Pathogenesis and Clinical Management of Gouty Arthritis

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Gout, the most common of the crystal arthritides is a result of disturbed uric acid metabolism and precipitation of urate crystals in extra cellular space of joints, periarticular tissue, bones and other organs.

In the West, gout affects around 1% of adult men over 45 years of age. The estimated incidence being 0.6 to 2.1 per 1000 per year, with a prevalence of 9.5 to 13.5 per 1000 persons of all ages.¹ The incidence of gout has been on rise globally; potentially attributable to recent shifts in diet, lifestyle, medical care, and increased longevity.²

This update aims to highlight recent developments in understanding pathogenesis of gout along with current management strategies.

Pathophysiology of Gout

Uric Acid Metabolism³,⁴,⁵

In humans, uric acid is the end product of purine metabolism in the liver (Figure 1).

![Urate biosynthesis](image)

Humans lack the enzyme uricase, which degrades uric acid to highly soluble allantoin. Two third of the urate load is excreted by the kidneys. Here post-secretary reabsorption in the S3 segment of proximal renal tubule is the major contributor for the reabsorption of filtered urate load. The major genes that encode ion transporters involved in urate renal transport have been identified.

The most important among these is the anion exchanger URAT1 encoded by SLC22A12 (solute carrier family 22 [organic anion/urate transporter] member 12) gene on chromosome 11q13 which drives urate anions reabsorption.⁶ The hexose transporter SLC2A9 (also called the glucose transporter 9, GLUT9, or fructose transporter encoded by gene on chromosome 4) is involved in voltage-dependent urate anion reabsorption at the proximal tubule.⁷ Genetic polymorphisms of SLC2A9 may point towards the mechanisms by which high fructose intake and hyperglycemia are linked with hyperuricemia and gout. Single nucleotide polymorphism (SNP) of ABCG2 (ATP-binding cassette subfamily G member 2), the key transporter for tubular secretion of urate, is strongly associated with hyperuricemia in men, post menopausal women and hormone therapy users.

Hyperuricemia and Gout

The natural history of articular gout is typically composed of four periods: asymptomatic hyperuricemia, episodes of acute attacks of gout (acute gouty arthritis) with asymptomatic intervals (intercritical gout), and chronic gouty arthritis. Hyperuricemia is a major contributor to gout, in 85% to 90% of people it develops because of underexcretion (excretion <330 mg/d) of urate while its overproduction (excretion >600 mg/d) accounts for only 10% to 15% of hyperuricemia cases (Table 1).

The common precipitants of an acute attack of gout such as strenuous exercise, cold, alcoholism and overeating, act by inducing accelerated degradation of ATP into AMP, (a precursor of uric acid)
Furthermore, ethanol ingestion contributes to hyperuricemia by associated dehydration and metabolic acidosis.

Crystal-Induced Inflammation

Hyperuricemia is necessary but not sufficient for the development of gout. The urate precipitation is modulated by lower temperature at the foot, intra-articular fluid dehydration (onset at night time), cation concentration and the presence of various nucleating agents, such as insoluble collagens, chondroitin sulfate, proteoglycans, cartilage fragments, and other crystals. Among these the immunoglobulin G (IgG) is prominent as monosodium urate (MSU) crystals from tophi and synovial fluid during acute gout are found to be coated with IgG. The nucleation and subsequent growth rates of MSU crystals are directly proportional to the degree of MSU supersaturation.

MSU crystals are pro-inflammatory and can initiate, amplify and sustain an intense inflammatory response. Innate immune system responds to a variety of pathogens and endogenous molecules (including urate crystals), through recognition of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). MSU crystals in the joint cavity, activate synovial endothelial cells followed by the recruitment and activation of mast cells and blood monocytes. Later, neutrophils get recruited, leading to further MSU crystal phagocytosis and cell activation. Normally MSU crystals are coated with serum proteins (apolipoprotein E or apolipoprotein B) which inhibits the binding of MSU crystals to cell receptors.

Initiation Phase (Figure 2)

In acute gout, Interleukin-1β (IL-1β) is the core inflammatory mediator released as a result of interaction of MSU to mononuclear and synovial lining cells. IL-1β can induce the expression of a wide range of inflammatory mediators leading to neutrophil influx in the synovium.

Phagocytosis of MSU crystals by macrophage and synovial fibroblasts and resulting cytokine release caused vascular endothelial cell activation and vasodilatation, increased plasma proteins permeability and leukocyte recruitment. This may require the presence of cell surface receptors of the innate immune system like: toll-like receptors-1 (TLR-1), TLR-2 or TLR-4, the TLR adapter protein, myeloid differentiation factor 88 (MyD88), or an adapter protein shared by TLR-2 and TLR-4: CD14. Triggering receptors expressed on myeloid cell 1 (TREM-1) present on monocytes and neutrophils, act as amplifier of the immune response.

Phagocytosis of MSU Crystals causes generation of reactive oxygen species through activation of NADPH oxidases leading to activation of NLRP3 (NACHT, LRR and pyrin domain containing protein) inflammasome. Inflammasomes are molecular platforms which function as pathogen sensors similar to TLRs.

Additional triggers for provoking inflammation include dietary factors such as long-chain

Table 1: Causes of Hyperuricemia

<table>
<thead>
<tr>
<th>Causes of Hyperuricemia</th>
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<tr>
<td>Drives causing hyperuricemia</td>
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<tr>
<td>Aspirin (low dose)</td>
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<td>Amiloride</td>
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<tr>
<td>Alcohol</td>
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<tr>
<td>Chlorothalidone</td>
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<td>Cyclosporine A</td>
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<td>Ethacrynic acid</td>
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<td>Ethambutol</td>
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<td>Nalp 3 Inflammosome activation</td>
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<td>Caspase 1 cleavage &amp; activation</td>
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<td>Cleavage of pro IL 1B</td>
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<tr>
<td>Maturation and secretion of IL-1B</td>
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<td>Interaction of IL-1B with IL-1 R-MyD88 complex</td>
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<td>Recruitment &amp; Activation of Neutrophils and Other Cells</td>
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<td>(MSU: Monosodium urate, IL: Interleukin, IL-1R: Interleukin-1 receptor: MyD88: Myeloid differentiation factor 88)</td>
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Fig. 2: Pathogenesis of urate-induced inflammation

Immune system responds to a variety of pathogens and endogenous molecules (including urate crystals), through recognition of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). MSU crystals in the joint cavity, activate synovial endothelial cells followed by the recruitment and activation of mast cells and blood monocytes. Later, neutrophils get recruited, leading to further MSU crystal phagocytosis and cell activation.
free fatty acids or ethanol, which act by activating TLRs, in particular TLR4. These TLR ligands include high-mobility group protein B1 (HMGB1), DNA and the calcium-binding proteins S100A8 and S100A9. A rapid change in ATP concentration causes activation of purinergic receptor P2X ligand-gated ion channel 7 receptor (P2X7R) which leads to rapid exit of intracellular potassium (P2X7R) which leads to rapid exit of intracellular potassium triggering NLRP3 inflammasome activation.13 NLRP3 inflammasome mediates the activation of caspase-1, causing cleavage of pro-IL-1β to the active form of IL-1β and IL-18. Besides IL-1β, both IL-6 and TNFα are also upregulated. Colchicine is thought to block IL-1β maturation by inhibition of NLRP3 inflammasome activation.14

Novel agents targeting elements of the NLRP3 inflammasome, IL-1β or the IL-1R-MyD88 complex may provide more directed therapies for prevention and treatment of acute gout.

In patients with chronic renal failure, MSU induced release of IL-1, IL-6, and TNF from the monocytes is blunted causing reduced gout attacks in spite of high degree of hyperuricemia in these patients.15

**Amplification Phase (Figure 2)**

After being secreted in the extracellular space, IL-1 β interacts with IL-1 receptor (IL-1R) complex leading to recruitment of MyD88 (an intracellular adaptor protein involved in IL-1R signaling), activation of endothelium; and chemokines (IL-8, S100 or macrophage inflammatory protein -2) and cytokines (IL-1, TNF-α) production.16

**Spontaneous Resolution of Acute Attack**

Subsidence of an acute gout attack occurs due to multiple feedback mechanisms, most important being the apoptotic clearance of damaged neutrophils, induced by peroxisome proliferator–activated receptor-γ (PPAR-γ) expression in monocytes. Formation of differentiated macrophage with increased anti inflammatory cytokines IL-10 and transforming growth factor (TGF-β1) in the synovial fluid, lowering endothelial activation, monocyte and neutrophil adhesion and recruitment, and reduced IL-1 and IL-1R expression.17

**Intercritical Gout**

Following resolution of an acute attack, the MSU crystals still persist either free or as microtophi in the synovium. These crystals promote a state of low-grade persistent inflammation in the synovium.18

**Formation of Tophi and Joint Damage**

In patients with repeated attacks of acute gout, tissue deposits of MSU crystals surrounded by granulomatous inflammation known as tophi are found in numerous tissues besides joint and skin, including the kidney and larynx. Tophi are associated with destruction of surrounding cartilage and bone brought about by crystal–chondrocyte cell membrane interactions. These include chondrocyte activation, and inducible nitric oxide synthase (iNOS), leading to nitric oxide release through TLR2 signalling via MyD88, IRAK1 (IL-1 receptor-associated kinase 1) and TRAF-6 (TNF receptor associated factor-6) resulting in NFkB (nuclear factor kappa B) activation and over-expression of MMPs (matrix metalloproteinases).

**Accurate Diagnosis of Gout**

**Typical Clinical Picture**

The presence of Acute monoarthritis involving first metatarsophalangeal (Podagra), where inflammation peaks in 24 hours, and may involve midtarsal, ankle, knee, wrist or elbow joints. There may be presence of tophi. A rapid response to colchicine further establishes a diagnosis of gout. Atypical gout is seen in elderly, as oligo/polyarticular subacute/persistent arthritis of unusual joints, also affecting bursae, tendon sheaths making distinction from chronic arthritides difficult.

**Serum Uric Acid Estimation**

Serum uric acid (SUA) is usually elevated but may be normal in about 30% patients during an acute attack because of IL-6 and endogenous cortisol secretion, which are uricosuric so SUA should be repeated after 2 weeks.

**Synovial Fluid (SF) Examination**

A fresh sample SF should be aspirated to demonstrate the presence of monosodium urate (MSU) crystals for a definite diagnosis of gout. SF if not examined immediately may be refrigerated for days to months. MSU crystal identification is considered the gold standard for diagnosis.19

The MSU crystals are needle shaped negatively birefringent crystals, easily detected by an ordinary polarizing microscope. The MSU crystals are yellow when parallel to slow axis of red compensator and blue when perpendicular to red compensator shining on the dark microscope field. Caution should be exercised not to take SF in formalin as urate crystals dissolve in formalin. Under light microscopy also MSU crystals may be seen as needle shaped crystals (Figure 3).

**Ultrasound (US)**

A short 4-joint (including both knees and both first MTP joints) US screening may be done as a useful complement to clinical
examination. Double contour (DC) sign on US (Figure 4) is very specific for non-tophaceous urate crystal deposition on articular cartilage.

The sensitivity and specificity of the DC in diagnosing gout is estimated to be 43.7% and 99%, respectively. Erosions are most commonly found in the first MTP joint (medial surface). Other synovial signs on US specific for gout are erosions, intrasynovial hyperechogenicity, hyperechoic gout are erosions, intrasynovial synovial signs on US specific for joint (medial surface). Other commonly found in the first MTP joint (medial surface). Erosions are most commonly found in the first MTP joint (medial surface).

**Diet and Lifestyle Changes**

1. Achieve ideal body weight
2. Cessation of smoking
3. Healthy diet and optimal exercise
4. Good hydration

**Avoid**

Purine-rich organ meat (liver and kidney, thymus and pancreas of calf and lamb, seafood), fructose-rich drinks (corn syrup, sweetened soft drinks, ice cream) and fruits (apples, oranges); alcohol use especially during attacks of gout and especially rich meals.

**Limit**

Beef, lamb, pork, and sea food (shellfish and sardines); natural sugars, sweetened beverages, desserts and table salts. Limit alcohol (esp. beer, also wine and spirits) in all gout patients to <2 servings/day for males and <1 serving/day for females.

**Encourage**

Low fat or non-fat dairy products and vegetable intake. Dairy products decrease SUA by uricosuric effect. The dairy fractions glycomacropeptide and G600 milk fat extract might inhibit triggering of the inflammasome by urate crystals thus may also have anti-inflammatory effects.

Dietary intake of vegetables, vitamin C and coffee has been associated with lowered serum urate levels and reduction of risk factors for urate urolithiasis.

**Management of Acute Gouty Arthritis**

Acute gouty attacks should be managed with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids, topical ice and IL-1 inhibitors.

Monotherapy is preferred if there is mild to moderate pain (<6 on a 1-10 visual analogue scale) limited to one or two joints. Severe pain or polyarticular involvement requires combination therapy.

**NSAIDs**

The choice amongst NSAID depends on the patients response and tolerability. In patients with gastrointestinal intolerance to NSAIDs, cyclooxygenase-2 (COX-2) inhibitors e.g. etoricoxib may be used.

**Topical Ice Application**

In addition to pharmacologic therapy this is an important relieving measure in acute attack.

**Colchicine**

Oral colchicine is first-line treatment for acute gout attacks along with oral NSAIDs.

It works best when commenced within 36 hours of first symptoms of an acute attack. A loading dose of 1 mg followed one hour later by 0.5 mg and then continued (up to 0.5 mg 3 times daily) until the acute attack resolves or the patient develops vomiting. A reduced dose of 0.5 mg daily or on alternate days is used in elderly or those with hepatic or renal dysfunction.

Colchicine has a narrow therapeutic index and dose-dependent gastrointestinal toxicity is common.

Colchicine myopathy may rarely be seen in elderly with renal impairment. Serum creatine kinase monitoring is recommended in these patients every six months.

Colchicine should be used at low doses and with caution in patients taking a cytochrome P450 3A4 inhibitor and P-glycoprotein inhibitors (Table 2). Corticosteroids (CS)

Aspiration of an affected joint followed by injection of corticosteroids is ideal treatment of acute monoarticular gout.
when colchicine, NSAIDs or oral corticosteroids are contraindicated. Where NSAIDs or colchicine cannot be used or are ineffective, oral prednisolone (0.5 mg /kg/day for five days) is preferred.

A single dose of depot methylprednisolone acetate 80 mg or triamcinolone 40-80 mg intramuscularly or methylprednisolone succinate (0.5-2.0 mg/kg) intravenously may also be given. ACTH 25-40 IU subcutaneously/ intramuscularly every 8 hours for 1-14 days, is another option. ACTH may inhibit gouty inflammation by activating melanocortin type 3 receptor peripherally.

**Biologic Response Modifiers**

IL-1 inhibition has been shown to be an effective first-line therapy for acute gout attacks when NSAIDs, colchicine or CS are contraindicated.27

Three biologic agents are available that bind and inactivate extracellular IL-1β: Anakinra, the IL-1 receptor antagonist that inhibits the activity of both IL-1α and IL-1β; rilonacept, a soluble decoy receptor fusion protein that binds IL-1α and IL-1β receptors; and canakinumab, a fully human anti-IL-1β monoclonal antibody.

Anakinra (100 mg subcutaneously daily for 3 days); or rilonacept (80-160 mg weekly); and canakinumab (150 mg subcutaneously)28 are beneficial in patients with frequent gout attacks (≥ 3 attacks in previous 12 months) in whom NSAIDs and colchicine are not tolerated, or are ineffective or contraindicated.

**Urate Lowering Therapy (ULT) During Acute Attack**

Current recommendation is that ULT can be started during an acute gout attack in low dosage, along with effective anti-inflammatory management which is contrary to the earlier practice when ULT was contraindicated in acute attack.19

**Long-Term Management of Gout**

The aim of long-term therapy is to ‘cure’ gout by lowering SUA levels to below the saturation point for urate (<360 μmol/l or 6 mg/dl); in the presence of tophi, target SUA level should be <5 mg%. Regular monitoring of SUA (every 2–5 weeks) during urate lowering therapy (ULT) should be done, once the serum urate target is achieved then SUA should be measured every six months to know the adherence.

**Urate-lowering Therapy (ULT)**

- Xanthine oxidase inhibitors (XOI)
- Uricosuric drugs
- Pegloticase

**Prophylaxis of Acute Gout Attacks during ULT**

ULT is preceded by anti-inflammatory measures as during the initial phase of ULT there may be an early increase in acute gout attacks. Anti-inflammatory measures are usually given for 3 months in patients without tophi and 6 months in patients with tophi, after target SUA is achieved.29

Colchicine is currently considered the standard of care for flare prophylaxis during initiation of ULT, alternatively, low-dose steroids and IL-1β inhibitors might be used.

**XOI**

XOI are the first-line ULT. XOIs reduce endogenous production of uric acid by inhibiting the conversion of hypoxanthine to xanthine and of xanthine to uric acid.

**Indications of XOI**

Any confirmed patient of gout with: (i) two or more attacks of gout, (ii) presence of tophi on clinical or imaging study, (iii) joint damage (erosive gout) due to chronic gouty arthritis, (iv) CKD stage 2 or worse, and (v) past history of urolithiasis.

**Allopurinol**

The most commonly used XOI, allopurinol should be started with 100 mg/day, to reduce early gout flares after ULT initiation, and to reduce the potential for severe hypersensitivity reactions.30 Allopurinol may be titrated up (up to 900 mg/day) till the target SUA is reached. In stage 4 CKD starting dose is 50 mg/day which may be titrated up to 300 mg/day if target SUA is not achieved, with regular monitoring for drug hypersensitivity.

**Adverse Events**

It is usually well tolerated, rash (3%), gastrointestinal events (2%), allopurinol hypersensitivity syndrome (AHS) (1%), fever (1%) and musculoskeletal events (1%)
have been reported. AHS includes Stevens Johnson syndrome and toxic epidermal necrolysis with mortality of 20-25%. Drug rash, eosinophilia and systemic symptoms (DRESS) can also occur with allopurinol. Pruritic rash, eosinophilia and elevated hepatic transaminases may be the first signs of impending AHS or DRESS. Risk factors for AHS include high initial dose, presence of renal impairment, concomitant use of thiazide diuretics, presence of HLA B5801 allele, concomitant use of colchicine and statins.

Febuxostat

Febuxostat, a non-purine, highly specific XOI, had been shown to be more effective than fixed-dose (300 mg) allopurinol as ULT. However, febuxostat should be used in patients who are intolerant of allopurinol or when it is contraindicated. Starting dose of febuxostat is 40 mg/day, after two weeks if target level is not achieved it may be increased to 80 mg then to 120 mg/day.

Adverse effects

Include abnormal liver function tests, diarrhoea and musculoskeletal symptoms. Liver function should be assessed at two and four months. Febuxostat also has cardiovascular toxicity like AV blocks, atrial fibrillation, cardiovascular thromboembolic events. It should be used with caution in patients with congestive heart failure stage III or IV, hepatic dysfunction and in patients with GFR less than 30 ml/min. hypersensitivity is rarely reported.

Febuxostat Versus Allopurinol

As a non-competitive XOI, Febuxostat has several theoretical advantages over the competitive XOI allopurinol, including greater potency, specificity and a reduced reliance on renal excretion.

Advantage of febuxostat over allopurinol is that it can be used without dose-adjustment or concern over toxicity in patients with CKD with GFR >30 ml/min although it is not recommended for use in those with an estimated glomerular filtration rate <30 ml/min/1.73 m². If one XOI is ineffective to achieve target level of SUA or intolerance develops to it then second XOI may be substituted.

Drug Interactions of XOI

XOI have interactions with drugs metabolized by xanthine oxidase enzyme e.g. azathioprine, 6-mercaptopurine and theophylline thus increasing their concentration and hence toxicity. Similarly, warfarin may have increased anti-coagulant effect with allopurinol. ACE inhibitors may increase risk of allergic reactions to allopurinol.

Uricosuric Drugs (Table 3)

Uricosuric drugs act predominantly on URAT1 to prevent reuptake of uric acid at the proximal renal tubule and thus increase renal excretion of uric acid. The resulting higher concentration of uric acid in the collecting tubules can predispose to uric acid stone formation, so the patient should remain well-hydrated. Urine should be made alkaline by potassium citrate to dissolve uric acid crystals.

These drugs should be given to those patients who cannot tolerate allopurinol or as an adjunctive therapy with XOI where SUA target is not achieved. Uricosuric drugs should be added and gradually the dose should be increased every 2-5 weeks till the target SUA is achieved. Most of the uricosuric drugs are either not available or have limited availability in India.

Pre-requisites of using Uricosuric ULT

Renal function should be normal (creatinine clearance >50 ml/minute).

Urate excretion should be <800 mg/24 hours.

There should be no evidence of uricolithiasis.

Probenecid

It is drug of choice among all the uricosuric drugs. Its half life is 3-8 hours, so given as twice or thrice a day therapy.

Benzbromarone

It may be used in those with mild to moderate renal impairment. The availability of benzbromarone became limited mainly due to reports of hepatotoxicity, particularly in Asia. Liver function should be frequently checked.

Other available uricosuric drugs

Losartan inhibits URAT1 and GLUT9, while fenofibrate inhibits only URAT1. These two drugs can be considered as useful adjunctive therapy if hypertension or hyperlipidemia are coexistent. Other drugs include vitamin C supplements and corticosteroids.

Pegloticase

It is polyethylene glycol uricase preparation i.e. pegylated form of recombinant uricase. Pegloticase therapy is not recommended as first-line ULT agent.

It reduces SUA by enzymatic degradation of uric acid to more water soluble and excretable allantoin. It is approved by USFDA for use in patients with severe gout disease burden, in actively symptomatic patients and in those who are refractory to, or intolerant of, conventional and appropriately dosed ULT.

Pegloticase (8 mg intravenously every 2 weeks) can bring about rapid tophus burden reduction and can achieve rapid improvements in clinical outcomes sometimes in months only whereas oral agents may take years.

Most common adverse reactions are gout flares, infusion related reactions, headache (11%) and nausea (7%). Antibody develop in nearly 90 percent of those receiving the active drug associated with loss of efficacy and increased infusion reactions.

Other ULT, such as allopurinol and febuxostat, should not be given to patients receiving pegloticase, because they may mask recognition of rising SUA.
Inhibits URAT1 and OAT 4 (organic anionic transporter 4) in renal tubule. Phase III studies have shown that it can be given as monotherapy to those who are intolerant to XOIs, or in combination with allopurinol or febuxostat.

Levodoseine

Oral, once daily novel purine nucleoside phosphorylase inhibitor which blocks production of uric acid at the step higher than xanthine oxidase inhibition. Phase 2 trials have been going on with this drug.

Levotofisopam

This ULT has also been undergoing phase 2 trial.

Arhalofenate and Tranilast

Inhibits URAT1 and other urate exchanger molecules and are undergoing Phase I and II trials.

Novel intestinal transporters of uric acid

In patients with CKD, total urinary uric acid falls and the principal burden of elimination shifts from the kidney to the gut, there is upregulation of intestinal ABCG2 exporters, this has become an important area of study to develop novel intestinal transporters which may become an alternative for those at risk of developing uric acid kidney stones with uricosuric agents.

Managing Comorbidities

In NHANES study of 5,707 participants in the 2007-2008, 74% had HTN, 71% had CKD stage 2 or higher, 53% were obese, 26% had diabetes, 24% had nephrolithiasis, 14% had myocardial infarction, 11% had heart failure, and 10% had suffered a stroke; the prevalence of these comorbidities increased with the degree of hyperuricemia, supporting the notion that serum urate is related to the presence of several gout comorbidities, either as a marker of disease or perhaps by itself exacerbating other diseases. These co-morbidities should be managed judiciously (Table 4).

Hypertension should be managed preferably by Losartan and calcium channel blockers as both increase uric acid excretion. Other antihypertensives like β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers other than losartan, increase SUA by reduced renal excretion.

Hyperlipidemia and hyperglycemia need to be managed aggressively as tight control of each can independently reduce SUA levels through improved renal excretion of uric acid. Agents decreasing insulin resistance also tend to reduce SUA levels.

Conclusion

Management of gout has undergone major change in the last couple of years. Proper control of SUA to less than 6.0 mg% (or lower in presence of tophi) is the main aim with optimum management of comorbidities and patient education are of paramount importance.

References

10. Pope RM, Tschopp J. The role of interleukin-1 and the inflammasome in


