Review on Treatment of Gout & Hyperuricemia

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Abstract

In the last few decades, both hyperuricemia and gout have increased markedly. Recent studies show new concept into the transporters that handle uric acid in the kidney as well as possible links between these transporters & hyperuricemia. There are changes in the treatment of established hyperuricemia. Febuxostat and PEGuricase are two novel treatments that have been evaluated and shown to be highly effective in the management of hyperuricemia. Monosodium urate (MSU) crystals are the inducers of inflammation. Within the joint, they trigger a local inflammatory reaction, neutrophil recruitment, and the production of proinflammatory cytokines as well as other inflammatory mediators. The uptake of MSU crystals by monocytes involves interactions with components of the innate immune system. The inflammatory effects of MSU are IL-1-dependent and can be blocked by IL-1 inhibitors. These advances in the understanding of hyperuricemia and gout provide new therapeutic targets for the future.

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Introduction

Hyperuricemia and gout is a common metabolic disorder all over the world as well as in Bangladesh[1,2]. Among the countries of the West, in the United States, the overall prevalence of gout and hyperuricemia was 41 per 1000 in 1999 and in the UK the overall prevalence of gout is 1.4%[3,4].

All patients with gout have hyperuricemia (supersaturation of serum for urate) at some point in their disease. However, most hyperuricemic individuals never experience a clinical event resulting from urate crystal deposition. Thus, the diagnosis of gout focuses on the fundamental pathophysiologic events defining the clinical state: tissue deposition of urate crystals; and the accompanying inflammatory and degenerative consequences. Within this framework, hyperuricemia is viewed as a necessary but not sufficient precondition for the development of urate crystal deposition disease, and is to be distinguished from gout, the clinical syndrome. Gout is a common medical problem, affecting at least 1 percent of men in Western countries, with a male: female ratio ranging from 7: 1 to 9: 1. Statistically normal uric acid levels in men and premenopausal women (7 mg per deciliter [416 ìmol per liter] and 6 mg per deciliter [357 ìmol per liter], respectively) are close to the limits of urate solubility (approximately 7 mg per deciliter at 37°C) in vitro, imposing a delicate physiologic urate balance. Hyperuricemia is central to gout but does not inevitably cause disease.

The classic symptom of gouty arthritis is recurrent attack of acute, markedly painful monoarticular or oligoarticular inflammation[77], but polyarticular gout and chronic arthritis can occur. Definitive diagnosis requires the direct identification of urate crystals in the joint and the exclusion of infection. Serum urate levels are frequently normal during attacks of acute gout. The accuracy of clinical diagnosis without crystal confirmation[5] is uncertain. For this reason diagnosis in our country is still a challenge as polarized microscopy is still not widely available.

Asymptomatic hyperuricemia is the term applied to settings in which the serum urate concentration is

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elevated, but neither symptoms nor signs of urate deposition have occurred. Although gout may develop in a hyperuricemic individual at any point, it is likely that two-thirds or more of hyperuricemic individuals will remain asymptomatic. [6-10]

Asymptomatic hyperuricemia alone has not been related to the development of clinically significant renal disease in large cohorts and in itself is not an indication for treatment unless rises above 12 mg/dl. [11] It remains uncertain whether gout and hyperuricemia are independent risk factors for vascular disease in humans. Large epidemiologic studies have shown that hyperuricemia is associated with an increased incidence of CHD and increased mortality in those with and without preexisting CHD[12-15].

Dietary association and contributory factors as long been discussed with gout. Many scientific studies have also been performed. Purine content of food has been the centre of discussion. Higher levels of meat and seafood consumption are associated with an increased risk of gout, whereas a higher level of consumption of dairy products is associated with a decreased risk[16-18]. however strict dietary restriction is no longer recommended.

The goal of therapy in an acute gout attack is prompt and safe termination of pain and disability. While symptoms will resolve without therapy within a few days to several weeks, symptoms improve more quickly with administration of any of a broad array of anti inflammatory drugs, with the most prompt and complete resolution when the treatment is introduced earlier[19,20].

Our aim & objective is to aware physicians & patients regarding pitfalls in the management of Hyperuricemia & gout. They also should be aware of several newer approaches that are emerged in the recent past.

Materials and methods

The material for this review was taken mostly from Rheumatology textbooks & electronic journal "Uptodate." To collect publication PubMed and the Cochrane database of systematic reviews was used. Some other relevant references were collected from personal database of papers on gout.

Clinical Features and Natural Course

There are four phases of gout characterized by asymptomatic hyperuricemia, recurrent attacks of acute arthritis, intercritical gout, and chronic tophaceous gout. Ten to fifteen percent of all the patients having hyperuricemia develop clinical gout[21,22]. After many years of asymptomatic hyperuricemia, patients may experience their first attack of a painful gouty arthritis. A family history of gout is identified in 10–25% of patients. Female patient accounts for just 5–8% of total gout cases. In female, during reproductive age gout is rare; however incidence is equal in both sexes during post menopausal period. Early onset in female is mostly associated with the use of cyclosporine, diuretic, or renal insufficiency, and may present with polyarticular attack[23]. The primary manifestation of acute gouty attack is very painful arthritis, usually monoarticular at first but later may be polyarticular and accompanied with fever. The pain peaks within 1–2 days and usually subsides within 3–10 days even without treatment but in rare occasion may last for a couple of weeks.

First metatarsophalangeal joint (podagra) comprises for at least 50% of initial attack. Eighty percent of patients experience an acute attack of first MTP in their life time. Following the first metatarsophalangeal, the sites of initial attack are, in order of frequency, the insteps, ankle, heel, knee, wrist, finger, and elbow joints. Notably, the proportion of initial ankle joint attacks recently has been increasing[24,25]. The hallmark of gout is the acute attack of inflammatory monoarthritis. Early attacks tend to subside spontaneously, and most of the patients do not have residual symptoms until the next episode. As acute gout tends to be recurrent, a history of previous self-limiting episodes is a helpful point for clinical diagnosis. Atypical presentations of gout include polyarthritis, inflammation of the periarticular structures and febrile reactions. Provocative factors include trauma, alcohol ingestion (particularly beer consumption), initiating urate-lowering drugs, excess purine in the diet, or surgery. The periods between gouty attacks are called interval (or intercritical) gout[77]. In most patients, second attacks occur within 6 months to 2 years. In the series described by Yu, 61% of patients had recurrence within the first year, 27% in 1 to 2 years, 5% in 2 to 5 years, 3% in 5 to 10 years, and 4% had experienced no recurrence at ten or more years. Thus, urate lowering drug is not recommended in first gouty attack rather patient should be kept under observation and if attack is frequent i.e. more than two attacks per year, then urate lowering drug should be started[26,27]. The natural course

of gout remains unclear because there was only one report in the pretreatment era by Gutman. Gutman found severe gout with 44% of 10 Gout and hyperuricemia patients developed tophi, and 30% of patients had demonstrable tophi 5 years after diagnosis of gout, which increased to 50% by 10 years, and up to 72% by 20 years. In the followup series of Gutman, reported by Yu in 1984, there were still 34% of gout patients with tophi[34,28]. In a recent study in Taiwan, 21.1% of hospital patients and 12.7% of community outpatients with gout had tophi[29]. In another large outpatient series reported by Chan, approximately 9% of gout had tophi[30]. Other large series reports on proportions of tophacious gout varied widely. Most reports included only hospital cases, and most patients were post treatment[31,66]. The 1977 American Rheumatism Association classification criteria provide a clinical diagnostic guide for gout. The presence of characteristic urate crystals in joint fluid, or a tophus demonstrated to contain urate crystals either chemically or by a polarized light microscopy means, or the presence of Six or more of the following criteria are needed to make a diagnosis: More than one attack of acute arthritis, Maximum inflammation developed within one day, Attack of monoarthritis, Redness over joints, Painful or swollen first metatarsophalangeal joint, Unilateral attack on first metatarsophalangeal joint, Unilateral attack on tarsal joint, Tophus (proved or suspected), Hyperuricaemia, Asymmetric swelling within a joint on radiograph, Subcortical cysts without erosions on radiograph, Joint fluid culture negative for organisms during attack.[33] The symptom free interval between acute attacks may last a few weeks to several years.

The development of subcutaneous tophi before first gouty attack is very rare. Invisible intraarticular tophi may present earlier than first gouty attack, which was induced by crystal shedding[34,35]. Extracellular urate crystals can be found in more than two thirds of aspirates from previously affected joints during asymptomatic intervals, while less than 5% of asymptomatic hyperuricemia subjects without gout have such crystals[36,37]. Gout can be diagnosed based on clinical features alone, but definite diagnosis requires aspiration and examination of synovial fluid, with identification of the causative crystals[38]. The main differential diagnosis of gout includes septic arthritis, cellulitis, pseudogout, palindromic rheumatism, bunion, seronegative spondyloarthropathy, and rheumatoid arthritis. In case of prolonged attack, one should consider infection (septic arthritis or concomitant septic and gouty arthritis)[39], loss of the golden time of initiation of colchicines (within 48-72 hours) for acute attack, drug-related serum urate level fluctuation, mixed crystals (monosodium urate and calcium pyrophosphate dihydrate) deposition disease, or reconsider if it is really gouty arthritis. Although hyperuricemia is a necessary condition for the development of gout, it is worthwhile to note that around 30% of gout patients had normal serum urate levels during acute gouty attack[40-43]. Tophi deposits are well known to cause joint destruction, gouty nephropathy, carpal tunnel syndrome, limited joint range of motion and joint deformity[46], spinal cord compression[47], concomitant with septic infection[48], and associated with life threatening necrotizing fasciitis[48].

Risk factors for Gouty arthritis

Risk factors other than inherited abnormality are obesity (excessive weight gain specially in youth), moderate to heavy alcohol intake, high blood pressure, and abnormal kidney function. Thiazide diuretics, low dose aspirin, niacin, cyclosporine, anti-tuberculous drugs (pyrazinamide, ethambutol) elevated serum uric acid level can also lead to gout. Diseases including leukaemia, lymphoma, and hemoglobinopathies are associated with raised uric acid in the blood. Dehydration, injury to the joint, fever, excessive eating, heavy alcohol intake, and recent surgery have been reported to precipitate gouty attack in patients at risk of developing gout[16-18].

How to diagnose?

Gout is suspected when a patient reports a history of attacks of painful arthritis, particularly at the base of the toes. Ankles and knees are the next most commonly involved joints in gout. Gout usually attacks one joint at a time, while other arthritis conditions, such as systemic lupus and rheumatoid arthritis, usually attack multiple joints simultaneously.

The most reliable test for gout is finding uric acid crystals in a sample of the joint fluid obtained by joint aspiration (arthrocentesis). Arthrocentesis is a common office procedure performed under local anesthesia. Using sterile technique, fluid is withdrawn (aspirated) from the inflamed joint using a syringe and needle. The joint fluid is then analyzed for uric acid crystals and for infection. Shiny, needle-like uric acid crystals are best

viewed with a special polarizing microscope. The diagnosis of gout can also be made by finding these urate crystals from material aspirated from tophi nodules and bursitis fluid.[34-37]

Sometimes patients with a classic history and symptoms of gout can be successfully treated and presumed to have gout without undergoing arthrocentesis. However, establishing a firm diagnosis is still preferable since other conditions can mimic gout. These include another crystal-induced arthritis called pseudogout, psoriatic arthritis, rheumatoid arthritis, and even infection in the joint.

X-rays can sometimes be helpful and may show tophi-crystal deposits and bone damage as a result of repeated inflammations. X-rays can also be helpful for monitoring the effects of chronic gout on the joints[44]. The characteristic radiography of gout comprises well-defined, punched-out erosions with overhanging edges, with preservation of the joint space, asymmetrical involvement, and soft tissue nodules shadow[44]. On magnetic resonance imaging, tophi generally have low signal intensity on both TI- and T2-weighted images and a variable enhancement pattern[45,46].

Treatment of gout and hyperuricemia

Treatment of Acute Gouty Arthritis

Acute gout is a self-limiting condition typically lasting less than one week, but treatment ensures pain relief and speeds recovery. The sooner drug treatment is started, the quicker the response. As gout is likely to recur, giving patients a supply of NSAIDs or colchicine to start treatment at the onset of the next episode is important. The mainstay of treatment during an acute gouty attack is the administration of non-steroid antiinflammatory drugs (NSAIDs), colchicine, or corticosteroids depending on the Comorbid conditions of the patient[78]. The basic principles of gout treatment are: (1) terminate acute attack as promptly and gently as possible, (2) prevent recurrence of acute gouty arthritis, (3) prevent or reverse complications resulting from deposition of monosodium urate in the joints, kidneys, or elsewhere, (4) prevent or reverse associated conditions such as obesity, hyperlipidemia, or hypertension, (5) prevent the formation of uric acid urolithiasis. The drug of choice for acute attack in most patients would be a NSAID provided that there were no contraindications. Cyclooxygenase-2 highly selective inhibitors are probably equally effective as traditional NSAIDs but have less short-term gastrointestinal toxicity[51]. Anti-inflammatory drugs should be gradually tapered when improvement occurs. The second choice drug is colchicine because of its narrow therapeutic index[52]. The choice of NSAID versus colchicine depends on individual assessment of cardiovascular, gastrointestinal, and renal risk factors. The American Association of Poison Control Centers toxic exposure system recorded 33 colchicine-related deaths from 1985 to 1997[53]. Owing to its narrow therapeutic margin, intravenous colchicine are no more recommended. Oral colchicine is more effective when administered in the first 24 hours after onset of an acute attack, before phagocytosis establishes itself. A standard oral regimen is 0.5 mg each hour or 1.0 mg every 2 hours until pain relief or side effects (vomiting or diarrhea) occur, or until a maximum of 6 mg is taken (but less than this amount of colchicine in those with renal insufficiency and in the elderly). However, up to 80% of patients are unable to tolerate an optimal dose owing to gastrointestinal side effects. A useful alternative approach is to add low doses of oral colchicine (0.6 mg qd–bid) as an adjunct to another better-tolerated primary treatment approach (e.g. NSAIDs). The administration of low daily dose of colchicines provides effective prophylaxis against further acute attacks[54]. Corticosteroids were advised when colchicine and NSAIDs are ineffective or are contraindicated during gouty attack. Intraarticular corticosteroids are usually reserved for patients suffering attacks of one or two large joints who also had contraindication or intolerance to NSAIDs or colchicines. In patients with polyarticular gout in whom other treatments are difficult, systemic corticosteroids are an option. Oral prednisolone (20–30 mg/day initially, then taper the dose gradually) or equivalent is also effective[55]. High doses of steroids have been reported to be associated with higher rates of rebound gouty attack.

Treatment of Chronic Gout

Gout is characterized by recurrent, painful attacks of acute arthritis. If left untreated, gout may become chronic and tophaceous depositions may result in destructive arthritis and loss of joint function. The pharmacological treatment of hyperuricemia in gout is generally very effective. The main reason for treatment failure is poor compliance, and patient education

improves compliance. Patients should be instructed that allopurinol or uricosuric drugs have no role in the treatment of the acute gouty attack, and that urate lowering drugs do not have anti-inflammatory properties. Drugs used to lower serum urate are aiming to reduce serum urate level to below the solubility limit (usually set at < 6 mg/dl for non-tophaceous and < 5 mg/dl for tophaceous gout patients). Urate-lowering therapy is a long term commitment and patients who have had just one or two acute episodes are unlikely to be compliant[56]. Recurrence is possible if treatment is intermittent or is withdrawn after apparent good control[57-58]. Current evidence does not support treating asymptomatic hyperuricemia[39,59,60]. Since only approximately 0% of asymptomatic hyperuricemic subjects develop gouty arthritis and the risk of urolithiasis in asymptomatic hyperuricemia subjects is small (just one case per 295 subjects each year), the risk of azotemia (follow up eight years) in asymptomatic hyperuricemia is 1.8% (2/113), compared with 2.1% (4/193) for the control subjects. The workup of gout and asymptomatic hyperuricemic subjects includes defining the cause of the hyperuricemia, which may disclose some other important diseases besides gout. Indications for the initiation of urate-lowering drug therapy are controversial but most physicians consider drug therapy in the event of two or more acute attacks of gout per year, tophi, bone destruction, uric acid urolithiasis, or to prevent acute uric acid nephropathy[32].

Urate-lowering Drug

Serum urate levels can be reduced by using medication that increases renal excretion of uric acid (uricosuric drug) or decreases uric acid production (xanthine oxidase inhibitor). Xanthine oxidase inhibitors (allopurinol, febuxostat) reduce uric acid production through competitive inhibition of xanthine oxidase, which converts hypoxanthine to xanthine and xanthine to uric acid. With rigorous medical compliance, allopurinol shrinks tophi and in time can lead to their disappearance. Resorption of extensive tophi requires maintaining a serum uric acid below 5 mg/dL, which may be achievable only with concomitant use of allopurinol and a uricosuric agent. Surgical excision of large tophi offers mechanical improvement in selected deformities. Allopurinol is usually initiated at a single daily dose of 100 mg and gradually increased[81]. Most patients require 300 mg/day, and the maximal dose is 800 mg/day. Oxipurinol is the major metabolite of allopurinol and has a half-life ranging from 18 to 30 hours, thus allopurinol can be given once daily. Since oxipurinol is largely excreted in the urine, its half-life is prolonged in patients with renal insufficiency and the dose of allopurinol thus should be reduced in patients with renal insufficiency[61]. If allopurinol and azathioprine are used together, the doses of azathioprine should be reduced by 75% as both drugs are metabolized by xanthine oxidase[62]. Uricosuric drugs (probenecid, sulfinpyrazone, and benzbromarone) increase urinary uric acid excretion by inhibiting renal tubular urate reabsorption. Uricosuric drugs are risky if urinary urate excretion is >800 mg/day while on a normal diet, and are contraindicated in individuals with uric acid calculi. Urine alkalinization can be indicated in a few high risk patients, particularly in those with a history of uric acid urolithiasis, and uricosuric drugs are absolutely required. Giving sodium bicarbonate at a dose of one gram three to four times daily, or giving potassium citrate, minimizes crystallization, which is likely to occur in acidic urine. It is important to ensure adequate urine amount and fluid intake to reduce the risk of uric acid stone formation. The transient increase in uric acid excretion during uricosuric drugs treatment may lead to the development of uric acid urolithiasis in a small proportion of gout patients. To avoid this complication, uricosuric drugs may be initiated at low doses and gradually increased as necessary. Precautions with uricosuric drugs include maintaining a daily urinary output of 2000 mL or more in order to minimize the precipitation of uric acid in the urinary tract. This can be further prevented by giving alkalinizing agents (eg, potassium citrate, 30–80 mEq/d orally) to maintain a urine pH of above 6.0. Uricosuric drugs are avoided in patients with a history of uric acid nephrolithiasis. Aspirin in moderate doses antagonizes the action of uricosuric agents, but low doses (325 mg or less per day) do not; doses greater than 3 g daily are themselves uricosuric. Probenecid and sulfinpyrazone might be ineffective in patients with creatinine clearance of below 30–50 ml/min, while benzbromarone (not available in the United States) might be ineffective given creatinine clearance of below 25 ml/min[63]. Probenecid is usually initiated in doses of 250 mg twice a day, and increased over several weeks to the dose necessary to achieve the target goal (serum urate < 6.0 mg/dl). A total dose of 1 g/d is appropriate for roughly 50% of patients, and the

maximal dose should not exceed 3 g/d. Because the half-life is 6 to 12 h, probenecid should be administered in two or four evenly spaced doses per day. Sulfinpyrazone is usually started at a dose of 50 or 100 mg twice a day and gradually increased to a maintenance dose of 300 to 400 mg/d, administered in three or four doses. The maximal dose is 800 mg/d. Benzbromarone is usually started at 50 mg/day, and the maximal dose is 100 mg/day (maximal dose is 150–200 mg/day for unmicronized benzbromarone). Benzbromarone associated fulminant hepatic failure has been reported[64,65]. Urate lowering drugs are of equal effectiveness. However, drug safety is of paramount importance in choosing hypouricemic agent. Almost all currently available urate-lowering agents have side effects, which are sometimes severe and life-threatening. Although the risk is very low, it exists and continuously happens[66,67]. Choosing the most appropriate urate-lowering agent for a patient may avoid unnecessary complication. Treatment with urate-lowering drugs should be carefully evaluated and considered on an individual basis. Generally, uricosuric drugs such as probenecid, sulfinpyrazone, or benzbromarone, are safer than allopurinol[66,67]. Whether febuxostat[40], a novel nonpurine selective inhibitor of xanthine oxidase, is safer than allopurinol but requires large scale post-marketing surveillance. Febuxostat is superior to allopurinol both in short and long term treatment in lowering serum uric acid and resolving tophi[79]. Febuxostat is approved for use in European countries at 80 and 120 mg daily. The FDA approved febuxostat for use in the USA in February, 2009[80]. Side effects of febuxostat include rash and elevation of hepatic enzymes, diarrhoea, and arthralgia may occur[80]. Benzbromarone and allopurinol have the advantage of once daily dosing. Benzbromarone have been reported to be associated with hepatotoxicity[64,65] and have been withdrawn from certain European countries, either by the government or by pharmaceutical company policy[66]. This has lead to allopurinol becoming the only urate-lowering medication available for gout in the Netherlands, and whether this action increases allopurinol-related morbidity and mortality deserves further observation. Allopurinol has been considered the drug of choice for hyperuricemia by some[67] because it can be conveniently administered once daily, and might prevent urolithiasis. The use of allopurinol should have indication to avoid the unnecessary, rare but potentially life threatening complications[52,53]. Specific indications for choosing allopurinol over a uricosuric drug include: (1) increased urinary uric acid excretion (>800 g/d on a general diet), (2) impairment of renal function with creatinine clearance of less than 30–50 mL/ min, (3) uric acid urolithiasis, and (4) gout not controlled by uricosuric drugs because of ineffectiveness or intolerance. Severe allopurinol hypersensitivity is more likely to occur in patients with renal impairment or in those receiving thiazide diuretics or ampicillin. Hung et al. indicated that HLA-B*5801 allele is a genetic marker for severe allopurinol hypersensitivity syndrome[70]. If uricosuric drugs are contraindicated and the reaction is mild, patient can be desensitized by administering an initial dose of 25–50 ìg of allupurinol. Febuxostat and oxipurinol are other alternative approaches. Allopurinol and a uricosuric drug may be used simultaneously in a few patients who cannot be controlled with a single medication. Uricase catalyses the conversion of urate to more soluble allantoin and is very effective at reducing urate level[71], but is potentially antigenic and contraindicated in G-6-P D deficiency. Pegluticase, a formulation of uricase with polyethylene glycol reduces antigenicity and prolongs the half-life of uricase, and may have a role in difficult gout patients in the future.

Treating Asymptomatic Hyperuricemia

Antihyperuricemic drug therapy for the great majority of individuals with asymptomatic hyperuricemia is not justifiable by risk/benefit analysis. As mentioned above, gouty arthritis is readily treatable and reversible if it occurs. Similarly prophylaxis against stone disease is not warranted in most individuals, but therapy should be started after discovery of a stone. The primary therapeutic modality in this setting is urinary alkalinization with potassium citrate or potassium bicarbonate, not allopurinol. Specific circumstance that warrant at least consideration for the institution of antihyperuricemic treatment in asymptomatic subjects is persistent hyperuricemia in the infrequent patients with sustained serum urate concentrations greater than 13 mg/dL (773 µmol/L) in men and 10 mg/dL (595 µmol/L) in women. These high values may carry some nephrotoxic risk, perhaps related to the likelihood of some component of uric acid overproduction. This recommendation does not generally apply to patients with heart failure who may develop marked hyperuricemia due to renal hypoperfusion and reduced

urate excretion. Such patients typically have advanced heart failure with limited life expectancy (unless they undergo transplantation) and are therefore at low risk for chronic urate nephropathy. Excretion of urinary uric acid in excess of 1100 mg (6.5 mmol) daily is associated with a 50 percent risk of uric acid calculi[72,73]. Management of these individuals should begin with dietary purine restriction. Allopurinol should be used if dietary restriction does not reduce uric acid excretion to less than 1000 mg/day (5.9 mmol/day). The dose should be adjusted to reduce uric acid excretion below 800 mg/day (4.8 mmol/day). Patients about to receive radiotherapy or chemotherapy that is likely to result in extensive tumor cytolysis should be treated to prevent acute uric acid nephropathy and other manifestations of tumor lysis syndrome [74]. Preventive therapy in patients at risk includes intravenous hydration and either allopurinol or rasburicase (recombinant urate oxidase).

The Role of Diet Control in Gout and Hyperuricemia

Previous studies have shown that purine rich diet produces only a minor and transient serum urate increase of approximately 1–2 mg/dl. Conversely, an iso caloric purine free diet for 7–10 days achieves a slight (1– 2 mg/dl) reduction in serum urate. Recent 14 Gout and hyperuricemia data confirm the long-held association of gout and hyperuricemia with high intake of meat, seafood, and alcohol (especially beer), but not with "high-purine vegetables" such as beans, peas, and lentils[72-75]. Gouty patients are advised to avoid foods or drinks known to precipitate acute attacks, such as excess meat, seafood, and beers. Crash dieting and fasting should be avoided as they can also precipitate acute attacks. Patients should also receive specific management and instruction for the associated cardiovascular disease risk factors and metabolic syndrome. Dessein et al. demonstrated that increasing protein and unsaturated fat intake while restricting carbohydrates significantly reduces uric acid, serum cholesterol, triglyceride, weight and frequency of gouty attacks[76]. Furthermore, identification of elevated mean serum urate levels in general population during recent decade merits further investigation and lifestyle modification.

In 2006, European league against rheumatism(EULAR) published evidence based recommendations for gout(general, acute management, and chronic management)[81] which are as follows

EULAR evidence based recommendations for gout (general, acute management, and chronic management)[81].

1 Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to:

(a) specific risk factors (levels of serum urate, previous attacks, radiographic signs)

(b) clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout)

(c) general risk factors (age, sex, obesity, alcohol consumption, urate raising drugs, drug interactions, and comorbidity)

2 Patient education and appropriate lifestyle advice regarding weight loss if obese, diet, and reduced alcohol (especially beer) are core aspects of management

3 Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity, and smoking should be addressed as an important part of the management of gout

4 Oral colchicine and/or NSAID are first line agents for systemic treatment of acute attacks; in the absence of contraindications, an NSAID is a convenient and well accepted option

5 High doses of colchicines lead to side effects, and low doses (for example, 0.5 mg three times daily) may be sufficient for some patients with acute gout

6 Intra-articular aspiration and injection of long acting steroid is an effective and safe treatment for an acute attack

7 Urate lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout.

8 The therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent crystal formation; this is achieved by maintaining the serum uric acid below the saturation point for monosodium urate (360 mmol/l)

9 Allopurinol is an appropriate long term urate lowering drug; it should be started at a low dose (for example, 100 mg daily) and increased by 100 mg every 2–4 weeks if required; the dose must be adjusted in patients with renal impairment; if allopurinol toxicity occurs, options include other

xanthine oxidase inhibitors, a uricosuric agent, or allopurinol desensitisation (the latter only in cases of mild rash)

10 Uricosuric agents such as probenecid and sulphinpyrazone can be used as an alternative to allopurinol in patients with normal renal function but are relatively contraindicated in patients with urolithiasis; benzbromarone can be used in patients with mild to moderate renal insufficiency on a named patient basis but carries a small risk of hepatotoxicity

11 Prophylaxis against acute attacks during the first months of urate lowering therapy can be achieved by colchicine (0.5–1 mg daily) and/or an NSAID (with gastro-protection if indicated)

12 When gout associates with diuretic therapy, stop the diuretic if possible; for hypertension and hyperlipidaemia consider use of losartan and fenofibrate, respectively (both have modest uricosuric effects)

Prognosis

Without treatment, the acute attack may last from a few days to several weeks. The intervals between acute attacks vary up to years, but the asymptomatic periods often become shorter if the disease progresses. Chronic gouty arthritis occurs after repeated attacks of acute gout, but only after inadequate treatment. The younger

the patient at the onset of disease, the greater the tendency to a progressive course. Destructive arthropathy is rarely seen in patients whose first attack is after the age of 50.

Patients with gout are anecdotally thought to have an increased incidence of hypertension, renal disease (eg, nephrosclerosis, interstitial nephritis, pyelonephritis), diabetes mellitus, hypertriglyceridemia, and atherosclerosis.

Conclusion

Only 15% of all hyperuricemia develop gout. Asymptomatic hyperuricemia usually does not require treatment. Gout is rare in reproductive age of women. S. uric acid may be normal during acute attack. Strict dietary restriction is no longer recommended. Rapid lowering of uric acid is not recommended. Allopurinol should not be prescribed during acute attack. Allopurinol if prescribed should be continued for indefinite period. Colchicine also indicated as an adjunct during initiation of allopurinol therapy. Oral colchicine is effective for acute gout but frequently causes unpleasant side effects. For patients who cannot take NSAIDs or colchicines and who are not candidates for intraarticular corticosteroid injection because of polyarticular disease, oral glucocorticoids are recommended. Prednisolone in doses of 30 to 50 mg/day (or other equivalent glucocorticoid) for one to two days, then taper over seven to ten days. Treatment options in patients who are unable to take oral medications include intraarticular or intravenous glucocorticoids, intramuscular or subcutaneous ACTH, and in locales where it is still available, cautious use of intravenous colchicine. For patients unable to take oral medications, with only one or two actively inflamed joints, and in whom infection has been ruled out, intraarticular injection of glucocorticoids may be used. For patients with polyarticular involvement, existing or easily established intravenous access, and no contraindications to glucocorticoids, systemic administration of a parenteral glucocorticoid also may be used. The dose and frequency depend upon the agent chosen. Patients who are taking antihyperuricemic therapy due to previous episodes of acute gout should be warned that antihyperuricemic therapy alone is not effective. Therapeutic recommendations for acute attacks in these patients are the same as in patients not taking antihyperuricemic therapy. If indicated, patient should be put on hypouricemic drug e.g allopurinol and should be continued for life long. Interleukin-1 inhibition has been reported to be effective in some cases but randomized controlled trials are needed to better assess the usefulness and safety of this approach and it is not recommended at this time. Newer agents like Febuxostat and Pegloticase seems to be promising.

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