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HYPERURICEMIA: A RISK FACTOR BEYOND GOUT

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ABSTRACT

Gout is the most common inflammatory type of arthritis in men affecting 1-2% of adults in Western countries, with male to female ratio of 3.6:1, but rare in pre-menopausal women and its incidence and prevalence increases with age. It is characterized by chronic hyperuricaemia which is defined as serum urate levels above 6.8 mg/dl (≥ 400μmol/L), the level above which the physiological saturation threshold is exceeded. Risk factors for gout include high dietary purine consumption, e.g. various types of meat, seafood and certain vegetables, ethanol intake, obesity and the use of diuretics and low dose aspirin. Symptoms of an acute gout attack include pain, inflammation and erythema of the afflicted joint. The above-mentioned inflammation is caused by the release of various cytokines, including interleukin-1β (IL-1β). IL-1β is an inflammatory cytokine that is associated with the leukocytosis and fever that often accompany acute gouty attacks. All patients with gout should be screened for renal dysfunction and metabolic bone syndrome. An acute attack of gout is very painful and should be treated with either joint aspiration with intra-articular glucocorticoid injection, low dose oral colchicine, oral glucocorticoid, NSAIDs or Cox 2 inhibitors depending on the patient's co-morbidities. On introducing the urate lowering therapy, prophylaxis therapy should be considered to prevent any precipitation of acute attack of gout. The starting of low dose of allopurinol or benzbromarone with slow titration may obviate the use of prophylaxis therapy. Lifestyle modification is important and should be considered in particular to tackle factors related to metabolic bone syndrome.

KEYWORDS: Gout, Hyperuricemia, NSAIDS

INTRODUCTION

Gout is the most common form of inflammatory arthritis and is characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain (referred to as acute gouty arthritis, or acute gout attacks, or acute gout flares) [1]. It has been described as a disease of the foot since antiquity. The search for new gout treatments has increased considerably due to the large increase in the incidence of gout, as well as the renal and cardiovascular consequences of this disease.

The current increase in the prevalence of gout could be related to overweight and the development of metabolic syndrome and change in our diet with high intake of meat, seafood, fructose sweetened beverages and beer, and also to the increase in life expectancy. However, the main reason for gout and hyperuricaemia is related to the renal uric acid hypo-excretion, which can be multifactor in origin including both genetic and environmental factors such as diuretic use, low dose of aspirin and high alcohol consumption [2].

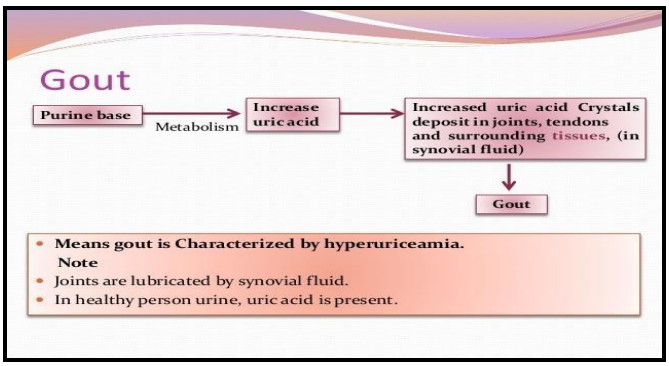

Figure 1: Causes of Hyperuricemia and Gout

DO ALL PATIENTS WITH HYPERURICEMIA DEVELOPE GOUT?

Based on an estimated prevalence of gout of 3.9% (8.3 million) and hyperuricemia (i.e., serum uric acid level >7.0 mg/dL in men and >5.7 mg/dL in women) of 21.4% (43.3 million) among US adults, approximately 1 in 5 people with hyperuricemia develop symptoms of gout.

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Although the prevalence of hyperuricemia is similar among men (21.2%) and women (21.6%), the prevalence of gout is approximately 3 times higher in men than in women (5.9% and 2% of adults in the United States, respectively); the disparity between sexes lessens after menopause. The overall prevalence of gout increases with age, from 3.3% in adults over the age of 40 years to 9.3% in adults over the age of 70 years Family history may also play a small role [3].

PREVALENCE

A 4.1% prevalence of hyperuricaemia was found in a previous study in people older than 75 years. However, care should be taken when comparing prevalence rates of gout in different studies, as there are so many variables to take into consideration. Examples of these variables include diagnostic criteria, sample size and even seasonal changes in levels of serum uric acid [4].

CAUSES OF GOUT

The causes of gout are unclear but appear to be multifactorial, including a combination of genetic, hormonal, metabolic, and dietary factors. Family history, advancing age, male sex, or, in women, early menopause have been associated with a higher risk of gout and/or gout attacks (flares). Hyperuricaemia causes an accumulation of monosodium urate crystals, which are deposited in the supersaturated body fluids and then are deposited in tissues and around joints during the asymptomatic hyperuricaemic gout stage [5-7].

SIGNS AND SYMPTOMS OF GOUT

Symptoms of an acute gout attack include pain, inflammation and erythema of the afflicted joint. The above-mentioned inflammation is caused by the release of various cytokines, including interleukin-1β (IL-1β). IL-1β is an inflammatory cytokine that is associated with the leukocytosis and fever that often accompany acute gouty attacks. Both intracellular and extracellular signals activate the cryoprin (NLRP3) inflammasome, which in turn activates Caspase 1. Caspase 1 then cleaves pro-IL-1β to form active IL-1β [8-10].

As stated previously, current treatments for gout are aimed at decreasing levels of serum uric acid and treat one of the causes of gout. New research is currently under way to explore the potential use of an IL-1β blocker to treat gout [8].

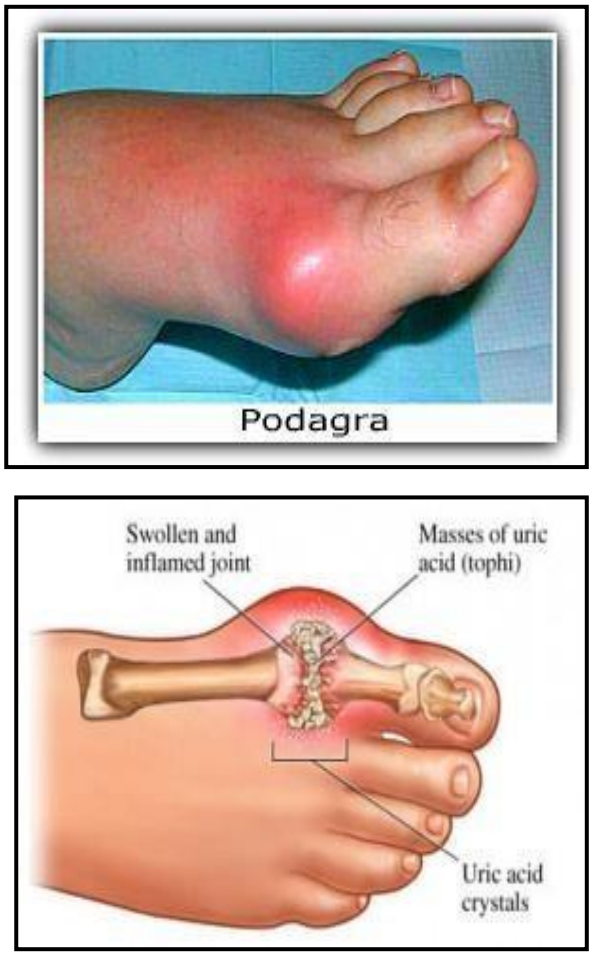

Figure 2A & B: Chronic gout with Tophi

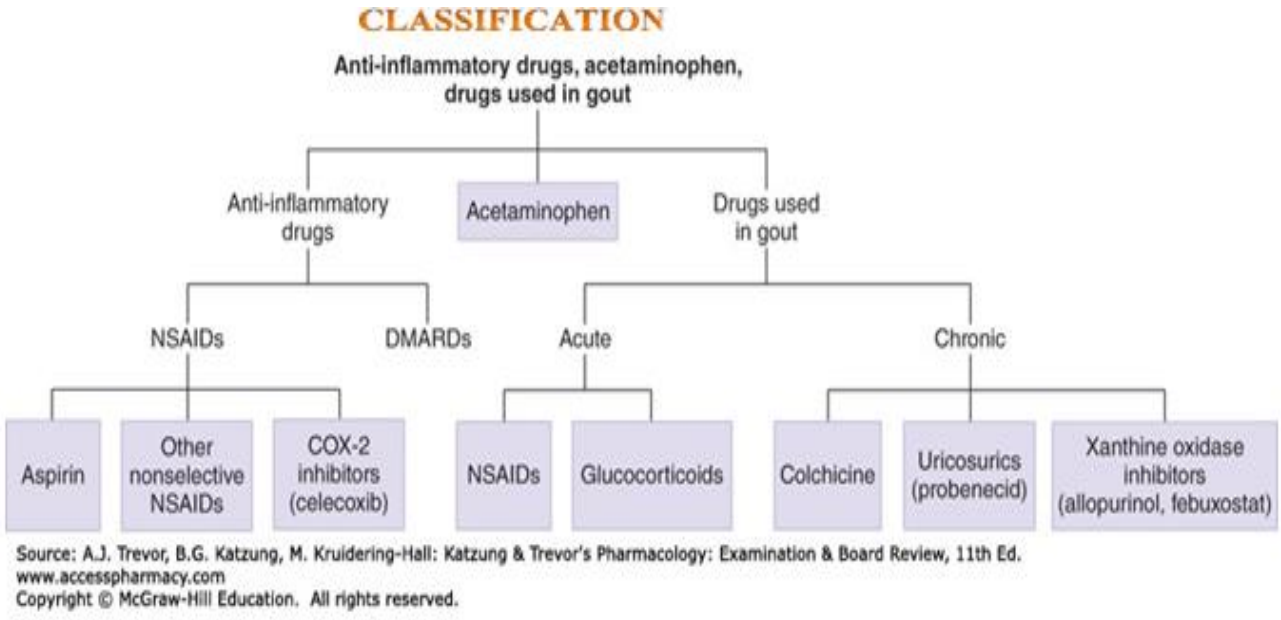

Figure 3:Classification of Drugs used in gout

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CLINICAL PHASES OF GOUT

There are four recognized clinical stages in the development of gout, namely asymptomatic hyperuricaemia, followed by the acute gouty attack or recurrent gout, then the intercritical period and, lastly, chronic tophaceous gout [11-15].

1. *Asymptomatic Hyperurecemia*

Asymptomatic hyperuricaemia appears to have adverse cardiovascular and/or renal effects. Is it possible that serum urate-lowering therapy could decrease these adverse effects? The LIFE study, in which Losartan decreased adverse cardiovascular outcomes, is perhaps an example of this. Losartan is an angiotensin receptor blocker, but the authors of the study attributed the decreased adverse cardiovascular outcomes to Losartan's urate-lowering properties. Numerous risks are associated with the prophylactic treatment of asymptomatic hyperuricaemia, including the induction of gout flares, but there is also the possibility that prophylactic treatment at this stage would prevent progression to acute/recurrent gout. However, the use of prophylactic treatment for asymptomatic hyperuricaemia has been discouraged by numerous authors. Lifestyle modification is recommended instead.

2. *Acute Gouty Arthritis*

The acute phase of gout is self-limited and characterized by recurrent attacks of synovitis (articular inflammation) that present with pain, erythema, and swelling, most frequently in the large toe but other joints, tendons, bursae or other areas may be involved.

Primary treatments for acute gout attacks have included non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids (intraarticular), colchicine, and pituitary adrenocorticotropic hormone (ACTH, specifically animal-derived ACTH preparation) for the control of pain and inflammation [16-20].

3. *Chronic Gout*

Although initial episodes may be brief and rare, acute episodes may increase in frequency and duration over time and lead to the development of chronic gout. In addition to more frequent attacks, chronic gout may be associated with deposits of uric acid crystals known as tophi.

Tophi may develop in joints, cartilage, bone, and auricular or other cutaneous tissues. The average interval between the onset of gout and appearance of tophi, in the absence of treatment, is approximately 10 years.

4. *Intercritical gout*

In a study of the uricosuric drug, probenecid, it was found that 70% of intercritical gout patients with a serum urate level of above 9 mg/dL had one or more gouty attacks in one year. Studies performed with the drugs allopurinol, benzbromarone and febuxostat have all shown that lowering serum urate levels to below 6 mg/dL decreases gouty attacks, depletes monosodium urate crystals in the joints, inhibits the formation of new tophi and decreases the size of existing tophi [21-22].

5. *Lifestyle Changes*

Non-pharmacologic methods advocated for management of chronic gout include a combination of lifestyle changes, including weight loss, exercise, hydration, and dietary changes. Such changes include reduction of dietary purines and alcohol intake, based on observational studies assessing associations between dietary components and risk for gout or trials assessing the effect of specific foods or supplements on serum uric acid levels. Dietary risk factors for gout have been postulated to include alcohol consumption, as well as consumption of meat, seafood, sugar- sweetened soft drinks, and foods high in fructose, whereas dairy foods and coffee have been associated with a lower risk of incident gout and in some cases a lower rate of gout attacks (flares). The evidence for the efficacy of specific dietary changes in managing gout (preventing attacks) is a topic of this review [23-24].

6. *Pharmacologic Agents*

Pharmacologic management of chronic gout consists primarily of agents that lower serum urate. These agents include xanthine oxidase inhibitors (XOIs- allopurinol and febuxostat) to reduce serum urate production; uricosurics (probenecid), which prevent renal reabsorption of uric acid (and increase urinary uric acid excretion); and uricases, which stimulate the breakdown of uric acid (pegloticase). These agents can be used alone or in specific combinations (e.g., XOI plus probenecid). Pegloticase will not be included in this review because it would not be prescribed in a primary care setting [25].

Table 1: lists the drugs used to treat gout and notes the ones covered in this systematic review.

Drug Class	Agent (Generic/Brand)	Manufacturer
1. **Anti- agents for gout attack inflammatory**	**NSAIDs** (diclofenac, ibuprofen, COX- 2 inhibitors)	Numerous
	Corticosteroids/adrenocorticotropic Hormone (ACTH) formulations	Numerous
	Colchicine/USP authorized generic	Takeda
	IL/1B Receptor antagonist: Anakinra/Kineret	Sopi
2. **Urate Lowering Agents**	**Uricosurics:** Probenecid/Benemid	Multiple
	Xanthine Oxidase Inhibitor: Allopurinol	Prometheus Labs
	Febuxostat: Uloric	Tejin Pharma Ltd,Takeda
	Uricase: Pegloticase	Crealta
	Combination Agents; Colchicine-Probenecid/Proben-C	Merck

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These agents will not be considered in this review, because these are not FDA approved for treating gout or are not prescribed in primary care setting [26-30].

Several interleukin-1ß-inhibitory anti-inflammatory agents currently approved for treatment of rheumatoid arthritis are in Phase II and III trials for treatment of gout, including anakinra, canakinumab, and rilonacept, and will not be included in this systematic review, because they are not prescribed in the primary care setting (see below). These treatments do not act by lowering serum urate levels. Additional off-label agents that have been proposed as useful in the management of gout include the lipid lowering agent, fenofibrate; the angiotensin 2 receptor blocker, losartan; estrogen; and calcium channel blockers (in patients being treated with these agents for other indications).

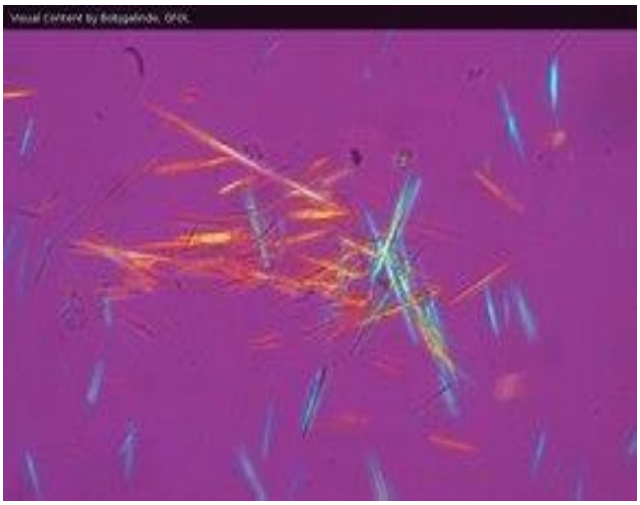

Figure 4: Strongly negative birefringent crystal of gout (monosodium urate monohydrate crystals, MSUM).

PATHOPHYSIOLOGY

Gout initially presents as an episode of acute inflammatory arthritis, most commonly involving the first meta-tarsal-phalanx joint, a condition commonly referred to as podagra. Typical attacks during the first few years last 7 to 14 days before resolving. Although the primary risk factor for gout is hyperuricemia, not all patients with hyperuricemia go on to develop clinical gout; hyperuricemia that does not progress to gout is known as asymptomatic hyperuricemia. Patients with asymptomatic hyperuricemia may or may not have evidence of urate deposits in their joints (as documented by advanced imaging methods). The causes of gout are unclear but appear to be multifactorial, including a combination of genetic, hormonal, metabolic, and dietary factors. Family history, advancing age, male sex, or, in women, early menopause have been associated with a higher risk of gout and/or gout attacks (flares)

Uric acid is formed from the breakdown of purines. Increased uric acid production may be caused by various factors, including nutritional, haematological and genetic factors. Other miscellaneous factors, such as obesity and excessive alcohol consumption, also increase urate production. While certain medications, such as some cytotoxic drugs, may increase uric acid levels in the body, other medications, such as cyclosporine, may decrease the renal excretion of uric acid. Various other renal, metabolic and genetic factors also decrease the excretion of uric acid [31-35].

Hyperuricaemia is caused by an imbalance in the rates of production and excretion of uric acid. This causes the body fluids to become supersaturated with uric acid, which means a level of 6.8 mg/dL. In men and postmenopausal women, hyperuricaemia is defined as a serum uric acid level of greater than 7.0 mg/dL. In premenopausal women, hyperuricaemia is characterised by a serum uric acid level that is greater than 6.0 mg/dL.

Hyperuricaemia causes an accumulation of monosodium urate crystals, which are deposited in the supersaturated body fluids and then are deposited in tissues and around joints during the asymptomatic hyperuricaemic gout stage. The monosodium urate crystals form tophi. The tophi cause inflammation, which leads to the symptoms of an acute gouty attack. The presence of tophi can lead to soft tissue damage and destruction of the afflicted joint, which can cause the deformities associated with gout. However, it is important to note that, while hyperuricaemia is a risk factor for gout, not all patients with hyperuricaemia develop gout. Many medicines prescribed for the treatment of gout patients specifically target hyperuricaemia.

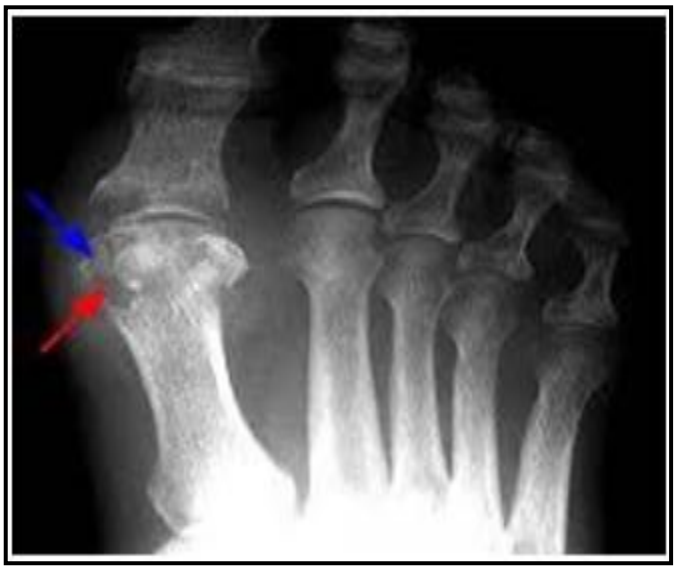

Figure 5: X-ray of toe of patient with chronic gouty arthritis with clear punch of lesions.

DIAGNOSIS

An accurate diagnosis of gout forms an important part in accurately assessing and interpreting the results of clinical trials. An incorrect diagnosis would lead to an incorrect interpretation of the results [36-40].

The main diagnostic features for gout is the recurrent attack of acute mono arthritis of the 1st metatarsophalangeal or tarsal joints with maximum inflammation producing significant redness developing very acutely within hours and in the presence of tophus. There are many important clinical features which are highly suggestive of gout such as the presence of tophi and the involvement of the 1st MTP joint with significant joint pain, redness, swelling, the development of unilateral podagra (involvement of the big toe), the development of the attack at night with the maximum inflammation within one day and the previous response to colchicine. The occurrence of the acute attack in male patients with a high BMI above 25 kg/m2 is another feature which is highly suggestive of gout.

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1. ***Chronic gouty arthritis with tophi***

The laboratory finding which is associated with the high likelihood of gout is the presence of serum uric acid level of >7.06 mg/dl (420 µmol/l) in males and >5.72 mg/dl (340µmol/L) in females and the presence of GFR of >60 ml/min. However, the most important diagnostic test is the identification of the crystal itself, the monosodium urate monohydrate crystals (MSUM) from synovial fluid analysis [41-43].

2. ***Strongly negative birefringent crystal of gout (monosodium urate monohydrate crystals, MSUM).***
3. ***Gout with the involvement of the 1st MTPs (Podagra=Moth)***

Recently, crystals could be easily identified by imaging, which is one of the most advances in non-invasive crystals identification methods. The crystals deposits could be clearly identified by the use of the dual energy CT imaging or by ultrasound through seeing double contours punctiform deposits in synovial membrane which carries a high likelihood of gout. Both ultrasound and dual energy CT finding showed better performance than most of the clinical features. Convectional radiography could abnormal in recurrent attacks or in chronic form of gout. It shows joint destruction with punchout erosions and joint destruction.

4. ***Patient with chronic gouty arthritis with clear punch out lesions.***

Another criteria is clinical gout diagnosis (GCD)

Clinical gout diagnostic criteria (CGD):

The cut-off of ≥ 4.0 carries a high likelihood for the diagnosis of gout:

1. Acute attack of gout
2. Mono/oligoarthritis
3. Rapid progression of pain and swelling (within 24 hours)
4. Podagra (the involvement of big toe)
5. Erythema
6. Unilateral tarsitis
7. Tophi (probable) 8. Hyperuricaemia (>7 mg/dl for male and >6 mg/dl for female).

PREVENTION

Monosodium urate crystal formation is reversible, and crystals will dissolve when the sUA level drops below the limit of solubility (~6.8 mg/dL). This will result in the disappearance of gout flares and a reduction in the size and number of tophi. The lower the sUA level, the faster the crystal deposits (and tophi) resolve. Therefore, the goal of long-term gout management is to lower the sUA level below the limit of solubility. In addition, the management of patients with gout should include prevention and treatment of associated cardiovascular and other diseases

Evidence from randomized, blinded studies is lacking regarding alteration of lifestyle factors translating into improved outcomes in patients with gout. However, diet, exercise, and weight loss have been associated with a modest reduction in the sUA level in some clinical trials; therefore, every patient should be encouraged to make such changes as best as possible [44-45].

Lifestyle management (eg, reducing excess body weight, regular exercise, smoking cessation, and avoiding excessive alcohol and sugar-sweetened drinks) has a greater role in reducing the risk and optimizing management of life threatening co morbidities in patients with gout.

TREATMENT [21, 46-54]

PATHOGENESIS OF HYPERURICAEMIA

Serum urate concentrations in women are lower than in men. There is a normal distribution but with an upper skew. Hyperuricaemia is often asymptomatic and does not need treatment. Most gouty individuals lie within the upper range and outside the normal population range, which in the UK is <0.42mmol/l for men and <0.36mmol/l for women. Gout can, however, develop as long as the urate level is above the supersaturation level, which is >0.36mmol/l at 35°C and>0.30mmol/l at 30°C. Thus, a normal urate does not absolutely preclude the diagnosis.

Treatment is based on the particular clinical phase of gout that the patient is experiencing. Treatment for acute gout is aimed at reducing the pain and inflammation that accompany acute gout attacks, whereas treatment for the intercritical period of gout aims to maintain low levels of serum uric acid in order to prevent the formation of tophi. Chronic tophaceous gout is treated by initiating long-term hypouricaemic therapy. There currently is no evidence for the efficacy of treatment of asymptomatic hyperuricaemia. Treatment can also be divided into three groups, based on the purpose of the treatment. One group of drugs is intended to treat acute gout and the attacks that occur during this phase. The second group of drugs is used for the prevention of recurrences of gout, while the third group of drugs is aimed at lowering serum uric acid.

Non-steroidal anti-inflammatory drug (NSAID), glucocorticoids and colchicine are all evidence based, cost effective treatment for the acute attack of gout. All the above agents are non-selective inhibitors for the neutrophil driven inflammation that occurs in acute gout.

1. ACUTE GOUT

1. ***NSAIDs***

These are considered to be the drugs of choice to treat acute gout. NSAIDs are also used to prevent the occurrence of future attacks. In the treatment of an acute attack, high doses of NSAIDs are prescribed during the first three to four days of an attack. Thereafter standard doses are prescribed for maintenance. In a study comparing the use of rofecoxib, diclofenac sodium and meloxicam in the treatment of acute gout, rofecoxib was found to be the most effective.

Etoricoxib and lumiracoxib are two cyclo-oxygenase 2-selective inhibitors that have the same efficacy as NSAIDs in the treatment of acute gout. However, all NSAIDs are associated with risks of potential adverse effects and drug interactions particularly in elderly patients and those with chronic kidney disease or diabetes and they should be avoided in patients with renal impairment [46-50].

-Diclofenac 100mg immediately then 50mg every 8 hours

-Naproxen 500mg immediately then 500mg every 8–12 hours

-Indomethacin 50mg every 6–8 hours.

2. ***Colchicine***

Colchicine has been found to be efficacious when compared to placebo in randomized controlled trial, but low dose of colchicine carries a better safety profile as compared to the high dose. Colchicine has a very small

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therapeutic index and as such can easily cause the gastrointestinal side effects associated with colchicine, namely nausea, cramping and diarrhea. Colchicine accumulates in patients with renal insufficiency, and as such is only recommended in patients with mild to moderate renal failure. Long-term side effects of colchicine include neuropathy, neutropenia and vacuolar myopathy. These long-term side effects require monitoring.

Both NSAIDs and colchicine can be used for the prophylaxis of gout. Colchicine is recommended over NSAIDs in gout patients with renal failure and is also used as prophylaxis in the treatment of gout. Also, there is a drug interaction between CYP3A4E-glycoprotein inhibitors and colchicine in particular in the presence of hepatic and renal dysfunction which should be taken into consideration on using colchicine. In mild to moderate renal impairment with GFR >30 ml/min colchicine can be used in reduced dose.

-Colchicine 1000µg loading dose then 500µg every 6–8 hours, tapering [51].

3. *Prophylaxis against Acute Gout Attacks*

- NSAIDs, with gastroprotection if indicated may be used.
- Diclofenac 50mg twice daily
- Naproxen 500mg twice daily
- Indomethacin 50mg twice daily
- Colchicine 500–1000µg daily
- Prednisolone 5–10mg daily

4. *Urate Lowering Agents*

Allopurinol

In patients with normal kidney function, allopurinol is initiated at a low dosage (100 mg/d) and increased by 100 mg/d increments every 2 to 4 weeks if required, to reach the uricemic target.

In patients with renal impairment, EULAR guidelines recommend adjusting the allopurinol dosage downward due to the risk of serious cutaneous adverse events. ACR guidelines, however, recommend increasing allopurinol until the sUA target level is reached in these patients, while monitoring for drug toxicity. The ACR recommendation is based on several small series of patients in which no increased incidence of severe reactions was demonstrated in patients whose allopurinol dosages were progressively titrated above those recommended, based on creatinine clearance and the level of renal impairment.

Dose should be adjusted as per renal function. In treating patients with gout, we have to keep in mind that allopurinol at a dose of 300 mg daily will only achieve the serum urate target level of <6 mg/dl (360µmol/l) in around 40% of patients with normal renal function.

- Titrate the dose with the serum urate level.
- Allopurinol 100–300mg, increasing to maximum 900mg daily (lower doses in renal impairment).
- Sulfinpyrazone 200mg, increasing to maximum 800mg daily (avoid in renal disease or with renal stones)
- Benzbromarone 50mg, increasing to 200mg daily.

5. *Newer Urate-Lowering Agents for Refractory Gout*

1. *Febuxostat*

Febuxostat is approved by the FDA at a starting dosage of 40 mg/d, uptitrated to 80 mg/d if patients do not achieve a sUA level <6 mg/dL after 2 weeks. ACR guidelines suggest up titration to as much as 120 mg/d (an investigational dosage) if necessary to achieve the target sUA level.

Febuxostat is approved by the FDA at a starting dosage of 40 mg/d, up titrated to 80 mg/d if patients do not achieve a sUA level <6 mg/dL after 2 weeks. ACR guidelines suggest up titration to as much as 120 mg/d (an investigational dosage) if necessary to achieve the target sUA level. Its main adverse effect is rash which could occur in 2% of the patients using it, but without any reported severe reaction. Diarrhea and elevated liver enzyme occur also in a few patients.

There is some recent report to suggest that there is no difference between allopurinol and febuxostat with regards to cardiovascular diseases risk. As compared to allopurinol, febuxostat carry a higher risk of inducing acute gout flare on its introduction. Also as it is xanthine oxidase should not be used with azathioprine [52].

2. *Pegloticase*

-Pegloticase must be administered under supervision at an infusion center, due to the high risk of serious allergic reaction, including anaphylaxis.

-Pegloticase is administered as an 8-mg IV infusion every 2weeks, and should not be combined with other urate-lowering medications.

- Febuxostat 80–120mg daily
- Pegloticase (only under specialist care)
- Anakinra (only under specialist care)

6. *Dietary and lifestyle advice for gout*

- Lose weight gradually to achieve an ideal body weight

-Avoid foods that contain purines

– Liver, kidneys, shellfish and yeast extracts

- Reduce alcohol intake and avoid beers, fortified wines and spirits
- Avoid fruit juices and fructose-containing soft drinks
- Move to a low saturated fat diet
- Increase the intake of vegetable

Furthermore, diet and lifestyle modification has the dual benefit of not only improving gout symptoms, but also many of the diseases associated with gout, such as hypertension, hyperlipidemias and diabetes mellitus [53-54].

CONCLUSION

Hyperuricaemia, one of the major risk factors for the development of gout, is caused by an imbalance between the rates of production and excretion of uric acid. An excess of uric acid thus supersaturates the body fluids, leading to the deposition of monosodium urate crystals in tissues and joints, which in turn leads to the initiation of an acute attack of gout. Gout is a painful, occasionally debilitating disease and is divided into four clinical phases, namely asymptomatic hyperuricaemia, acute gouty attack or recurrent gout, intercritical gout and chronic tophaceous gout. Each of these phases has various possible treatments. NSAIDs, colchicine, corticosteroids and corticotrophin are used for the treatment of acute gout attacks in order to relieve pain. NSAIDs and colchicine are prescribed for the prophylaxis of gout. Allopurinol, probenecid and other uricosurics are used in long-term hypouricaemic therapy in order to decrease serum uric acid levels and to prevent long-term damage to joints. Due

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to the untoward and, in some cases, potentially life threatening side effects of the various gout therapies, there most definitely is a need for novel therapies to treat gout. Detailed patient evaluation forms the basis of a clinician's decision on the choice of therapy for gout patients. As such, more attention needs to be given to patient evaluation in order to personalize gout therapy for every patient. Emphasis should also be placed on the importance of diet and lifestyle modifications in addition to gout therapy so as to prevent gout and acute gout attacks.

With regard to the diagnosis, we feel that the most important diagnostic test is the identification of the crystals by joint aspiration, ultrasound imaging or the use of dual energy CT scan. However, the diagnosis of gout is likely in the presence of tophi, podagra and the rapid onset of the development of the acute attack with good response to colchicine. In patients with cardiovascular disease, Febuxostat should be used with caution. In patients with renal impairment, allopurinol should be stated at a lower dose of 50 mg once a day and then the dose titrated up according to the GFR. Benzbromarone is another valid option for patients with chronic kidney disease with the GFR as low as 20ml/min. Initially, we have to treat the patients with to a target of serum urate level to <300 µmol/L with the regular measure of serum uric acid level to titrate the dose as needed. However, for patients who have more severe disease with significant tophi, sustained reduction in serum uric acid well below 300µmol/L may be needed until everything is resolved. However, the long-term risk for suppression the antioxidant activities of uric acid at a very low level is uncertain and we are still awaiting for the study to confirm whether there is any clear risk with significant reduction of serum uric acid level in the long term such as the development of dementia or cardiovascular risk.

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