Abstract
Gout is an ancient disease dating back to the time of Babylon. Its name came from the Latin word gutta (drop), points to the belief that a poison falling into the joint drop by drop causing the disease. More recently, it became more prevalent and has increasing complexity which could be related to the development of metabolic syndrome and longevity. It is still on the increase and its prevalence has not plateaued yet. We also found that there are more patients refractory to conventional treatment. Clinically, gout is a syndrome caused by an inflammatory response to monosodium urate monohydrate crystals (MSUM) formed in humans with elevated serum urate concentration (hyperuricaemia). It could present with either acute relapsing attacks or it comes in chronic form. The acute attacks usually cause very severe inflammatory arthritis which is usually self-limiting and could take weeks before it completely settles. In the chronic form the MSUM crystals are usually deposited in and around the joint mainly in the form of what we call tophi leading to the bone and joint destruction. Gout usually comes as part of a complex condition associated with metabolic syndrome, hypertension, heavy alcohol intake, renal impairment and diuretic use. Some people have asymptomatic hyperuricaemia which could cause uric acid urolithiasis. This review will cover various aspects of gout including the best way of making a confident diagnosis, the role of co-morbidities including the metabolic syndrome, medications used to treat the acute attack and the factors influencing their choice, the role of lifestyle changes, the use of urate lowering therapies and factors influencing their choice with the timing of introducing them after the acute attack, how tophaceous gout should be managed, managing asymptomatic hyperuricaemia and its controversy, the treatment target for managing gout with some highlight about the new therapeutic strategies and option for management of gout.
**Background**

Gout is the most common inflammatory type of arthritis in men affecting 1-2% of adults in Western countries\(^1\), with male to female ratio of 3.6:1, but rare in pre-menopausal women and its incidence and prevalence increases with age\(^2\). It is characterised 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\(^3\).

Gout manifests itself as microscopic or macroscopic soft tissue deposit of monosodium monohydrate crystal (tophi) which triggers severe, but self-limiting acute attack of arthritis with excruciating pain. In chronic cases crystals deposition could promote a chronic type of inflammation and erosive arthritis. Patients with hyperuricaemia also could develop uric acid urolithiasis which is usually promoted by urine acidity\(^4\). Asymptomatic hyperuricaemia is common, but there is no study to confirm the incidence or prevalence of its occurrence. Patients with hyperuricaemia have increased incidence of developing clinical gout when the serum urate level exceeds 9 mg/dl (>530µmol/l); however, we have to keep in mind that only a minority of patients with hyperuricaemia actually develops gout\(^5\) and acute intermittent gout can still occur with lower level of serum urate than 9 mg/dl. Although clinically there are a few patients who develop tophi which could be seen, but a significant number of patients with gout have microscopic or non-clinical type of tophi in joints, periarticular area and various soft tissues. These microscopic tophi and crystals including the renal uric acid calculi could be easily seen by the dual energy CT scan or with high resolution ultrasound, which is one of the recent advances in identifying gout crystals and making a diagnosis of gout\(^6\).

Although there is clear evidence that soluble urate is an antioxidant\(^7\), however, urate can also be converted to pro-oxidant which could affect adversely the vascular endothelial cell function\(^8\). In observational studies, gout and asymptomatic hyperuricaemia shown to be directly promoting hypertension and vascular disease\(^9\). 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\(^10\). 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\(^7\).

**Keywords:** Gout, hyperuricaemia, diagnosis, management, recent advances.

**Diagnosis of Gout**

The main diagnostic features for gout is the recurrent attack of acute monoarthritis of the 1\(^{st}\) 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 (Fig 1) and the involvement of the 1\(^{st}\) MTP joint with significant joint pain, redness, swelling (Fig 2), 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\(^11\). The occurrence of the acute attack in male patients with a high BMI above 25 kg/m\(^2\) is another feature which is highly suggestive of gout\(^11,12\). However, we have to keep in mind that any individual clinical feature showed no diagnostic performance probably with the exception of the presence of tophi and excellent exception of the presence of tophi and excellent response to colchicine.
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\(^{\text{(11,12)}}\). However, the most important diagnostic test is the identification of the crystal itself, the monosodium urate monohydrate crystals (MSUM) from synovial fluid analysis (Fig 3).

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\(^{\text{(13)}}\) or by ultrasound through seeing double contours punctiform deposits in synovial membrane which carries a high likelihood of gout\(^{\text{(14,15)}}\). 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 (Fig 4). It shows joint destruction with punch-out erosions and joint destruction.
Several diagnostic criteria have been developed for gout (Table 1).

**Table 1: Rome and New York diagnostic criteria for gout.**

### 1963 Rome criteria for diagnosis of gout:
- Serum urate concentration >7 mg/dl in males and > 6 mg/100 ml in females
- Painful joint swelling with abrupt onset clearing in 2 weeks initially
- The presence of urate crystal in synovial fluid
- The presence of tophi
  - (≥ criteria needed)

### 1968 New York criteria for diagnosis of gout:
Chemical or microscopical demonstration of urate crystals in the synovial fluid or in the tissue or the presence of two or more of the following criteria:
1. Two or more attacks of painful limb joint swelling with abrupt onset, remitting in 2 weeks initially
2. A single such attack involving the great toe (podagra)
3. Response to Colchicine, with major disease and inflammation in 48 hours
4. The presence of tophus

However, both of these criteria proved to be unsatisfactory. In 1975, the American Rheumatism Association developed their criteria for the diagnosis of primary gout (Table 2).

**Table 2: ARA criteria for acute primary gout.**

### ARA criteria for acute arthritis of primary gout:
1. >1 attack of acute arthritis
2. Maximum inflammation developed within one day
3. Monoarthritis attacks
4. Redness observed over joints
5. 1st MTP joint painful or swollen
6. Unilateral 1st MTP joint attack
7. Unilateral tarsal joint attack
8. Tophus (proven or suspected)
9. Hyperuricaemia
10. Asymmetrical swelling within the joints on x-ray
11. Sub-cortical cyst without erosion on x-ray
12. Monosodium urate monohydrate microcrystals in the joint fluid during an attack
13. Joint fluid culture negative for organism during an attack

3. The presence of 6 out of 12 clinical, laboratory and radiographic features excluding item 12. The above criteria of ARA carry sensitivity of 98%.

Other diagnostic criteria for acute gouty arthritis in primary care without the use of synovial fluid analysis developed by Janssen 2010 (Table 3).

**Table 3: Primary care diagnostic criteria for gout.**

<table>
<thead>
<tr>
<th>Items</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Male sex</td>
<td>2</td>
</tr>
<tr>
<td>2. Self-reported attack</td>
<td>2</td>
</tr>
<tr>
<td>3. 1st MTP involvement score</td>
<td>0.5</td>
</tr>
<tr>
<td>4. Maximum inflammation within one day</td>
<td>2</td>
</tr>
<tr>
<td>5. Redness of the joints</td>
<td>2.5</td>
</tr>
<tr>
<td>6. Co-morbidity, hypertension or cardiovascular disease</td>
<td>1.5</td>
</tr>
<tr>
<td>7. Serum uric acid &gt;5.88 mg/dcl</td>
<td>3.5</td>
</tr>
</tbody>
</table>

The maximum score is 13 and the proposed cut of values for Janssen’s criteria:
- ≤4: gout is very unlikely and ≥ 8.0 gout is likely

Another criteria is clinical gout diagnosis (GCD) (Table 4).

**Table 4: Clinical gout diagnostic criteria.**

### Clinical gout diagnosis (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) | |

It is very essential to consider the diagnosis of septic arthritis in any patients with possible gout, which could occur on its own or even in combination of gout. Accordingly, as part of any diagnostic work up synovial fluid should be send for gram stain and culture and sensitivity and if there is suspension of septic arthritis, patient should be treat as such till culture and sensitivity result became available. The confusing thing is that patients with gout and pseudogout may have leucocytosis and...
fever, but usually the onset is very acute over hours in crystal arthropathy as compared to acute septic arthritis which is over 1-3 days.

**Management for the acute attack of gout**

Non-steroidal anti-inflammatory drug (NSAID), glucocorticoids and colchicine are all evidence based, cost effective treatment for the acute attack of gout\(^{19,20,21}\). All the above agents are non-selective inhibitors for the neutrophil driven inflammation that occurs in acute gout\(^{22}\).

1. **Colchicine**

Colchicine has been found to be efficacious when compared to placebo in randomised controlled trial\(^{23}\). It has also been very clearly confirmed that high and low dose of colchicine has similar effectiveness, but low dose of colchicine carries a better safety profile as compared to the high dose\(^{24}\).

Accordingly, high dose of colchicine should be avoided which carries significant gastrointestinal side effects. The usual dose should be 2-4 tablets a day, which has similar efficacy, but with much less risk of side effect. Intravenous colchicine is associated with potential fatal adverse event and should be avoided. 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.

2. **Non-steroidal anti-inflammatory drugs**

Most of non-steroidal anti-inflammatory drugs have similar efficacy with regard to treating acute attack of gout\(^{25,26,27}\). Also it has been found that Cox 2 inhibitor has the same efficacy as conventional non-steroidal anti-inflammatory drugs, but with better GI profile\(^{28,29}\). 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\(^{19}\).

3. **Glucocorticoids**

There is no placebo controlled trials for systemic glucocorticoids in gout, but when compared to NSAIDs, glucocorticoids are as effective as NSAIDs and has better safety profile\(^{21,30,31}\). It has also been found that the ACTH 40 IU intramuscular has significantly faster onset of action as compared to NSAIDs with complete relief of the pain in 3 versus 24 hour respectively\(^{30}\). Corticosteroid is a good option for patient with renal impairment or for those at high risk from NSAIDs induced GI side effect. Oral corticosteroid could be used in a dose of around 30 mg daily for about five days to treat any acute gouty attacks. This option is also important for those with moderate to severe chronic kidney disease. Intra-articular glucocorticoids injection is another option which can give an excellent and quick pain relief but this should be avoided in patients with suspected septic arthritis.

4. **Biologics**

Anti-interleukin-1 drug (canakinumab in a dose of 150 mg is more effective than a single IM glucocorticoid steroid injection of triamcinolone 40 mg and has a similar safety profile\(^{32}\).

**Prophylaxis for gout through serum urate lowering agents:**

Any patients with frequent attack of gout possibly two or more a year, patients who have tophi, uric acid over-presentation, have urolithiasis, have severe or difficult to treat attacks or with chronic persistent of gouty arthritis, should routinely be treated with urate lowering therapy.

There are various options and strategies which have been recommended to limit the gout flares and to suppress hyperuricaemia such as an achievement of ideal weight, to decrease the insulin resistance, moderation of alcohol consumption and diet control. They all have some effect on prophylaxis\(^7\). However, the
above measures at its best will achieve only modest reduction in the serum uric acid level which could be up to 1 mg/dl or up to 15%. Accordingly, pharmacological options with the urate lowering agent are necessary for most patients with gout. Currently, we have many options with the urate lowering agents including allopurinol, febuxostat, uricosuric agents and uricases. However, the most important advance in the management of gout is the strategy to treat to target, in which the serum uric acid level should be our main target. The target for the serum uric acid should be dropped to a level of ≤300µmol/l (as per the British Society of Rheumatology guidelines\textsuperscript{[33]}, or the level of ≤360 µmol/l as per EULAR guidelines for management of gout\textsuperscript{[34]}. Americans use the same level as EULAR with a target serum urate to be <6 mg/dl (360µmol/l) and this has been very well established\textsuperscript{[35]}. However, a temporary lower serum urate level, such as <4 mg/dl (240µmol/l) may be needed for a limited period for tophaceous debulking in patients with chronic gouty arthritis\textsuperscript{[36]}.  

1. Allopurinol
It is the most well-established and cheap urate lowering agent available and it should be our first line option. Allopurinol dose should be titrated from a starting dose of 100 mg daily and increase by 100 mg monthly until the target serum urate level is achieved with up to a maximum of 800 mg daily\textsuperscript{[37]}. 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) and in around 40% of patients with normal renal function\textsuperscript{[38,39]}. Increasing the allopurinol dose up to 600 mg daily will achieve the target serum urate level in about 80% of patients who have preserved renal function\textsuperscript{[40]}. Unfortunately, the majority of the patients are still under treated with allopurinol. In a recent audit in 2010 showed that only 9% have achieved the BSR serum uric acid target level of <300µmol/l. Re-audit of the same cohort in 2011-2012, with the application of the suggested recommendations and with the establishment of the specialist gout clinic showed that the achievement of the target with regard to the BSR increased to 29% and for the EULAR target only 60% of the patients achieved the EULAR target level of serum uric acid of <360µmol/L\textsuperscript{[41]}. The allopurinol dose should be adjusted as per the renal function but unfortunately the dose adjustment will not only fail to prevent allopurinol hypersensitivity but also fails to adequately normalise the serum urate level in most of the patients\textsuperscript{[42]}. In patients with renal impairment allopurinol should be started at a lower dose of probably 50 mg once a day and the dose should be increased gradually after that. Allopurinol is contraindicated in patients on azathioprine as azathioprine is metabolised by xanthine oxidase enzyme which is inhibited by allopurinol which will increase azathioprine toxicity.

2. Febuxostat
Like allopurinol, this is a selective xanthine oxidase inhibitor which does not have purine-like structure\textsuperscript{[38,39]}. Febuxostat is usually metabolised by liver. Accordingly, unlike allopurinol, renal elimination has a minor role in febuxostat. Its main adverse effect is rash which could occur in 2% of the patients using it, but without any reported severe reaction. Diarrhoea and elevated liver enzyme occur also in a few patients. Febuxostat has been approved at a dose of 80 mg daily in the States and up to 120 mg daily in Europe. In view of its cost as compared to allopurinol, febuxostat is reserved for patients with allopurinol hypersensitivity, intolerance or treatment failure. Febuxostat at a dose of 80 - 120 mg achieve the target serum urate level of <6 mg/dl (360µmol/l), whereas most of the patients on allopurinol 300 mg usually fail this target\textsuperscript{[38,39]}. In patients with chronic kidney disease stage 2 and 3, febuxostat at a dose of 40-80 mg is superior to allopurinol at a dose...
of 200-300 mg daily in achieving the target serum urate level <6 mg/dl (360µmol/l).\textsuperscript{39} Febuxostat may be used without dose adjustment in patients with mild to moderate renal impairment. However, there is some worry in their use in patients with established cardiovascular diseases and should be only used in caution in these patients, although 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.

3. Uricosuric therapy
Other urate lowering medication which could be used is the uricosuric agents such as sulfinpyrazone, probenecid and benz bromarone. These agents enhance renal uric acid excretion primarily by decreasing the urate reabsorption in the renal tubules. In patients with adequate renal function, uricosuric agent can be effective.\textsuperscript{43} Uricosuric therapy can also provide extra benefit in combination with xanthine oxidase inhibitor in patients who fail to achieve the target serum urate level.\textsuperscript{35} Uricosuric agents’ main disadvantage is related to the increase risk of urolithiasis in particularly in acid urine which is unfortunately a feature of metabolic syndrome which could be associated with gout.\textsuperscript{4} Sulfinpyrazone should be used in a dose of 100-200mg daily with food with gradual increment every 3 weeks up to 600mg daily. Probenecid is much less used. Benz bromarone at a dose of 50-200 mg incremental dose is an important uricosuric agent which could be used in patients with chronic kidney disease with the GFR as low as 20ml/min. Accordingly, it is a valid option for patients with significant renal impairment and in those who cannot tolerate other urate lowering agent or when the s uric acid level target cannot be achieved by using other medications. Benz bromarone is a highly effective with 100% of patients achieving target urate levels as compared to Allopurinol.\textsuperscript{44} Benz bromarone is a cheap medication, but it is not available in some areas. Its main disadvantage is the association with hepatotoxicity, with a risk of 1:17000; accordingly LFTs monitor is essential prior and after the initiation of the treatment with benz bromarone and before any increase in its dose. All uricosuric agents should be avoided in patient with urolithiasis and patient should be very well hydrated during their use. Low dose aspirin reduce their effect. Urine alkalisation is advisable in particular in patients with renal impairment or metabolic syndrome.

4. Biologic “uricases” agents
It only could be used in a very limited situation to enable the acceleration of resolution of tophi. Uricases therapy such as pegloticase has been used in the prevention of tumour lysis syndrome and it could be effective in debulking of tophi in chronic gout.\textsuperscript{45} Pegloticase at a dose of 8 mg once every two weeks has been found to drop the serum urate level to <6 mg/dl at six months in 42% of patients with severe gout and to completely resolve tophi in 40% of patients by 25 weeks.\textsuperscript{46} However, these biological agents are usually associated with infusion reaction, increases the risk of acute attack gouty and they may lose benefit over time due to the development of antibodies. Short and long-term safety is not yet clearly defined for uricases therapy and they should only be considered as monotherapy in patients with severe gout resistant to other form of therapy.

**Other issues related to gout control**
The use of losartan and fenofibrate alone or in combination with urate lowering therapies could have an extra value in the prevention and management of hyperuricaemia in patients with hypertension and dyslipidaemia.\textsuperscript{7}
Ideally, all patients with gout or asymptomatic hyperuricaemia should be screened for renal dysfunction, cardiovascular disease and other metabolic syndromes and this should be treated accordingly. The achievement of ideal BMI, the avoidance of high alcohol consumption in particular beer and spirits and tackling other factors related to metabolic syndrome should be part of the prevention and treatment of gout.

Other issues is related to the possibility of precipitating acute attack of gout on introducing the urate lowering therapy and this has been found to be more likely with Febuxostat as compared to allopurinol. Accordingly, prophylaxis therapy should be considered for up to six months on introducing the urate lowering therapy, in particular the febuxostat. Medication which could be used in this scenario includes Colchicine 0.5 mg up to twice a day or a low dose of non-steroidal anti-inflammatory medication or even IM long-acting corticosteroid. With regard to allopurinol and benzbrromarone the starting dose should be small and titrated gradually to a higher dose which will help to prevent any acute attack while introducing these urate lowering therapies.

Tophi should be managed by achieving a sustained reduction in serum uric acid level to well below 300µmol/L (possibly ≤240µmol/l till all tophi resolved). Surgical intervention should be considered in specific circumstances such as nerve compression, mechanical impingement or sepsis.

Urate lowering therapy should not be used routinely in asymptomatic hyperuricaemia but may be considered in patients with renal impairment to prevent renal deterioration and in patients with marked hyperuricaemia. However, lifestyle factors associated with metabolic syndrome should be addressed in these patients.

Summary of chronic gout management has been given in Table 5.

**In conclusion, recently we have more understanding about gout and its relation to metabolic syndrome.** We know very well that the prevalence and complexity of gout has increased in recent years. 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. 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. In patients with cardiovascular disease, Febuxostat should be used with caution. In patients with renal impairment, allopurinol should be started 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.

References
Review Article
Gout AW Al-Allaf