Gout

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Gout is a crystal deposition disease caused by raised levels of uric acid in the blood (hyperuricaemia) with persistence of hyperuricemia at levels higher than a serum saturation of 6.8 mg/dl leads to formation of monosodium urate (MSU) crystals and their deposition in joints and other tissues. However, only a minority of individuals with elevated serum uric acid (sUA) levels ever develop gout, emphasizing the importance of other factors in determining crystal formation including Genetics, Gender, age, Diet and alcohol intake, Obesity, some medications and medical conditions a correct diagnosis of gout is essential for the appropriate management, in 2011 the European League Against Rheumatism (EULAR) published an updated evidence based recommendations for diagnosis of gout. Although gout is well understood condition and good therapeutic options are available, it tends to be poorly managed, so The 2012 The American College of Rheumatology (ACR) guidelines for Management of Gout were designed to emphasize safety and quality of therapy and to reflect best practice. New approaches to urate lowering have led to mechanism-based therapies such as: non-purine, selective inhibitor of xanthine oxidase, URAT-1 inhibitors and a recombinant chimeric mammalian uricase. Three IL-1β antagonists — anakinra, rilonacept and canakinumab are being evaluated as an emerging therapies for gout.

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Introduction

Gout is a crystal deposition disease caused by the formation of monosodium urate (MSU) crystals in joints and other tissues; it is one of the most common rheumatic diseases of adulthood, with a self-reported prevalence in the USA recently estimated at 3.9% of adults (8.3 million individuals). The prevalence of gout has increased over the last few decades, mediated by factors such as an increased prevalence of comorbidities that promote hyperuricemia, including hypertension, obesity, metabolic syndrome, type 2 diabetes mellitus, and chronic kidney disease (CKD). Other factors responsible for the increasing prevalence of gout include certain dietary trends and widespread prescriptions of thiazide and loop diuretics for cardiovascular diseases [1]. Gout is caused by elevated levels of uric acid in the blood (hyperuricemia), with persistence of hyperuricemia at levels higher than a serum saturation of 6.8 mg/dl leading to deposit of urates on articular cartilage. However, only a minority of individuals with elevated serum uric acid (sUA) levels ever develop gout, emphasizing the importance of other factors in determining crystal formation [2]. The solubility of urate in joint fluids, however, is influenced by other factors in the joint. These factors include temperature, pH, concentration of cations, level of articular dehydration, and the presence of such nucleating agents as nonaggregated proteoglycans, insoluble collagens, and chondroitin sulfate [3]. Variations in these factors may account for some of the differences in the risk for gout associated with a given increase in serum urate level. Furthermore, these factors may explain the predilection of gout in the first metatarsal phalangeal joint (a peripheral joint with a lower temperature) and osteoarthritic joints (degenerative joints with nucleating debris), and the nocturnal onset of pain (because of intra-articular dehydration) [4]. Hyperuricemia can be caused by overproduction of urate, or, far more commonly, by inefficient excretion by the kidneys (which accounts for >90% of cases) or a combination of these two mechanisms [2].

Risk factors

Many factors contribute toward hyperuricemia, including the following:

Genetics

Monogenic disorders that result in the overproduction of uric acid through enzyme defects in purine metabolism are extremely rare. Nevertheless, common primary gout in men often shows strong familial predisposition, although the genetic basis remains unknown.

Recent interest has particularly focused on genes regulating urate transport. The SLC22A12 gene codes for human urate transporter 1 (URAT1), a member of the organic anion transporter family, that, together with other recently identified transporters, is

important in controlling reabsorption of uric acid from the renal tubules. A polymorphism of this gene has been associated with 'underexcretion' of uric acid and hyperuricemia [5].

The glucose and fructose transporter SLC2A9 (GLUT9) which is encoded by the SLC2A9 gene has recently been shown to act as a high capacity urate transporter in proximal renal tubules. Polymorphisms in this gene have been reported to influence sUA levels [6].

Sex and age

Men have higher urate levels than women and an increased prevalence of gout at all ages, although less pronounced in older age; after menopause, urate levels increase and gout becomes increasingly prevalent.

Age is an important risk factor in both men and women [7].

Diet and alcohol intake

Increased meat and seafood intake was associated with an increased risk for gout, with no increase in risk with the intake of purine-rich vegetables or total protein intake, and reduced risk with low-fat dairy intake [8].

Alcohol consumption, particularly consumption of purine-rich alcoholic beverages such as beer, is also correlated with an increase in the risk for hyperuricemia and gout [9].

High dietary intake of fructose (sugar-sweetened soft drinks) contributes significantly toward hyperuricemia [10].

Obesity

The risk of gout correlates with truncal obesity, as measured by BMI and waist-to-hip ratios [11].

Medications

Thiazide diuretics are strongly linked to the development of gout. Several other medications can increase uric acid levels such as low doses of aspirin, pyrazinamide, ethambutol, nicotinic acid, and ciclosporin [12].

Medical conditions

Gout frequently occurs in combination with other medical problems. Metabolic syndrome, a combination of abdominal obesity, hypertension, insulin resistance, and abnormal lipid levels, occurs in nearly 75% of cases. Other conditions commonly complicated by gout include polycythemia, lead poisoning, renal failure, hemolytic anemia, psoriasis, and solid organ transplants [13].

Clinical features

Gout can be described in four stages: asymptomatic hyperuricemia, intermittent acute gout, intercritical gout (intervals between acute attacks), and advanced or chronic tophaceous gout initial episode, which is usually monoarticular, presenting as severe and painful inflammatory arthritis, mostly of the first metatarsophalangeal joint (podagra). Other joints involved include insteps, knees, wrists, and fingers.

It occurs suddenly and in most patients, it disappears completely within 5–14 days. Gout attacks can be precipitated by rapid changes in the serum urate level caused by trauma, alcohol consumption, medications, and increased consumption of purine-rich foods [14].

Women may present with atypical signs and symptoms of gout; they are usually one decade older than men when experiencing their first attack of gout and present less frequently with metatarsophalangeal involvement; instead, polyarticular gout affects the ankles or joints of fingers and upper limbs [15].

Diagnosis

A correct diagnosis of gout is essential for appropriate management; in 2011, the European League Against Rheumatism (EULAR) published updated evidence-based recommendations for the diagnosis of gout [16] including the following:

(1) In acute monoarticular attacks of the lower extremities, the rapid development of severe pain, swelling, and tenderness that reaches its maximum within 6–12 h, especially with overlying erythema, is highly suggestive of crystal inflammation, although nonspecific for gout.
(2) Although only the demonstration of MSU crystals in synovial fluid or tophus aspirate constitutes a definite diagnosis of gout, a clinical diagnosis alone is reasonably accurate in patients with a typical presentation of gout.
(3) Despite being the most important risk factor for gout, sUA levels do not confirm or exclude gout as many patients with hyperuricemia do not develop gout and sUA may be normal during acute attacks.
(4) In available synovial fluid samples obtained from undiagnosed inflamed joints, a routine search for MSU crystals is recommended.
(5) When the diagnosis is in doubt, identification of MSU crystals from asymptomatic joints may allow a definite diagnosis during the intercritical period.
(6) Gout and sepsis may coexist; therefore, when septic arthritis is suspected, gram staining and

culture of synovial fluid should still be performed, even if MSU crystals are identified.

(7) Assessment of renal uric acid excretion is rarely necessary in patients with gout. It should, however, be considered in those with early-onset gout (age < 25 years).

(8) Patients with gout have a high incidence of renal stones and those with stones should undergo a lithogenic workup.

(9) Radiographs may be useful for differential diagnosis and may show typical features in gout; they are not useful for confirming the diagnosis of early or acute gout and should only be performed when fracture is suspected.

(10) Risk factors for gout should be assessed including features of metabolic syndrome, CKD, medications, family history, and lifestyle.

Management

Although gout is a well-understood condition and good therapeutic options are available, it tends to be poorly managed by

(1) Insufficient patient evaluation,
(2) Inappropriate use of traditional and new medications, and
(3) Low patient adherence.

Therefore, the 2012 American College of Rheumatology (ACR) guidelines for management of gout are designed to emphasize the safety and quality of therapy and to reflect best practice.

The new guidelines were presented in two parts.

Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia [17]

(1) Patient education on diet, lifestyle, treatment objectives, and management of comorbidities is a recommended core therapeutic measure in gout.

(2) Xanthine oxidase inhibitor (XOI) therapy with either allopurinol or febuxostat is recommended as the first-line pharmacologic urate-lowering therapy (ULT) approach in gout.

(3) Serum urate level should be lowered sufficiently to achieve long lasting improvement in signs and symptoms of gout, with the target less than 6 mg/dl at a minimum, and often less than 5 mg/dl.

(4) The starting dosage of allopurinol should be no greater than 100 mg/day and less than that in moderate to severe CKD, followed by gradual upward titration of the maintenance dose, which can exceed 300 mg daily even in patients with CKD.

(5) Regular monitoring of serum urate (every 2–5 weeks) during ULT titration, including continuing measurements, once the serum urate target is achieved (every 6 months).

(6) The maximum FDA-approved dose is 800 mg daily for allopurinol and 80 mg daily for febuxostat.

(7) Probenecid was recommended as an alternative first-line pharmacologic ULT option in the setting of contraindication or intolerance to at least one XOI agent, but in gout patients with a creatinine clearance 50 ml/min, probenecid is not recommended as first-line ULT monotherapy.

(8) Urinary uric acid should be measured before the initiation of uricosuric ULT and elevated urine uric acid indicative of uric acid overproduction contraindicates uricosuric ULT.

(9) A history of urolithiasis contraindicates first-line use of uricosuricurate-lowering monotherapy.

(10) Use of agents other than probenecid with clinically significant uricosuric effects, such as fenofibrate and losartan, can be therapeutically useful as components of a comprehensive ULT strategy.

(11) Combination oral ULT with one XOI agent and one uricosuric agent is appropriate when the serum urate target has not been met by appropriate dosing of an XOI.

(12) Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options.

Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis [18]

Therapy for acute gouty arthritis

(1) An acute gouty arthritis attack should be treated with pharmacologic therapy and treatment should be initiated within 24 h of the onset as early treatment leads to better patient-reported outcomes. Established pharmacologic ULT should be continued, without interruption, during an acute attack of gout.

(2) In attacks of mild/moderate severity particularly those involving a few small joints or one or two large joints, initiation of monotherapy may be appropriate, with recommended options being oral NSAIDs, systemic corticosteroids, or oral colchicine, with no rank one therapeutic class over another, with continuation of the initial treatment regimen at the full dose until the acute gouty attack is completely resolved.

(3) In the unique case of colchicines, it must be initiated within 36 h of symptom onset, with a loading dose of 1.2 mg, followed by 0.6 mg 1 h later, and then 0.6 mg once or twice daily 12 h later until the gout attack is resolved.

(4) Initial combination therapy is an appropriate option for an acute, severe gout attack, particularly

with the involvement of multiple large joints or polyarticular arthritis. Acceptable combination options are colchicine and NSAIDs, oral corticosteroids and colchicine, or intra-articular steroids with any other modalities.

(5) For patients not responding adequately to initial pharmacologic monotherapy, inclusion of a second appropriate agent is an acceptable option.

(6) Use of a biologic interleukin-1 (IL-1) inhibitor (anakinra 100 mg subcutaneously daily for 3 consecutive days or canakinumab 150 mg subcutaneously) is an option for severe attacks of acute gouty arthritis refractory to other agents. Given a lack of randomized studies for anakinra and the unclear risk/benefit ratio and lack of FDA approval for canakinumab, the role of IL-1 inhibitor therapy in acute gout remains uncertain.

Anti-inflammatory prophylaxis of attacks of acute gout

(1) Given the high frequency of gout attacks in early ULT, pharmacologic anti-inflammatory prophylaxis was recommended for all cases of gout where ULT was initiated.

(2) Low-dose colchicine (0.5 or 0.6 mg) orally once or twice a day, or low-dose NSAIDs (such as naproxen 250 mg orally twice a day), with proton pump inhibitor therapy.

(3) As an alternative gout attack prophylaxis strategy in patients with intolerance or contraindication or refractoriness to both colchicine and NSAIDs, the use of low-dosage prednisone or prednisolone (defined as <10 mg/day) may be recommended.

(4) The prophylaxis should be continued for more than:
   (a) Continue the prophylaxis for 6 months' duration,
   (b) 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination,
   (c) 6 months after achieving the target serum urate level, where there has been resolution of tophi previously detected on physical examination, which is longer.

New and emerging therapies for gout

Novel approaches toward reduction of urate have led to mechanism-based therapies such as:

(1) Urate synthesis inhibitors (febuxostat was already FDA approved in 2009 and BCX4208 is under development). Febuxostat is a novel nonpurine, selective inhibitor of xanthine oxidase, metabolized and excreted by the liver; thus, no dose adjustment appears to be necessary in patients with mild-to-moderate renal impairment. Febuxostat has been approved at doses of 40 and 80 mg daily in the USA and at up to 120 mg daily in Europe.

(2) URAT1 inhibitors promoting renal uric acid excretion (lesinurad).

(3) Pegloticase (approved in 2010) is a recombinant chimeric mammalian uricase that presents a novel and effective option for the subset of patients with severe, refractory gout in whom normalization of serum urate levels cannot be achieved with conventional therapy. Its therapeutic effect results from the oxidation of urate to allantoin, a highly soluble purine metabolite that is excreted by the kidney. Pegloticase is administered intravenously at a dose of 8 mg every 2 weeks.

IL-1β is now known to play a central role in acute gouty inflammation. Three IL-1β antagonists, anakinra, rilonacept, and canakinumab, are being evaluated for gout treatment and/or prophylaxis [19].

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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