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Abstract

Introduction:

Gout is the most common rheumatic disease in adults, with prevalence ranging from 0.1% to about 10%. It results from the accumulation of monosodium urate crystals (MUC) in the joints and tissues. A thorough understanding of the clinical presentation, diagnostic factors and available treatment options can significantly reduce the prevalence of gout attacks, minimize joint damage and improve patients' physical function. The aim of this article is to provide clinicians and patients with a summary of the most recent information regarding this condition in order to decrease risk of joint damage and ultimately enhance patient's quality of life.

Review methods:

A review of the literature from PubMed (2010-2023) was conducted. The articles were selected based on specific keywords and then evaluated for their significance and suitability for inclusion in this review.

Description the state of knowledge:

Gout is an inflammatory arthritis associated with hyperuricemia, defined as elevated level of uric acid in the blood (> 7 mg/dl (420 μ mol/l)). Initially, acute gouty arthritis is characterised by sudden onset of severe pain, erythema and swelling, significantly reducing range of movement. However, as disease progresses, chronic, tophaceous gout can develop potentially leading to bone deformities and other complications. Treatment of gout includes management of the attacks and chronic uric acid-lowering therapy.

Summary:

Gout is a complex disease with various factors contributing to its clinical presentation. Its management requires a multidisciplinary approach including medication management, dietary counselling and lifestyle modification. Early diagnosis as well as appropriate treatment are essential to optimise patient outcomes and maintain patients' physical function.

Keywords: gout, arthritis, chronic gout, hyperuricemia

Introduction

Gout is a common inflammatory arthritis resulting from deposition of monosodium urate crystals in joints and as disease progresses, in tissues in various localization. The disease most commonly affects men over 40 years of age and postmenopausal women. Its prevalence has significantly increased over recent years. Recent estimates in the United States indicate a concerning prevalence of 3.9% among adults.[1] Noteworthy, the estimated occurrence of gout worldwide varies from 0.1% to about 10%.[2]

Hyperuricemia, an elevated level of uric acid in the blood, is the primary risk factor for the deposition of MUC and eventually the development of gout. Its incidence is related to primary cause, which stems from genetic disorders in purine metabolising enzymes, or secondary, resulting from an underlying condition. It may be either an increased production or decreased secretion of uric acid. In some cases, it may be a combination of both.[3] However, the exact mechanism of uric acid crystallisation is still unknown.

Clinical presentation results from the inflammatory response to monosodium urate crystals. Effective management depends on treatments that dissolve these crystals and reduce uric acid levels to prevent future attacks, and progression to chronic form of gout. [4]

The aim of this review is to summarise the latest information on the clinical presentation, risk factors, diagnosis and various treatment options for gout. Understanding the key aspects of this disease is crucial for effective management and risk reduction of joint damage, preserving physical activity, especially in the older patient population.

Materials and methods

We carried out a thorough review of the scientific literature on gout by conducting a systematic search using the PubMed database. We focused on articles published between January 1, 2010 and December 31, 2023, to enclose the most relevant research advancements. Inclusion criteria included articles written in English, original research studies, meta-analyses, clinical trials, and review articles. Exclusion criteria encompassed non-english articles published outside of the specified date range, case reports, commentaries, and letters.

A combination of MeSH terms and key phrases relating to gout was used, such as “gout”, “hyperuricemia”, “uric acid crystals”, “chronic gout”, “treatment”, “gout epidemiology”. Next, the articles were evaluated to determine their relevance and suitability for inclusion in this review.

Review

Clinical presentation

Gout is characterised by distinct phases:

- Hyperuricemia without symptoms
- Acute gouty arthritis
- Periods between acute attacks
- Chronic (tophaceous) gout

Hyperuricemia

Hyperuricemia, characterised by elevated levels of uric acid in the blood (> 7 mg/dl (420 μ mol/l)), is the main risk factor for the onset of gout.

Uric acid is the end product of purine metabolism. Normally, uric acid undergoes renal filtration, and is eliminated through urine. However, when the body produces too much uric acid or the kidneys excrete too little, uric acid can accumulate, in the form of needle-like urate crystals which can be found in a joint or surrounding tissue. [5] Noteworthy is that increased level of uric acid is associated with higher risk of incidence of acute gouty arthritis, but the majority of these patients never develop an acute attack. This suggests that other factors also play a role in the pathogenesis of gout, including genetics, renal function, and individual response to metabolic stress. [6]

Subsequently, deposition of MUC causes inflammation in the joint and distinct symptoms associated with a gout attack.[7] Triggers that contribute to hyperuricemia are provided in Table 1.

Table 1. Factors contributing to elevated serum uric acid levels

Triggering factors for hyperuricemia	
Diet: consumption of foods with high purine content	<ul style="list-style-type: none"> -red meat -organ meats: heart, liver, kidney, thymus -fish and seafood: anchovies, sardines, trout, mackerel, herring, tuna and salmon [8] -alcohol: especially beer [9] -high-fructose corn syrup [10]
Renal failure	<ul style="list-style-type: none"> - decreased level of eGFR -albuminuria -chronic kidney disease [11]
Medications	<ul style="list-style-type: none"> -cyclosporine [12] -diuretics [13] -antitubercular drugs: pyrazinamide and ethambutol [14]
Genes	<ul style="list-style-type: none"> -SLCA9 [15] -ABCG2 [16] -SLC22A11 [17] -SLC22A12 [18]

Moreover, the relationship between hyperuricemia and other comorbidities such as hypertension, cardiovascular diseases, and renal dysfunction further complicate the clinical picture of gout.

Hyperuricemia has been studied for its potential influence on hypertension. Several mechanisms are suggested for how elevated serum uric acid levels may contribute to the development or exacerbation of high blood pressure. These include endothelial dysfunction, renal damage, activation of the renin-angiotensin system, induction of inflammation and oxidative stress in vascular cells.[19-21]

Elevated level of uric acid may also play a role in renal failure, but the exact relationship is complex. Deposition of MUC can directly damage kidney structures through inflammation

and scarring, ultimately leading to chronic kidney disease (CKD). Moreover, hyperuricemia stimulates the renin-angiotensin system, causing vasoconstriction and decreased glomerular filtration rate. [20] Although numerous studies have established an association between hyperuricemia and CKD, the relationship remains unclear. The key issue is to establish the connection between hyperuricemia as a trigger for the onset of CKD or as a consequence of the disease process.[22]

Acute gouty arthritis and periods of remission

Acute gouty arthritis is a common inflammatory arthritis that is characterised by sudden, severe attacks of pain, swelling, erythema, and tenderness in the joints. The overlying skin appears erythematous, taut and shiny. The severity of the inflammation can restrict movement in the affected joint.

In most cases, acute gout flares manifest as monoarticular arthritis. The metatarsophalangeal joint of the big toe is the primary site of inflammation, although other joints of the extremities may be affected, especially those with underlying osteoarthritis. In addition, tendons and bursae around the joints may also be the site of MUC deposition. [23]

Acute gout flares can be triggered by several factors, including consumption of purine-rich foods, alcohol use, beverages with high fructose content, dehydration, injuries, excessive physical activity and fasting or rapid weight loss. According to the literature, low temperature and drugs which increase the level of uric acid also promote deposition of MUC in joints. An attack of gout usually starts at night or in the morning, waking the patient from sleep. It reaches a peak over the next 24 hours. Untreated gout flares typically resolve within 3-14 days. Following an initial gout attack, recurrent episodes can be expected within 6 months to 2 years, with variable remission durations.[24-25]

Chronic (tophaceous) gout

As disease progresses, the frequency of gout flares may increase, potentially transforming into chronic polyarthritis. Over time, the repeated deposition of urate crystals can lead to bone destruction and deformities that contribute to chronic pain, reduced of range of motion and ultimately decreased physical activity. Unlike acute gout, which typically manifests with acute flares, chronic gout is related to constant joint inflammation and eventually deformations.

Tophi are chalky deposits of MUC that accumulate in joints and soft tissues, with involvement of the vascular network contributing to local inflammation. They can be found in areas such as the fingers, wrists, elbows (olecranon bursa), knees, tendons and in other tissues such as the auricles. MUC can also form kidney stones, which often present as renal colic.[26-27]

Diagnosis

Diagnosing gout can be challenging because its symptoms can mimic other conditions, such as joint infections or rheumatoid arthritis. Moreover, the level of uric acid in the blood may not always reflect the presence of gout symptoms. Diagnostic approaches may include analysing synovial fluid to detect the presence of MUC (a gold standard), conducting imaging studies like ultrasound or dual-energy CT scans, and assessing clinical symptoms.

The most important clinical features for the diagnosis of a gout attack are the typical characteristics of the pain, the location and the recurrent nature of the symptoms. In addition, the presence of gout nodules in typical locations also facilitates diagnosis.[28]

Laboratory tests focus on the measurement of serum uric acid levels (> 7 mg/dl (420 μ mol/l), although they may not always be elevated during an attack. The definitive laboratory test for gout is the identification of monosodium urate crystals in synovial fluid drawn from the affected joint. Needle-like crystals with negative birefringence are observed under polarised light microscopy, confirming the diagnosis. [28]

Imaging techniques such as X-rays can reveal long-term changes associated with gout including urate crystals deposits and bone deformation. Ultrasound and dual-energy computed tomography are also capable of revealing urate deposits in joints. In Ultrasonography, hyperechoic enhancement over the cartilage, also known as a double contour sign is crucial in confirming the diagnosis. Furthermore, dual-energy computed tomography can detect and assign colour codes to tophaceous deposits, as well as give a summary of the amount of tophi in a specific joint region. This helps in evaluating the extent of joint involvement and monitoring disease progression. [29]

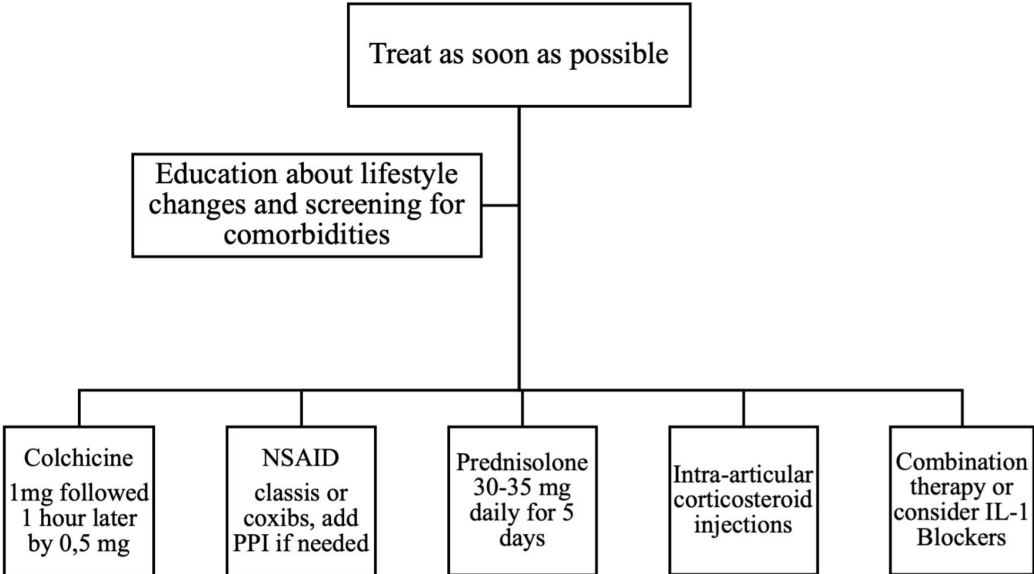
Treatment

The non-pharmacological treatment of gout consists mainly of lifestyle changes aimed at reducing serum uric acid levels. Dietary changes include limiting the intake of purine-rich

foods and choosing low-fat dairy products. Patients are also advised to reduce alcohol consumption, especially beer and spirits, and to avoid high-fructose drinks. Maintaining proper hydration is also crucial. Weight management through a balanced, low-calorie diet and regular exercise is recommended, as obesity is a significant risk factor for gout. In addition, comorbidities such as diabetes mellitus, cardiovascular diseases, hypertension and hyperlipidaemia should be well controlled. Educating patients about the importance of these lifestyle changes can significantly reduce the frequency and severity of acute gout attacks. [30]

Pharmacological treatment options for gout include both acute and long-term management. Acute gout attacks can be treated with colchicine, non-steroidal anti-inflammatory (NSAID) drugs and glucocorticoids. Colchicine is particularly effective when given early in the attack. However, it is not recommended for patients with chronic kidney disease. Nonsteroidal anti-inflammatory drugs are often prescribed and provide a rapid relief of symptoms. Another option for patients with multiple comorbidities is the use of glucocorticoids, which can be administered orally or injected directly into the inflamed joint. The choice of medication and dosage needs to be individualised, taking into account the patient's medical history, medications, and potential adverse events. [31,32] Additional information and the treatment algorithm for acute gout attacks are shown in Figure 1.

Figure 1. Algorithm for treatment of acute gout attacks. Based on EULAR 2020 guidelines. [32]



Long-term pharmacological treatment focuses on lowering serum uric acid levels to prevent future flares and the progression of gout-related complications. There are two main approaches to the long-term management of gout: reducing uric acid production and increasing its excretion. Allopurinol, a xanthine oxidase inhibitor, remains the first-line drug for reducing uric acid synthesis. Febuxostat is an alternative. Allopurinol should be used initially at a low dose (≤ 100 mg/d p.o., especially in patients with chronic kidney disease), increasing by 100 mg every 2-4 weeks until uric acid levels are effectively reduced.[32]

According to the 2020 EULAR guidelines, initiating urate-lowering therapy (ULT) for all patients with confirmed gout who have:

- subcutaneous tophi (urate crystal deposits under the skin)
- radiographic evidence of gout-related joint damage
- two or more gout flares per year. [32]

The guidelines advise against starting long-term ULT in most patients after their first gout attack and for occasional attacks, unless they have kidney stones, stage $\geq G3$ chronic kidney disease or a uric acid level above 9 mg/dL ($540\mu\text{mol/l}$). [32]

Furthermore, it is generally recommended to maintain anti-inflammatory prophylaxis for gout flares during the initial stages of ULT, which typically last 3 to 6 months. Low-dose colchicine or an NSAID may be prescribed to prevent gout flares. [32]

Another class of drugs, uricosuric agents such as probenecid, increase the excretion of uric acid in the urine. It is recommended for patients who do not respond to allopurinol therapy. Noteworthy is that allopurinol might be more effective in combination with a uricosuric drug. Pegloticase, an intravenous medication, can be a treatment choice for severe gout or for patients who can't tolerate other options. It works by enzymatically converting uric acid into allantoin which is a more soluble form that is easier for the kidneys to eliminate.[32]

Conclusions

In conclusion, gout is a major health challenge and its management requires a comprehensive and multidisciplinary approach. Effective treatment involves using a wide-ranging approach that includes medication in form of acute and long-term management and lifestyle modifications. Prompt diagnosis and proper treatment are crucial to reduce the frequency of gout attacks, maintain physical function and significantly improve patients' quality of life.

Disclosure

Author's contribution

Conceptualization: Joanna Wojtania and Kacper Pleska; Methodology: Michał Łepik and Krzysztof Rosiak; Software: Zofia Uszok; Check: Kacper Reguła and Andrzej Czajka; Formal analysis: Zofia Uszok and Joanna Wojtania; Investigation: Szymon Piaszczyński and Kacper Pleska; Resources: Szymon Piaszczyński and Andrzej Czajka; Data curation: Krzysztof Rosiak; Writing - rough preparation: Zofia Uszok, Bartłomej Szymański and Kacper Reguła; Writing - review and editing: Joanna Wojtania and Kamil Waloch; Supervision: Michał Łepik; Project administration: Kamil Waloch and Bartłomej Szymański;

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Conflict of interest

The authors deny any conflict of interest.

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