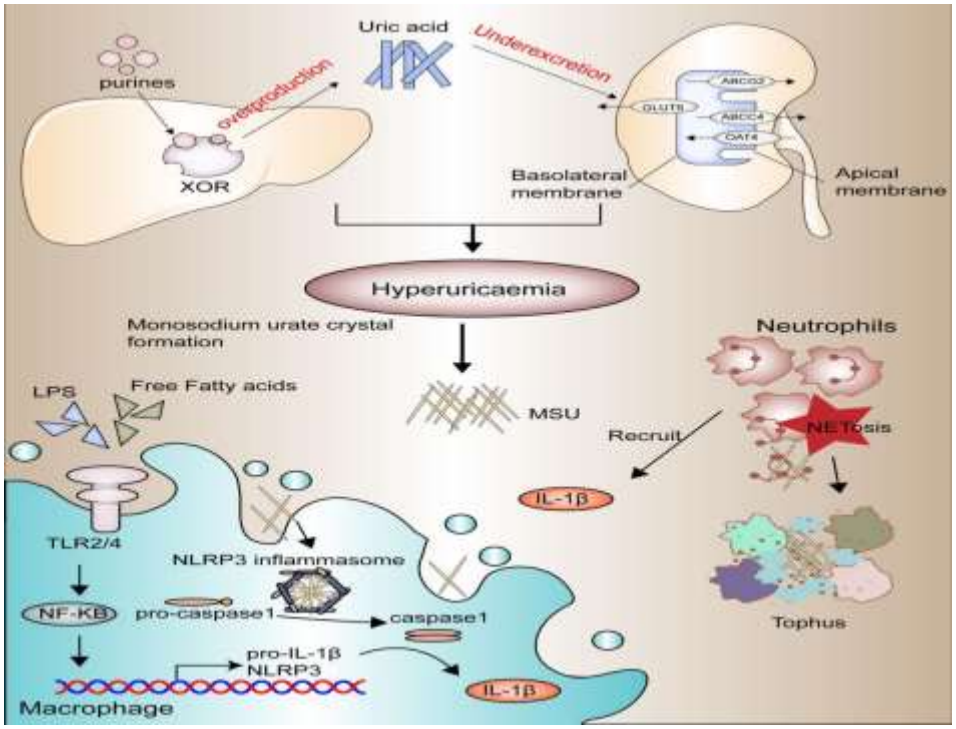


Figure 6

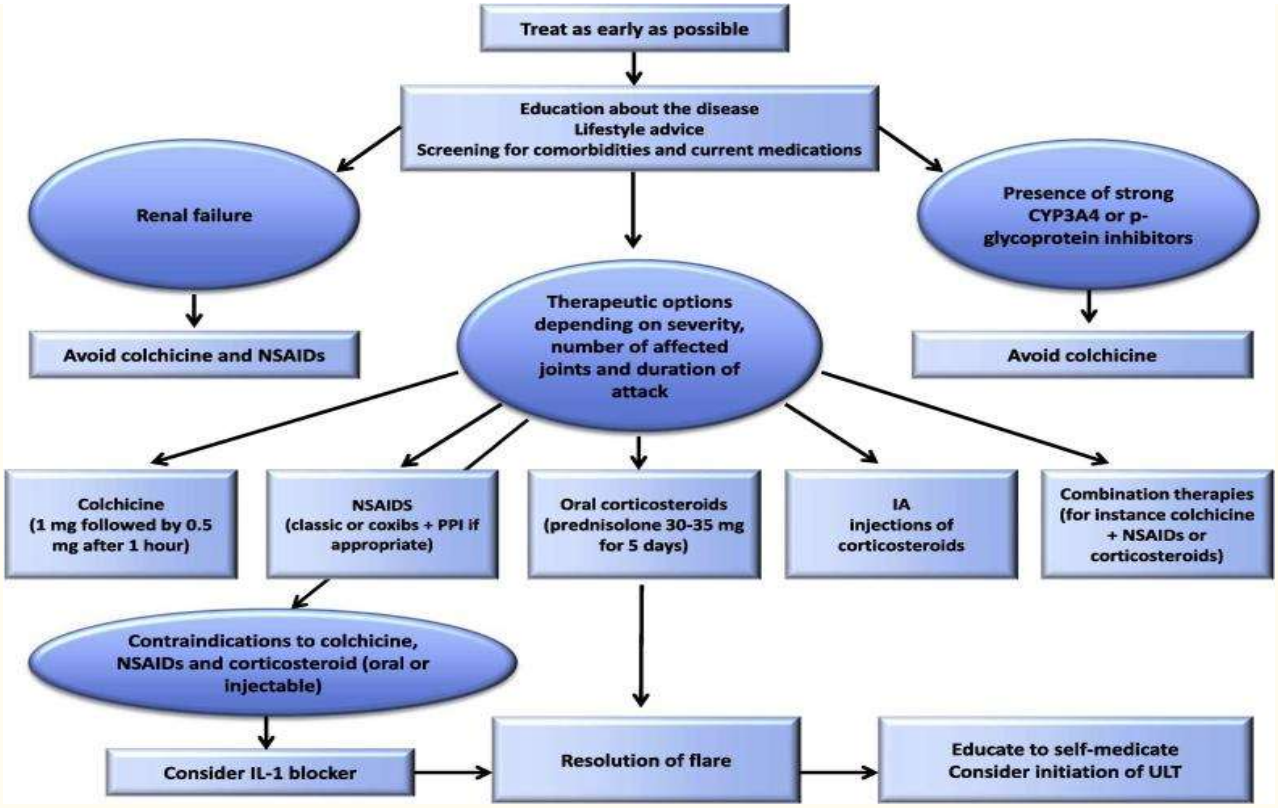


Figure 8

When taken within 12 h after flare onset, 1.8 mg (1.2 mg then 0.6 mg one hour later) of colchicine has been shown to be as effective as the traditional higher doses. In clinical practice this drug appears as much less efficient when given long after the flare onset. The EULAR and American College of Rheumatology (ACR) have restricted the use of colchicine to patients presenting within 12 and 24 h of flare onset respectively.

Practitioners should keep in mind that colchicine has a narrow therapeutic toxicity window and can be very toxic when used inappropriately. Gastrointestinal intolerance (diarrhea, nausea, or vomiting) is common. It is usually the first feature of colchicine toxicity and should lead to dose reduction or interruption. Further toxicity includes neutropenia and multi-organ failure, which can be lethal. The maximum daily dose has been recently reduced to 2 mg (in divided doses) in France. Renal failure decreases colchicine excretion. Doses should be limited to 0.5–0.6 mg/d in patients with moderate renal insufficiency (eGFR from 30 to 60 mL/min) and to 0.5–0.6 mg every 2 or 3 days in those with eGFR from 15 to 30 mL/min. Colchicine is contra-indicated in CKD stage 5 patients (eGFR < 15 mL/min or dialysis).

Doses should also be reduced in patients with hepatic failure, as the drug is predominantly eliminated through the hepato-biliary system. Inhibitors of cytochrome P450 3A4 or P glycoprotein increase plasma concentration and toxicity of colchicine. The doses of colchicine

should be reduced to 0.3 mg every 3 days when cyclosporine, ketokonazole, erythromycin, retronavir are co-prescribed and to 1.2 mg every 3 days when diltiazem or verapramil are used . The French regulatory agency contraindicates co-prescription of macrolide antibiotics and colchicine, even though azythromycin has been found to have no pharmacokinetic interaction with colchicine. Muscle toxicity, including rhabdomyolysis has been reported with the concomitant use of colchicine and statins, especially in renal failure patients. Nerve and muscle toxicity can be observed in long term low dose colchicine users who have kidney transplant or chronic kidney disease CKD, usually with 30 mL/min of eGFR or less. This toxicity is usually slowly reversible after drug cessation and requires CK monitoring.

Management of chronic gout and prevention of flares

Uricemia targets

To obtain MSU crystal dissolution, SUA should be lowered to values which are under the MSU saturation point. Both the ACR and the EULAR indicate that the SUA target is below 6 mg/dL in all gouty patients and below 5 mg/dL in severe gout patients, to allow more rapid dissolution of the crystal load. Hyperuricemia must be routinely checked by measuring SUA levels . This approach has been recently challenged by the American College of Physicians (ACP) who recommended to treat gout to control symptoms rather than to target an uricemia level. The main reason for this GP guideline is the present lack of rigorous treat to target trial. Such a trial is underway in New-Zealand and should definitively settle the issue. However, numerous clinical and pathophysiological data already tell us that lowering uricemia under the saturation point is the best and most reliable way to control gout symptoms in the long run, and that prescribing ULTs without checking that uricemia is lowered enough is a frequent cause of gout treatment failure. This ACP guideline therefore appears, in our view, as detrimental and should not be followed.

Allopurinol

Allopurinol is an oral xanthine oxidase inhibitor, first introduced to the clinic in the sixties. Allopurinol is a purine, which is rapidly converted into its active metabolite, oxypurinol, by the xanthine oxidase enzyme. Xanthine accumulation has been seldom reported to cause urinary xanthine stone which can be fully prevented by sufficient fluid intake. In addition to inhibiting xanthine oxidase, oxypurinol inhibits the synthesis of purines, a mechanism that requires the intervention of the enzymes hypoxanthine guanine phosphoribosyl transferase and phosphoribosyl pyrophosphate synthetase and is not observed when these enzymes are deficient. Excretion of oxypurinol is mainly through the kidney and is decreased by renal failure and increased by

uricosurics. Dose requirements to reach uricemia targets are increased by body weight increase and diuretic use . ABCG2 loss of function polymorphism decreases its urate-lowering effect .

Because oxypurinol has a long half-life, allopurinol can be prescribed once a day. The urate-lowering effect is dose dependent. Over the world, allopurinol is prescribed at the dose of 300 mg/d or less in more than 90–95% of gouty patients . At the daily dose of 300 mg, allopurinol used to bring uricemia to less than 6 mg/dL in nearly every gouty patient when the drug was initially launched . But this has now largely changed, possibly because gouty patients' uricemia and weight have substantially increased since the sixties: recent studies have shown that only a minority of patients receiving 300 mg/d of allopurinol reached the desirable uricemia target (<6 mg/dL) .

Allopurinol is usually well tolerated. Abdominal discomfort, nausea and diarrhea, liver or bone marrow toxicity , acute interstitial nephritis are very rare early side effects which can be part of the allopurinol hypersentivity syndrome; gynecomastia and peripheral neuropathy have been observed, very rarely, during long-term allopurinol treatment. Patients should be told that cutaneous side effects may develop during the 2 or 3 first months of treatment and should lead to immediate, life-long, allopurinol cessation. They include benign maculo-papular rash, reported in 2–4% of allopurinol initiators, and life- threatening severe skin reactions which can take the form of an acute generalized exanthematous pustulosis , toxic epidermolysis/Steven Johnson syndrome or Drug Related Eosinophilia with Systemic Symptoms (DRESS) syndrome . The incidence of these severe skin reactions has been estimated at 0.7 [95%CI0;5–9.9] per 1000 allopurinol initiators-years in the USA , but they are more frequent in Asia, due to more common genetic predisposition .

Risk factors include recent (<3 months) allopurinol initiation, use of allopurinol for asymptomatic hyperuricemia, female gender, a history of skin reaction to allopurinol, HLA∗B-5801 carriage, high initial dose and renal failure.

Febuxostat

Febuxostat is an oral, once a day, non-purine xanthine oxidase inhibitor, which is available as 40 and 80 mg tablets in the USA and 80 and 120 mg tablets in Europe. At the doses of 80 and 120 mg/d, the maximum doses approved in the USA and Europe respectively, febuxostat is a more potent ULD than allopurinol 300 mg/d. Because of its mixed renal and hepatic metabolism, the drug can be prescribed with no dose reduction in patients with moderate renal failure. Recent small studies have suggested that efficacy and safety is maintained in patients with creatinine clearance

below 30 mL/min . Because the drug inhibits xanthine oxidase, febuxostat should not be co-prescribed with azathioprine or 6-mercaptopurine.

Uricosurics

Uricosurics lower uricemia by increasing uric acid output in the urine. Therefore they expose the patients to the risk of uric acid stone, which is worse at the onset of treatment. When uricemia has decreased, uricuria and the risk become lower, as uricuria also decreases. They should not be administered as a monotherapy in patients with a history of uric acid stone or hyperuricuria and should be taken with abundant water intake; the urinary pH should also be checked and kept above 6 to decrease the concentration of uric acid in urine, which governs the risk of lithiasis. Except for lesinurad, uricosurics can be used alone; they are now most often used in combination with xanthine oxidase inhibitors, when these fail to obtain the uricemia targets.

Probenecid has been the first commercialized ULD and was at first a very popular drug. When allopurinol became available, probenecid was much less used because it had to be given in divided doses and required high fluid intakes and adjustment of the urine pH. In addition, probenecid, which was first developed to decrease the renal excretion of penicillin, could interfere with the excretion of other organic acid drugs and gastro-intestinal or cutaneous intolerance were fairly common. It has been recently confirmed to be a decent ULD, including those patients with moderate kidney involvement and remains one of the therapeutic options in patients intolerant or refractory to allopurinol. The initial dose is 250 mg twice daily, which can be weekly increased up to 1 g twice daily. Larger doses expose to major central nervous system toxicity..

Urate oxidases

Rasburicase is a short-life IV uricase, which is approved for the management of tumor lysis syndrome. Its non-licensed use has been reported in tophaceous gout. Pegloticase is a PEGylated uricase which has been approved, in the USA and Europe, for the management of severe gout, refractory to oral ULDs, and is commercially available in the USA. The drug is administered by IV infusions of 8 mg every 2 weeks and has been shown to be very effective. Antibodies develop at high titers in about half of the patients, leading to loss of uricemia response and to an increased risk of serious infusion reactions. It is therefore recommended to measure uricemia in the 24 h preceding every planned reinfusion and to stop the drug if uricemia is not decreased. No other ULD should be prescribed concomitantly to keep this warning signal (Fig.).

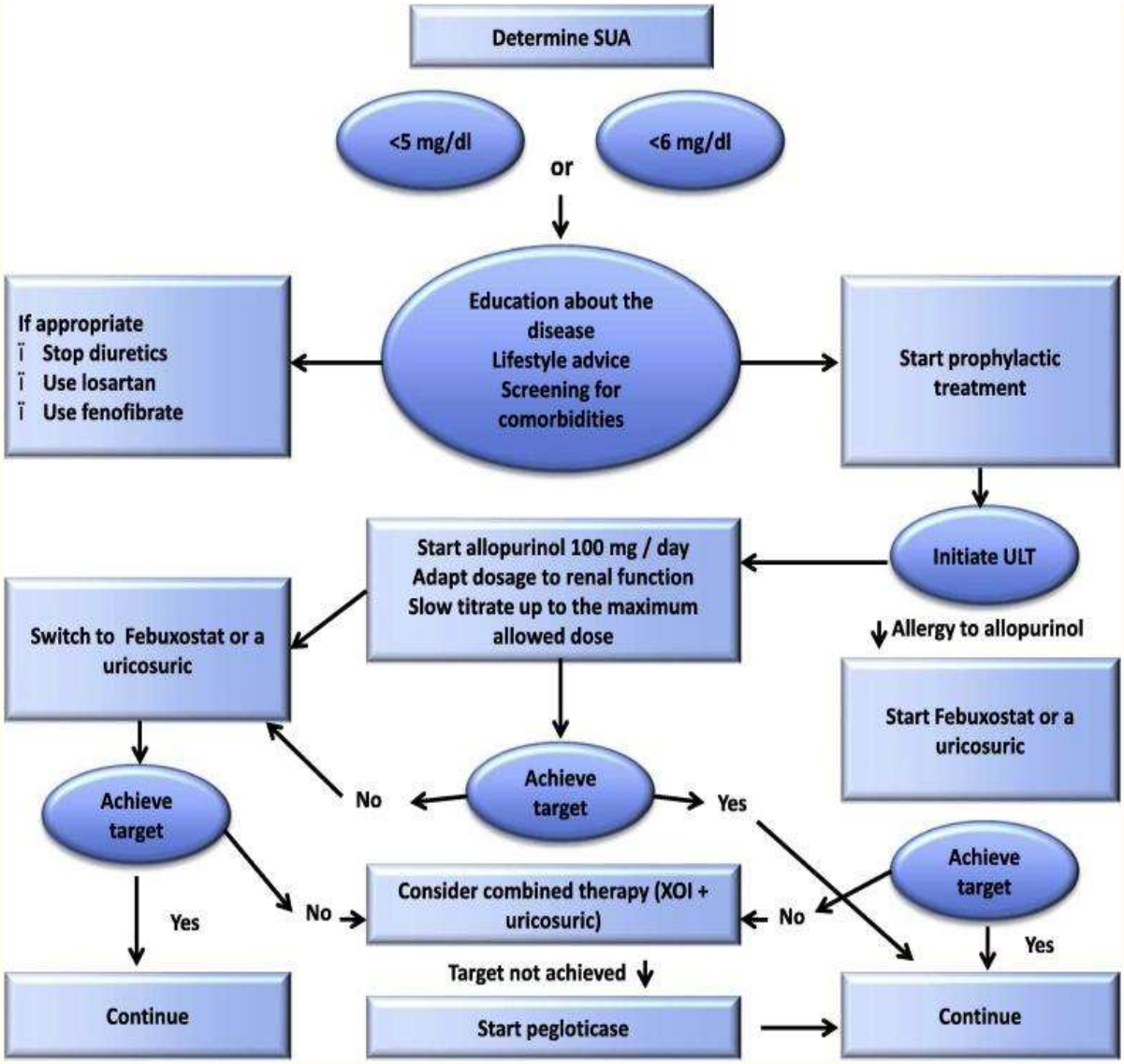


Figure: 9 EULAR recommendations for the management of hyperuricemia in patients with gout

FEBUXOSTAT

Febuxostat, a novel, orally administered, potent, non–purine analogue, xanthine oxidase / xanthine dehydrogenase inhibitor in the management of hyperuricemia in patients with gout & chronic tophaceous gout. It completely inhibits activity of xanthine oxidase enzyme by obstructing substrate binding but has minimal effects on activity of other enzymes in purine metabolism. It inhibits both oxidized and reduced forms of xanthine oxidase. Febuxostat is more potent than allopurinol in inhibiting xanthine oxidase. Recommended dosage in hyperuricemia and gout is 40 mg OD or 80 mg OD or 120 mg OD. Febuxostat, at a daily dose of 80 mg or 120 mg, was more effective than allopurinol at the commonly used fixed daily dose of 300 mg in lowering serum urate, significant number of patients achieves target levels of serum uric acid (< 5 mg/dl) with

febuxostat as compared to allopurinol and uric acid ↓ effect is sustained with febuxostat. No dose adjustments are required in hepatic impairment, renal impairment or elderly patient.

Hyperuricemia is defined as a serum urate concentration exceeding the limit of solubility (about 6.8 mg per deciliter). The clinical manifestations of gout (acute gouty arthritis, gouty arthropathy, chronic tophaceous gout, uric acid urolithiasis, and gouty nephropathy) result from deposition of monosodium urate or uric acid crystals from supersaturated body fluids. The solubility of monosodium urate in extracellular fluids is influenced by a variety of factors; including pH, temperature, and sodium ion and protein concentrations. The most frequently used pharmacologic urate-lowering strategies involve reducing urate production with a xanthine oxidase inhibitor and enhancing urinary excretion of uric acid with a uricosuric agent. Urate lowering agents are limited and allopurinol, a xanthine oxidase inhibitor, is the most commonly prescribed of these agents. The average dose is 300 mg per day, although dosing recommendations range from 100 to 800 mg per day, titrated to serum urate and creatinine clearance. The side effects of allopurinol, although uncommon, may be severe or life-threatening and occur more often in patients with renal insufficiency. Febuxostat is a potent xanthine oxidase inhibitor, has minimal effects on other enzymes involved in purine and pyrimidine metabolism , and is metabolized mainly by glucuronide formation and oxidation in the liver.

Gout is the most common cause of inflammatory arthritis worldwide. Despite clinical cure being achievable and multiple evidence-based guidelines having been published, the incidence and prevalence continues to increase and the condition remains undertreated. Concerns regarding allopurinol have limited its use in those with renal impairment. Febuxostat, a novel xanthine oxidase inhibitor requiring no dose adjustment in mild−moderate renal impairment was launched in the United Kingdom (UK) in 2010. We review published data on the efficacy, safety and tolerability of febuxostat and provide an opinion on its place in the management of gout in the UK in the context of other published guidelines. One phase II trial, multiple phase III trials [febuxostat *versus* allopurinol controlled trial (FACT), APEX, CONFIRMS] and two open-label extension trials have demonstrated febuxostat given at the doses commonly used in UK practice (80 mg, 120 mg) to reduce serum urate more effectively than those receiving fixed-dose allopurinol. Overall adverse event rates were comparable across treatment groups aside from gout flare (more common in febuxostat-treated patients) and concerns regarding cardiovascular toxicity are being further evaluated in two large trials. If the outcomes of these are favourable, we would anticipate a marked increase in the use of febuxostat in the UK market. We would advocate the use of febuxostat to target a serum urate < 0.3 mmol/l (5 mg/dl) as a second-line urate-lowering

therapy in patients with hyperuricaemia, and clinical gout in those intolerant of allopurinol, or in those in whose renal function precludes optimal dose escalation to achieve target serum urate. We would advise prophylaxis against gouty flare with colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or Cyclo-oxygenase-2 selective NSAID (COXIB) after febuxostat initiation.

Chemical structure:

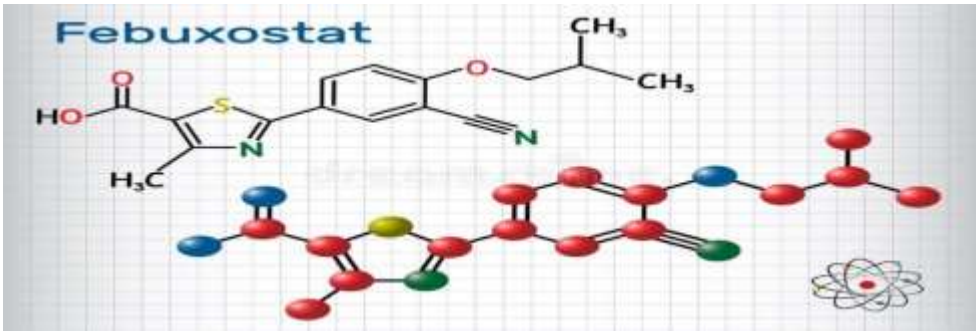


Figure 9

Mechanism of action:

Febuxostat, a xanthine oxidase inhibitor and inhibits both oxidized and reduced forms of xanthine oxidase (XO). enzyme by obstructing substrate binding and inhibits both oxidized and reduced forms of xanthine oxidase (XO). Activities of other enzymes in purine and pyrimidine synthesis and metabolism at therapeutic concentrations is affected by < 4%.

Pharmacodynamics:

Effect on Uric Acid and Xanthine Concentrations:

In healthy subjects, febuxostat resulted in a dose dependent decrease in 24-hour mean serum uric acid concentrations, and an increase in 24-hour mean serum xanthine concentrations. Febuxostat in dose of 40 mg, 80 mg & 120 mg significantly reduces uric acid levels within 2 weeks after initiation of therapy and the effect is seen to be sustained as compared to allopurinol 300 mg in various studies. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Effect on Cardiac Repolarization: The effect of febuxostat on cardiac repolarization as assessed assessed by the QTC interval was evaluated in normal healthy subjects and in patients with gout. Febuxostat in doses up to 300 mg daily, at steady state, did not demonstrate an effect on the QTC interval.

Pharmacokinetics:

In healthy subjects, maximum plasma concentrations & AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life (t½) of approximately 5 to 8 hours.

Absorption:

The absorption of radio labeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 to 1.5 hours post-dose. Febuxostat may be taken without regard to food or antacid.

Distribution:

The mean apparent steady state volume of distribution of febuxostat was approximately 50 liters (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses. Metabolism: Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes and oxidation via cytochrome p450 (CYP) enzymes including and non-p450 enzymes. In urine and feces ,acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites (~10% of the dose) and a secondary metabolite form, (~14% of the dose) appeared to be the major metabolites of febuxostat in vivo. Elimination: Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of 14c-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%). The apparent mean terminal elimination half-life (t½) of febuxostat was approximately 5 to 8 hours.

Safety and tolerability

Studies to date suggest febuxostat to be safe and well tolerated. The overall rates of adverse events reported in the placebo arm of APEX, the only phase III work to contain a placebo arm, were similar to those in the febuxostat groups. As with all drugs, acute hypersensitivity reactions have been reported [European Medicines Agency, 2012] and as with the administration of all drugs, this should be borne in mind when assessing a patient recently commenced on any new medication. Hypersensitivity to allopurinol is not a contraindication to febuxostat. Although it is recommended that patients to be treated with febuxostat have liver function checked prior to therapy and rechecked thereafter on a ‘discretionary’ basis, while liver function derangement was seen more commonly in the febuxostat groups in APEX, none of the trials discussed showed combined transaminase and bilirubin increases, aside from those attributable to biliary tract disease.

Febuxostat in the management of gout

Febuxostat is undoubtedly effective at reducing serum urate, both in the short and long term. When used for a long period, it is also effective at reducing the burden of tophi and in abolishing gouty flare. The lack of need for dose adjustment in those with mild−moderate renal impairment makes it an attractive choice in that group of patients.

However, it is currently contraindicated in those with ischaemic heart disease and congestive cardiac failure, which, of course, occur commonly in the gout population.

There is also a question of the relevance of the trials discussed to optimal management of gout in the UK. None of the trials comparing febuxostat with allopurinol used a gold standard allopurinol regime, whereby patients are uptitrated to achieve target serum urate, although this strategy is suggested by multiple guidelines of international significance. We appreciate that one potential justification for these study designs is that failure to adopt this strategy of allopurinol dose titration to target is somewhat representative of real-world practice where patients commonly remain on subtherapeutic allopurinol doses and no reassessment of urate is made, or where it is, no uptitration of therapy occurs [Roddy *et al.* 2007]. Where 300 mg of allopurinol was the maximum dose in these studies, it is widely acknowledged that at these doses, <50% of patients will reach target with some patients needing up to 900 mg per day [Jordan *et al.* 2007]. A double-blinded trial comparing an uptitrating allopurinol regime with febuxostat would be desirable (if unlikely to be undertaken) to demonstrate whether either regime would be superior to the other.

In addition, the BSR [Jordan *et al.* 2007] suggests a serum urate target of <0.3 mmol/l (5 mg/dl) whereas the primary endpoints in the studies were <0.36 mmol/l (6 mg/dl) making it difficult to generalize conclusions to the UK population.

METHODOLOGY

Study Design **:** Prospective Observational Studies.

Study Site **:** Studies are carried out at SREE AHOBILA SUPER SPECIALITY HOSIPITAL, KAKINADA.

Study Duration **:** 6 Months

Sample Size **:** 100 cases.

Material **:** Case sheet standard questionnaire.

Study Criteria:

Inclusion Criteria: Patients of all groups were included in the study. Both male and female, pediatrics and geriatrics were included.

Exclusion Criteria: Patients with normal serium uric acid levels.

Source of Data: Data was collected from the case sheets of both in patients and out patients.

Method of data collection: Patients demographic details such as Age, Gender, Past Medical history, Family history, Laboratory Investigations, Therapy for gouty arthritis were collected in a specialized pro-forma for the data collection of cases.

Doses drugs and duration of drug were noted from patient drug chart.

RESULTS AND DISCUSSION

In the six months of period 100 gouty arthritis patients were assumed randomly with inclusion and exclusion criteria. They were treated with drug febuxostat along with anti-inflammatory drugs. There was a marked reduction in pain and serum uric acid levels. Patients with gouty arthritis were given with the febuxostat shown the significant improvement in

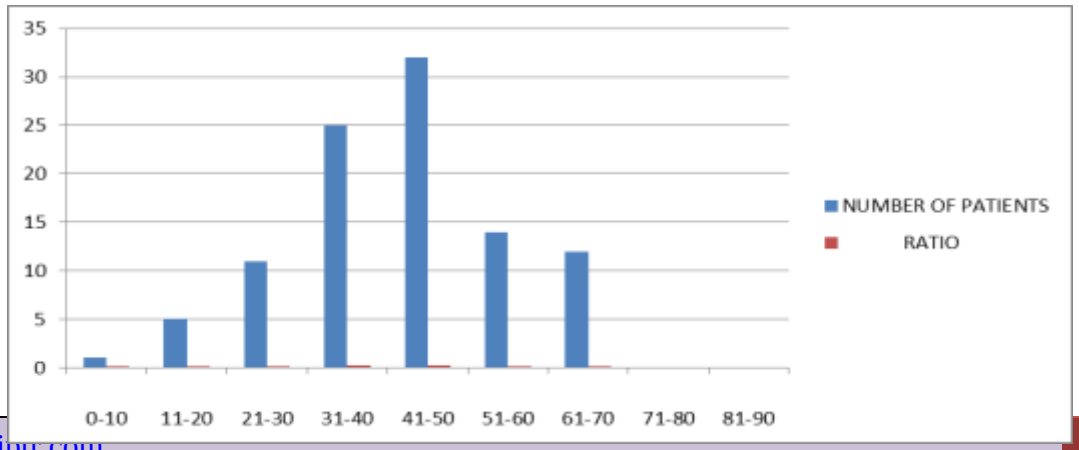
1. Pain assessment
2. ROM assessment
3. ADL assessment
4. General well being
5. Overall clinical improvement
6. Safety.

Table: Number of patients admitting in the hospital according to the age in 100 members of gouty arthritis patients

Age	Number of patients	Ratio
0-10	1	1.25%
11-20	5	5.0%
21-30	11	11.25%
31-40	25	23.75%
41-50	32	28.0%
51-60	14	16.0%
61-70	12	13.0%
71-80	0	0%
81-90	0	0%

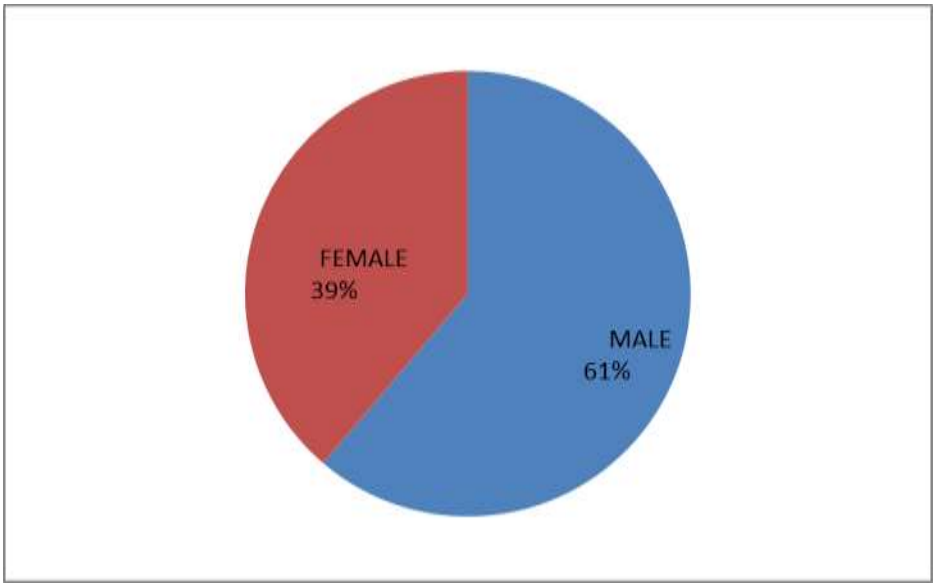
Ratio of Age

Ratio of patients

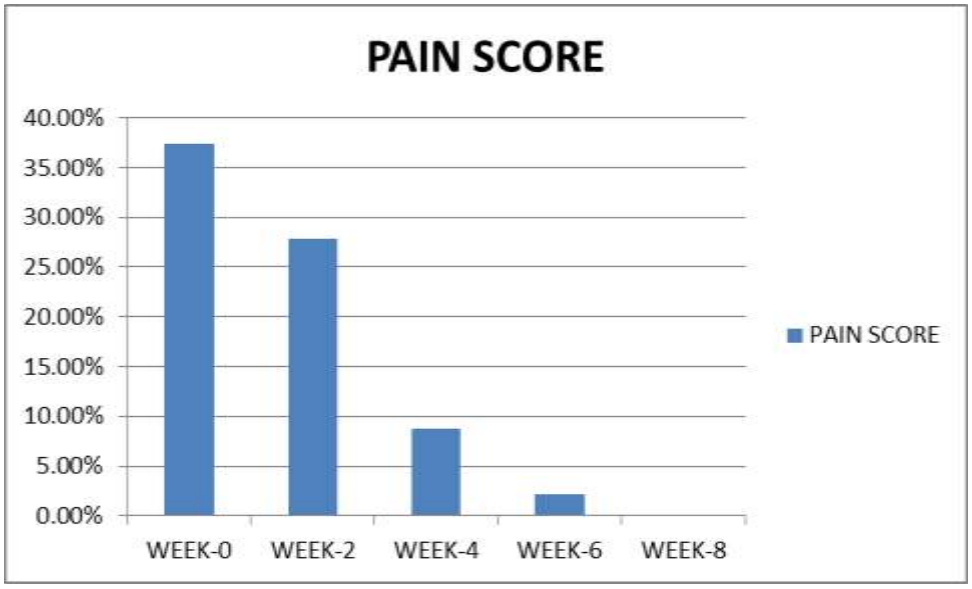


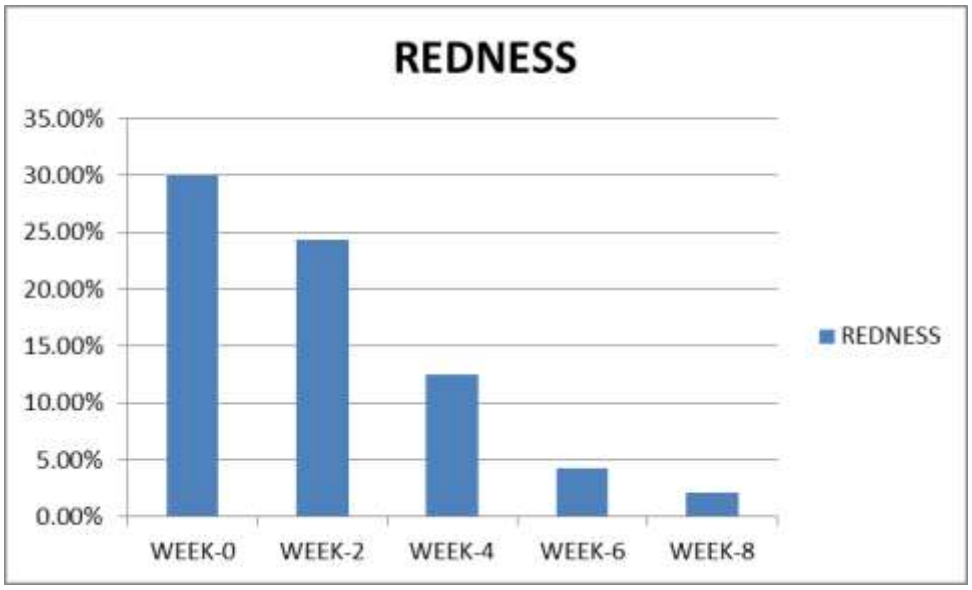
according to their gender:

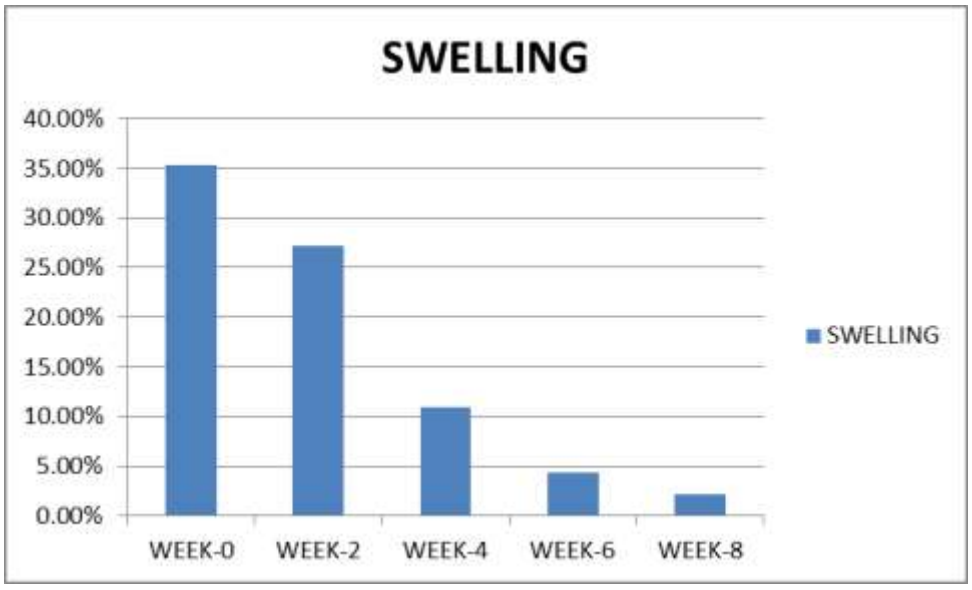
Male	Female
61.25	38.75

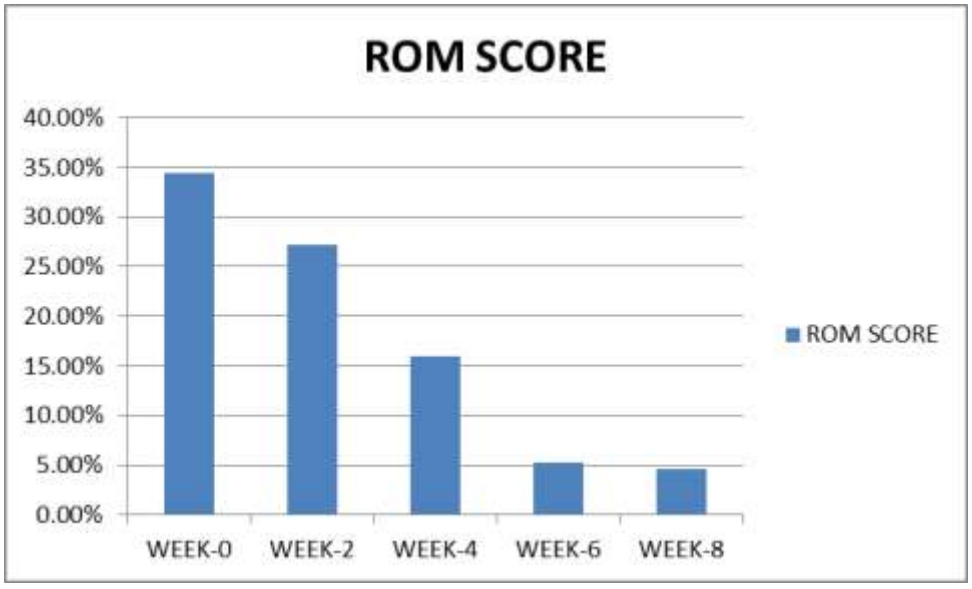


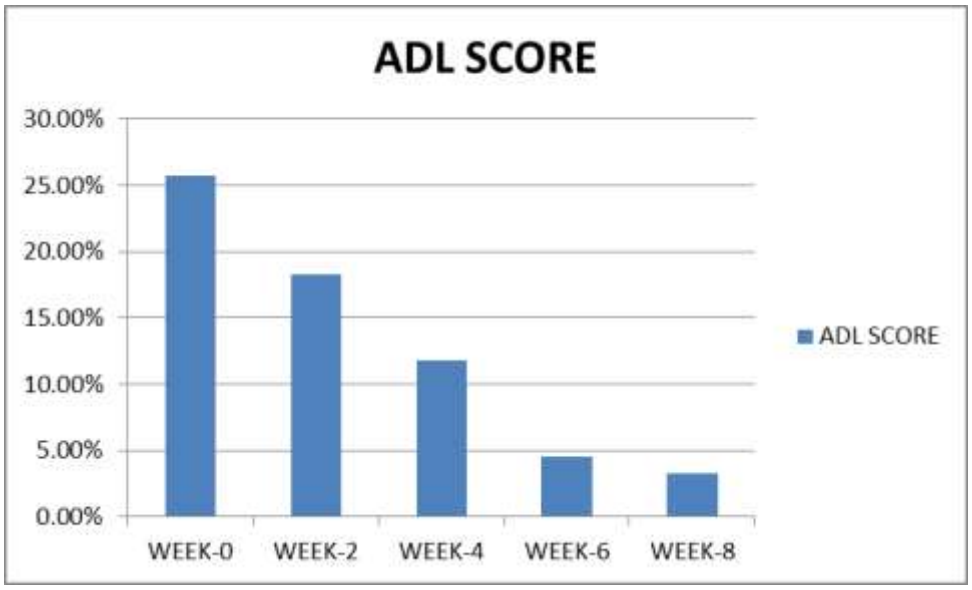
Assessment	Week-0	Week-2	Week-4	Week-6	Week-8
Pain score	37.37%	27.87%	8.75%	2.12%	0
Redness	30.0%	24.37%	12.5%	4.3%	2.1%
Swelling	35.31%	27.18%	10.93%	4.37%	2.18%
Rom score	34.37%	27.18%	16.0%	5.31%	4.6%
Adl score	25.75%	18.25%	11.75%	4.5%	3.25%
Su acid level	397.67	336.07	204.04	64.27	19.5

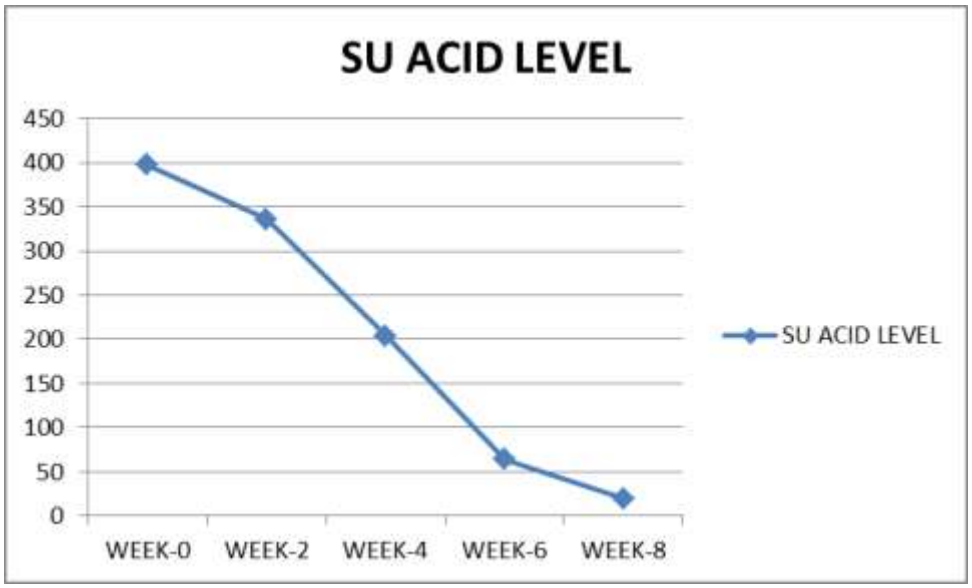



REDNESS
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
WEEK-0
WEEK-2
WEEK-4
WEEK-6
WEEK-8
REDNESS


SWELLING
40.00%
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
WEEK-0
WEEK-2
WEEK-4
WEEK-6
WEEK-8
SWELLING


ROM SCORE
40.00%
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
WEEK-0
WEEK-2
WEEK-4
WEEK-6
WEEK-8
ROM SCORE





DISCUSSION

Pain assessment for gouty arthritis patients using febuxostat:

Among the 100 gouty arthritis cases using febuxostat drug, collected from the hospital, the pain score is high with the percentage of 37.37% in the initial week, the pain score is reduced to 27.87% in the second week and further reduced to 8.75% in the 4th week, and the least pain score is 2.12% observed in the 6th week. These results were represented in bar graph.

Redness assessment for gouty arthritis patients using febuxostat:

Among the 100 gouty arthritis cases using febuxostat drug, collected from the hospital, the REDNESS score is high with the percentage of 30% in the initial week, and the redness is reduced to 24.37% in the second week and further reduced to 12.5% in the 4th week, 4.3% in the 6th week

and the least redness score is 2.1% observed in the 8th week. These results were presented in the bar graph.

Swelling assessment for gouty arthritis patients using febuxostat:

Among the 100 gouty arthritis cases using febuxostat drug, collected from the hospital, the Swelling score is high with the percentage of 35.31% in the initial week, and the swelling is reduced to 27.18% in the second week and further reduced to 10.93% in the 4th week, 4.37% in the 6th week and the least swelling score is 2.18% observed in the 8th week. These results were presented in the bar graph.

ROM assessment for gouty arthritis patients using febuxostat:

Among the 100 gouty arthritis cases using febuxostat drug, collected from the hospital, the ROM score is high with the percentage of 34.37% in the initial week, and the ROM is reduced to 27.18% in the second week and further reduced to 16% in the 4th week, 5.31% in the 6th week and the least ROM score is 4.6% observed in the 8th week. These results were presented in the bar graph.

ADL assessment for gouty arthritis patients using febuxostat:

Among the 100 gouty arthritis cases using febuxostat drug, collected from the hospital, the ADL score is high with the percentage of 25.75% in the initial week, and the ADL is reduced to 18.25% in the second week and further reduced to 11.75% in the 4th week, 4.5% in the 6th week and the least ADL score is 3.25% observed in the 8th week. These results were presented in the bar graph.

Serum uric acid assessment for gouty arthritis patients using febuxostat:

Among the 100 gouty arthritis cases using febuxostat drug, collected from the hospital, the Serum Uric ACID level is greater than 5mg /dl is high with the value of 397.67 in the initial week, and the SUA level is reduced to 336.07 in the second week and further reduced to 204.04 in the 4th week, 64.27 in the 6th week and the least SUA level is 19.5 observed in the 8th week.These results were presented in the bar graph.

CONCLUSION:

A short term prospective study on clinical improvement with febuxostat for patients with gouty arthritis by a group of four students in hospital with in the time period of 6 months. Gouty Arthritis is an inflammatory condition that occurs suddenly in joints affected by high serum uric acid levels of 5mg/dl, which contribute to the formation of deposits of monosodium urate(MSU)crystals. This study includes 100 gouty arthritis patients , 0treated with febuxostat. Febuxostat has been shown to be safe and effective in lowering serum urate according to the available clinical data. Doses of 80mg of febuxostat are more effective in lowering serum urate. Dose adjustment does not seem to

be necessary in patients with mild to moderate renal /liver insufficiently or advanced age according to data from these particular groups of subjects. The most common adverse reactions reported were abnormal liver function tests, headache, and gastro intestinal symptoms which were mild& transient. In summary, Febuxostat is a promising urate-lowering therapy as an alternative to allopurinol for the treatment of hyperuricemia and gout, although further observation on post-marketing safety and efficacy of long term treatment with febuxostat in patients with gout or hyperuricemia.

REFERENCES

1. Clebak KT, Morrison A, Croad JR. Gout: rapid evidence review. *Am Fam Physician.*2020;102:533–8.
2. Kim Y, Oh HC, Park JW, et al. Diagnosis and treatment of inflammatory joint disease. *Hip Pelvis.*2017;29:211–22. doi:10.5371/hp.2017.29.4.211.https://doi.org/10.5371/hp.2017.29.4.211.
3. Roddy E. Revisiting the pathogenesis of podagra: why does gout target the foot?*J Foot Ankle Res.*2011;4:13. doi:10.1186/1757-1146-4-13.https://doi.org/10.1186/1757-1146-4-13.
4. Galozzi P, Bindoli S, Doria A, Oliviero F, Sfriso P. Auto inflammatory features in gouty arthritis. *J Clin Med.* 2021; 10: 1880. doi:10.3390/jcm10091880.https://doi.org/10.3390/jcm10091880.
5. Dalbeth N, Merriman TR, Stamp LK. Gout.*Lancet.*2016; 388: 2039–52. doi:10.1016/S0140-6736(16)00346-9.https://doi.org/10.1016/s0140-6736(16)00346-9.
6. Ragab G, Elshahaly M, Bardin T. Gout: an old disease in new perspective -a review. *J Adv Res.*2017;8:495–511. doi:10.1016/j.jare.2017.04.008.https://doi.org/10.1016/j.jare.2017.04.008
7. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol.*2015;11:649–62. doi:10.1038/nrrheum.2015.91.https://doi.org/10.1038/nrrheum.2015.91
8. Kamei K, Konta T, Hirayama A, et al. A slight increase within the normal range of serum uric acid and the decline in renal function: associations in a community-based population. *Nephrol Dial Transplant.*2014;29:2286–92. doi:10.1093/ndt/gfu256.https://doi.org/10.1093/ndt/gfu256.
9. McCarty DJ, Hollander JL. Identification of urate crystals in gouty synovial fluid. *Ann Intern Med.*1961;54:452–60. doi:10.7326/0003-4819-54-3-452.https://doi.org/10.7326/0003-4819-54-3-452.
10. Emmerson BT. The management of gout. *N Engl J Med.*1996; 334:445–51. doi:10.1056/NEJM199602153340707.https://doi.org/10.1056/nejm199602153340707.

11. Mandal AK, Mount DB. The molecular physiology of uric acid homeostasis. *Annu Rev Physiol.*2015; 77:323–45. doi:10.1146/annurev-physiol-021113-170343.https://doi.org/10.1146/annurev-physiol-021113-170343.
12. Ichida K, Matsuo H, Takada T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. *Nat Commun.*2012; 3:764. doi:10.1038/ncomms1756.https://doi.org/10.1038/ncomms1756.
13. Enomoto A, Endou H. Roles of organic anion transporters (OATs) and a urate transporter (URAT1) in the pathophysiology of human disease. *Clin Exp Nephrol.*2005;9:195–205. doi:10.1007/s10157-005-0368-5.https://doi.org/10.1007/s10157-005-0368-5.
14. Kolz M, Johnson T, Sanna S, et al. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet.*2009;5:e1000504. doi:10.1371/journal.pgen.1000504.https://doi.org/10.1371/journal.pgen.1000504
15. Phipps-Green AJ, Merriman ME, Topless R, et al. Twenty-eight loci that influence serum urate levels: analysis of association with gout. *Ann Rheum Dis.*2016;75:124–30. doi:10.1136/annrheumdis-2014-205877.https://doi.org/10.1136/annrheumdis-2014-205877.
16. Emmerson B. Hyperlipidaemia in hyperuricaemia and gout. *Ann Rheum Dis.*1998;57:509–10.doi:10.1136/ard.57.9.509.https://doi.org/10.1136/ard.57.9.509.
17. Kanbara A, Seyama I. Effect of urine pH on uric acid excretion by manipulating food materials. *Nucleosides Nucleotides Nucleic Acids.*2011; 30:1066–71. doi:10.1080/15257770.2011.596498.https://doi.org/10.1080/15257770.2011.596498.
18. Towiwat P, Li ZG. The association of vitamin C, alcohol, coffee, tea, milk and yogurt with uric acid and gout. *Int J Rheum Dis.*2015;18:495–501. doi:10.1111/1756-185X.12622.https://doi.org/10.1111/1756-185x.12622.
19. Desai J, Steiger S, Anders HJ. Molecular pathophysiology of gout. *Trends Mol Med.*2017;23:756–68. doi:10.1016/j.molmed.2017.06.005.https://doi.org/10.1016/j.molmed.2017.06.005.
20. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)*Ann Rheum Dis.*2006;65:1312–24.
21. doi:10.1136/ard.2006.055269.https://doi.org/10.1136/ard.2006.055269.*BMJ Open.*2015;5(11):e009360.

22. Tan P.K., Ostertag T.M., Miner J.N. Mechanism of high affinity inhibition of the human urate transporter URAT1.*Sci Rep.*2016;6:34995.
23. Phipps-Green A.J., Merriman M.E., Topless R., Altaf S., Montgomery G.W., Franklin C. Twenty-eight loci that influence serum urate levels: analysis of association with gout.*Ann Rheum Dis.*2016;75(1):124–130.
24. Kolz M., Johnson T., Sanna S., Teumer A., Vitart V., Perola M. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet.*2009;5(6):e1000504
25. Liu R., O'Connell M., Johnson K., Pritzker K., Mackman N., Terkeltaub R. Extracellular signal-regulated kinase 1/extracellular signal-regulated kinase 2 mitogen-activated protein kinase signaling and activation of activator protein 1 and nuclear factor kappaB transcription factors play central roles in interleukin-8 expression stimulated by monosodium urate monohydrate and calcium pyrophosphate crystals in monocytic cells. *Arthritis Rheum.*2000;43(5):1145–1155.
26. Cronstein B.N., Sunkureddi P. Mechanistic aspects of inflammation and clinical management of inflammation in acute gouty arthritis. *J Clin Rheumatol: Practical Rep Rheumat Musculoskelet Dis.*2013;19(1):19–29.
27. Busso N., Ea H.K. The mechanisms of inflammation in gout and pseudogout (CPP-induced arthritis) *Reumatismo.* 2012;63(4):230–237.
28. Ea H.K. Mechanisms of gout inflammation. *Presse Med.*2011;40(9 Pt 1):836–843.
29. Dalbeth N., Lauterio T.J., Wolfe H.R. Mechanism of action of colchicine in the treatment of gout. *Clin Ther.*2014;36(10):1465–1479.
30. Steiger S., Harper J.L. Mechanisms of spontaneous resolution of acute gouty inflammation. *Curr Rheumatol Rep.*2014;16(1):392.
31. Grassi W., De Angelis R. Clinical features of gout.*Reumatismo.*2012;63(4):238–245.
32. Gonzalez E.B. An update on the pathology and clinical management of gouty arthritis. *Clin Rheumatol.*2012;31(1):13–21.
33. Schlesinger N., Thiele R.G. The pathogenesis of bone erosions in gouty arthritis. *Ann Rheum Dis.*2010;69(11):1907–1912.
34. Kosmadakis G., Viskaduraki M., Michail S. The validity of fractional excretion of uric acid in the diagnosis of acute kidney injury due to decreased kidney perfusion. *Am J Kidney Dis.*2009;54(6):1186–1187.

35. Burns C.M., Wortmann R.L. Latest evidence on gout management: what the clinician needs to know. *Therap Adv Chronic Dis.*2012;3(6):271–286.
36. Kanbay M., Huddam B., Azak A., Solak Y., Kadioglu G.K., Kirbas I. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clin J Am Soc Nephrol: CJASN.*2011;6(8):1887–1894.
37. Luk A.J., Levin G.P., Moore E.E., Zhou X.H., Kestenbaum B.R., Choi H.K. Allopurinol and mortality in hyperuricaemic patients. *Rheumatol (Oxford, England)*2009;48(7):804–806.
38. Yokose C., Chen M., Berhanu A., Pillinger M.H., Krasnokutsky S. Gout and osteoarthritis: associations, pathophysiology, and therapeutic implications. *Curr Rheumatol Rep.*2016; 18(10):65.
39. Mazzali M., Kanbay M., Segal M.S., Shafiu M., Jalal D., Feig D.I. Uric acid and hypertension: cause or effect? *Curr Rheumatol Rep.*2010;12(2):108–117.
40. Katsiki N., Papanas N., Fonseca V.A., Maltezos E., Mikhailidis D.P. Uric acid and diabetes: Is there a link? *Curr Pharm Des.*2013;19(27):4930–4937.
41. Roddy E. Revisiting the pathogenesis of podagra: why does gout target the foot?*J Foot Ankle Res* .2011;4(1):13.
42. Canoso J.J., Yood R.A. Acute gouty bursitis: report of 15 cases. *Ann Rheum Dis.*1979; 38(4):326–328.
43. Perez-Ruiz F., Castillo E., Chinchilla S.P., Herrero-Beites A.M. Clinical manifestations and diagnosis of gout. *Rheum Dis Clin North Am.*2014;40(2):193–206.
44. Pascual E., Batlle-Gualda E., Martinez A., Rosas J., Vela P. Synovial fluid analysis for diagnosis of intercritical gout. *Ann Intern Med.*1999; 131(10):756–759.
45. Chhana A., Dalbeth N. The gouty tophus: a review. *Curr Rheumatol Rep.*2015; 17(3):19.
46. Malik A., Schumacher H.R., Dinnella J.E., Clayburne G.M. Clinical diagnostic criteria for gout: comparison with the gold standard of synovial fluid crystal analysis. *J Clin Rheumatol: Practical Rep Rheum Musculoskelet Dis.*2009;15(1):22–24.
47. Zhang W., Doherty M., Pascual E., Bardin T., Barskova V., Conaghan P. EULAR evidence based recommendations for gout. Part I: diagnosis. report of a task force of the standing committee for international clinical studies including therapeutics (ESCISIT)*Ann Rheum Dis.*2006;65(10):1301–1311.
48. Atdjian M., Fernandez-Madrid F. Coexistence of chronic tophaceous gout and rheumatoid arthritis.*J Rheumatol.*1981;8(6):989–992.

49. Dincer H.E., Dincer A.P., Levinson D.J. Asymptomatic hyperuricemia: to treat or not to treat.*Clevel Clin J Med.*2002;69(8):594.7, 600-2 passim.
50. Badulescu M., Macovei L., Rezus E. Acute gout attack with normal serum uric acid levels. *Rev Med Chir Soc Med Nat Iasi.*2014; 118(4):942–945.
51. Underwood M. Diagnosis and management of gout. *BMJ (Clin Res Ed)* 2006; 332(7553):1315–1319.
52. Pascual E., Tovar J., Ruiz M.T. The ordinary light microscope: an appropriate tool for provisional detection and identification of crystals in synovial fluid. *Ann Rheum Dis.*1989;48(12):983–985.
53. Phelps P., Steele A.D., McCarty D.J., Jr. Compensated polarized light microscopy. Identification of crystals insynovial fluids from gout and pseudogout.*JAMA.*1968; 203(7):508–512.
54. Strasinger S.K., Di Lorenzo M.S. F. A. Davis Company; 2008. Urinalysis & body fluids.
55. Kramer H.M., Curhan G. The association between gout and nephrolithiasis: the National Health and Nutrition Examination Survey III, 1988–1994.*Am J Kidney Dis.*2002;40(1):37–42
56. Fernandes EA, Bergamaschi SB, Rodrigues TC, Dias GC, Malmann R, Ramos GM, et al. Relevant aspects of imaging in the diagnosis and management of gout. Revista brasileira de reumatologia. 2016.
57. Rettenbacher T., Ennemoser S., Weirich H., Ulmer H., Hartig F., Klotz W. Diagnostic imaging of gout: comparison of high-resolution US versus conventional X-ray. *Eur Radiol.*2008;18(3):621–630.
58. Namas R., Meysami A., Siegal D., Rubin B. Gout and ultrasound: the disease of kings and the queen of imaging. *Gout Hyperuricaemia.*2014;1:94–100.
59. Bloch C., Hermann G., Yu T.F. A radiologic reevaluation of gout: a study of 2,000 patients. *AJR Am J Roentgenol.*1980;134(4):781–787