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Management of Gout: Targeting Pain or Metabolic Control

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ABSTRACT

Background: Gout, a chronic crystallo-metabolic condition that necessitates early metabolic intervention. Employing a treat-to-target urate-lowering approach is crucial to prevent systemic complications, rather than simply managing acute inflammatory events.
Methodology: This article reviews current scientific literature on gout and hyperuricemia, focusing on their metabolic connections. It examines clinical guidelines and research supporting early urate-lowering therapy and a treat-to-target approach, emphasizing the value of early intervention to prevent disease progression and related health issues.
Main body of the abstract: The prevalence of hyperuricemia-related diseases is rising rapidly worldwide, imposing significant health and economic burdens. This trend is largely attributed to substantial lifestyle changes in both urban and rural populations. Hyperuricemia extends beyond joint pain; it represents a spectrum of diseases that can metabolically affect almost all bodily systems, and uric acid can be deposited in all organs. Addressing gout with a focus on its metabolic origins can mitigate the detrimental effects of hyperuricemia on other systems. Since gout is fundamentally a metabolic disorder, initiating early uric acid-lowering therapy can help preserve joint and organ health, mainly the vascular endothelium, rather than merely waiting for flare-ups. The current approach to gout management emphasizes a 'treat to target' strategy, aiming to lower serum uric acid levels below 6 mg/dL, rather than simply alleviating symptoms like pain. Furthermore, there is little justification for delaying the start of uric acid-lowering therapy; screening at the pre-hyperuricemia stage can help prevent the onset of gout.
Conclusion: Gout is fundamentally a metabolic disease with multisystem implications. Effective management requires early identification of hyperuricemia, prompt initiation of urate-lowering therapy, and adherence to a treat-to-target strategy, as well as managing comorbidities. In today's metabolic landscape, gout is both preventable and curable.
Key words: Gout, hyperuricemia, extra-articular manifestations of hyperuricemia, extra-articular uric acid deposition, advantages of early treatments of gout, treat to target, pitfalls in the current gout management, treatment of gout on metabolic background, gout is a curable disease.

INTRODUCTION

Gout has historically been known as "arthritis of the rich" [(1)]. Currently, it has been established that gout is a crystallo-

metabolic disorder involving UA (uric acid) accumulation and a self-limiting inflammatory arthritis [2]. The prevalence of hyperuricemia (HU) and UA associated disorders are surging recently. The pathophysiological understanding of this connection is now more evident. Previously, HU was viewed primarily as a marker for various diseases. However, researchers are now recognizing the causal pathophysiological mechanisms that lead HU to these conditions. HU is not limited to affecting joints; it encompasses a broad spectrum of metabolic and inflammatory effects. The adverse metabolic effects are mediated through oxidative stress, endothelial dysfunction, systemic inflammation, and insulin resistance.UA deposition in the endothelium causes local inflammation and fibrosis, which subsequently leads to organ damage. Among the HU patients only less than 6 percent develop gout. While the rest of the group may experience no pain, metabolic effects on other systems continue silently, including sub-clinical gout.

While managing a metabolic disorder, alleviating pain should not be the primary objective. Rather, the focus should be on achieving and maintaining optimal biochemical values, similar to the treatment approaches for Type 2 Diabetes Mellitus (T2DM), dyslipidemia, and hypertension. In preventive programs for metabolic disease, screening should be the primary focus. Gout, being a metabolic disease, the awareness of screening HU among healthcare professionals should be largely encouraged.

In the management of gout, the optimal timing for initiation, appropriate methods of starting treatment, ideal drug selection, duration of therapy, follow-ups, and management of comorbidities remain uncertain. As gout is a metabolic and lifestyle-related disease, implementing lifestyle measures is essential for effective treatment. The significance of lifestyle measures is not emphasized in some international guidelines. By maintaining serum uric acid (SUA) levels below pre-hyperuricemic levels (below 6mg/dL in men and 5mg/dL in women), it is possible to prevent the onset of gout and avoid urate deposition as well as hyperuricemia-related diseases [3]. Chronic medical conditions are linked to systemic inflammation. It is widely accepted that HU contributes to systemic inflammation. Hence, the management of gout should focus on addressing systemic inflammation rather than solely targeting joint inflammation. It is strongly advised that SUA be reduced promptly upon detection. These measures can prevent arthritis, UA deposition in various organs, and issues related to systemic disorders.

Search Strategy: Articles were sourced using a Google search and PubMed from 1975 to 2025, employing keywords such as uric acid, prehyperuricemia, hyperuricemia, gout, gout management, metabolic association, and extra-articular UA deposition.

Pathophysiology

Molecular Mechanism Induced by Hyperuricemia

Systemic:

Uric acid is the final metabolic product of purine. It is produced through cell turnover, food consumption, and de novo synthesis. Uric acid enters cells via specific organic anion transporters when it reaches a certain level. This process triggers an oxidative cascade in various cells, including vascular smooth muscle, endothelial, adipocytes, islet cells, renal tubular, and hepatocytes.HU is linked to non-communicable diseases (NCDs) by influencing molecular signals like inflammation, oxidative stress, insulin resistance, endothelial dysfunction, and endoplasmic reticulum stress, even before prehyperuricemia occurs [4,5,6,7,8]. Systemic inflammation markers, including leukocyte count, C-reactive protein, and cytokines like IL-6, IL-1RA, IL-18, and TNF-α, may increase in HU and prehyperuricemia [3,9,].

Articular:
In gout, the deposition of UA crystals results in acute crystal-induced inflammation and chronic destructive lesions in joints and bones, leading to the formation of tophi. The UA triggers a significant inflammatory response by activating macrophages within the tissues, which subsequently promotes the recruitment of neutrophils to the affected joint.
Gout was initially thought to be a crystal disease, but it was described as a metabolic disorder. Recent research and investigative methods recognize gout as a crystallo-metabolic disorder. First, metabolic issues develop, and UA crystal precipitation starts later. It was believed that UA crystal deposits occurred exclusively in the joints and the kidneys. However, as scientific research progressed, the understanding of gout has significantly evolved. With the introduction of advanced imaging techniques such as Dual-Energy Computed Tomography (DECT), it is now possible to visualize UA crystals in various extra-articular locations. The systemic effects of HU and the deposition of UA crystals outside the joints are believed to contribute to the development of multiple comorbidities in patients with gout. DECT has proven to be an invaluable tool for the accurate and efficient detection of UA crystal deposits [10].

The Metabolic Implications of Hyperuricemia Beyond Joints

In recent years, new comorbidities and complications associated with gout have been identified. These factors should be taken into consideration in the management of this condition [11].

Table.1 Metabolic disorders among gout patients have illustrated.

Condition	Percentage
Hypertension	74%
Chronic kidney disease	71%
Metabolic syndrome	60%
Diabetes	26%
NAFLD	21%
Myocardial infarction	14%
Heart failure	11%
Stroke	10%

These data highlight that metabolic disorders are of greater significance than articular issues. These comorbidities were found to be more severe in individuals with high SUA levels [12].

1. UA and cardiovascular disease.
Higher SUA levels are increasingly associated with a greater risk of sudden cardiac death and cardiovascular mortality [13,14]).

A. Hypertension: Reports indicate that 47% of patients with hypertension have HU [15], and that an increase in SUA by 1 mg/dL results in approximately a 13% increase in the incidence of hypertension [16]. Recent studies suggest that uric acid lowering therapy (ULT) has been associated with a reduction in blood pressure among adolescents [17].
B. Atherosclerosis: Young adults with HU may show signs of coronary artery calcification, and even high normal SUA levels can lead to subclinical atherosclerosis. SUA levels might increase pulse wave velocity, starting from 6.2 mg/dL, potentially increasing arterial stiffness and contributing to vascular aging [18].
C. Coronary Artery Disease (CAD): The risk of mortality from CAD increases by 15% for each 1 mg/dL increase in SUA levels [19]. Xiao et al. observed that elevated SUA levels are linked to higher CAD incidence in individuals under the age of 45 years. High SUA levels likely increase aortic pressure and stiffness [20].
D. Atrial Fibrillation (AFib): An elevated serum level enhances the probability of both chronic and paroxysmal AFib [21].
E. Heart failure: HU increases the risk of HF by 65%. Additionally, for each 1mg/dL increase in SUA, the risk of HF rises by 20% [22].

2. UA and metabolic syndrome (MetS):
Research by Choi et al. indicates that up to 60% of individuals with MetS have HU [23]. MetS can develop even when SUA levels are below 6 mg/dL. HU is currently seen as a

marker for the early diagnosis and prevention of MetS [24].

3. T2 Diabetes: The diabetogenic effect of SUA was identified in 1950 [25]. The likelihood of developing T2DM increases by 15-20% for each 1mg/dL rise in SUA levels, independent of other conditions [26]. The risk of future development of T2DM is directly correlated with SUA levels, independent of age.

4. UA and Lipid: Serum total cholesterol, LDL cholesterol, and triglycerides exhibit a direct correlation with SUA levels, while HDL cholesterol shows an inverse relationship [27].

5. UA and kidney: SUA is recognized as an independent risk factor for chronic kidney disease (CKD), regardless of the presence of T2DM [28]. Elevated SUA levels are associated with a reduction in the number of nephrons, renal tubular atrophy, and consequently, a decreased GFR [29,30]. In patients with T2DM, an elevated SUA level within the normal range may predict the onset of CKD even when renal function appears to be preserved. ULT has been shown to reduce inflammation and slow the progression of renal disease, including in patients with moderate CKD [31]. A study by Kanbay's indicated that reducing SUA levels can decelerate renal disease progression in HU populations, with noted improvements in renal function upon treating asymptomatic HU [32]. Similarly, Siu's research observed that addressing asymptomatic HU delays renal disease progression [33]. Renal impairment associated with T2DM can commence at a SUA level of 6.3 mg/dL, which is considered high-normal, and is linked to a poor prognosis [34].

6. UA and liver: The correlation between SUA and non-alcoholic fatty liver disease (NAFLD) was initially reported in a 2002 Italian study [35]. An increase of 1 mg/dL in SUA level raises NAFLD risk by 21% [36]. Lowering UA levels may help in preventing NAFLD [37].

7. UA and brain

A. Stroke: The pro-oxidant neurotoxic effect of UA may influence the outcome of acute stroke. Elevated SUA levels are correlated with a higher incidence of stroke and increased mortality rates [38].
B. Dementia: SUA levels are elevated in cases of vascular or mixed dementia [39]. Although UA has been reported to have a neuroprotective role due to its antioxidant properties in Alzheimer's disease and Parkinson's disease, recent studies have presented findings that do not support this observation.

8. Other associated disorders

Elevated SUA levels may be associated with chronic obstructive pulmonary disease (COPD), and higher SUA values could correlate with increased mortality rates [40]. In acute respiratory distress syndrome, higher SUA levels have prognostic significance. Hyperthyroidism causes HU through increased BMR and urate production, while hypothyroidism leads to HU due to reduced renal blood flow. Elevated levels of SUA were observed in patients with psoriasis and chronic dermatitis. Research indicates a correlation between elevated SUA levels in younger males and the incidence of androgenic alopecia [41]. SUA levels are high in young women with polycystic ovarian syndrome (PCOS). In 1917, Slemons and Bogert found that UA levels were elevated in pre-eclampsia/eclampsia, a finding now recognized as a stable biomarker for these conditions [42]. Elevated SUA levels during pregnancy may contribute to a 4% increased risk of developing gestational diabetes mellitus (GDM). HU may indicate a higher risk of erectile dysfunction (ED) and male infertility. Each 1 mg/dL increase in SUA levels is associated with a twofold heightened risk of ED [43]. Furthermore, there appears to be a connection between sexual dysfunction and gout in both men and women [44]. Ocular abnormalities such as retinopathy, dry eye syndrome, red eye, uveitis, macular degeneration, glaucoma, and cataracts have been linked to elevated UA levels [45,46]. Higher salivary UA is associated with periodontitis and recurrent aphthous ulcers.

Malignancy

Furthermore, a cohort studies show HU and gout relate to cancer incidence and mortality related to this [47]. Gout is considered a risk factor for cancer, especially urological cancers, digestive system cancers, and lung cancer.

Life span

A study conducted by researchers at the University of Limerick's School of Medicine indicates that elevated levels of SUA may reduce life expectancy by up to 11 years for men and six years for women [48].

Extra-articular urate deposition

Most research from the ancient period indicated that UA crystal formations were primarily confined to the kidneys and joints. Recent studies, however, have also shown that UA crystal deposition occurs in extra-articular locations. The utilization of advanced imaging techniques, such as DECT, now allows for the visualization of UA crystals in various extra-articular regions. Patients with HU may develop various comorbidities due to the deposition of UA crystals outside the joints. For the precise and effective detection of UA crystal deposition, DECT has accepted as a crucial tool.

1. UA deposition cardiovascular system

UA crystals were found to be deposited in the vasculature of patients with high SUA levels. This leads to the activation of the inflammatory response in the vessel wall. The inflammatory process increases the likelihood of forming vulnerable plaques that can rupture and lead to acute cardiovascular events. This can be compared to the occurrence of a gout flare [49]. Autopsies have confirmed UA deposits in the myocardium and endocardium, with histopathology revealing tophi in the myocardium and involvement of epicardial fat [50]. Involvement of the conduction pathways was observed in an autopsy specimen from a gout patient who had complete heart block [51]. A study by Abdellatif et al. [52], using DECT found UA crystals in the coronary arteries of 84.62% of patients with tophaceous gout. Andrés et al. [53] observed that UA deposition in coronary arteries is associated with increased coronary calcification and coronary artery disease. In an observational study, Park et al. [54] identified histological evidence of UA crystal deposition in coronary arteries, which may result in crystal-induced inflammation.

2. UA deposition in the eye

Gout-related tophi, or UA deposits, have been documented in various ocular structures. These include the corneal epithelium, stroma, Bowman's layer, conjunctiva, sclera, lens, orbital fossa, retina, tarsal plates of the eyelids, iris, and anterior chamber [55,56].

3.UA deposition in spine

The first reported case of UA crystal deposition in the spine was in 1950 [57]. Detecting spinal gout is challenging due to nonspecific MRI and CT findings. Spinal tophi can cause neurological impairment by compressing the nerve roots or the spinal cord [58].

4. UA deposition in the GIT

Several case reports have documented UA deposition within the gastrointestinal system. In these instances, tophi have been identified in the liver, pancreas, small intestine, and colon. Notably, several cases were initially misdiagnosed as malignancies. [59,60].

5.UA deposition in skin

Dermal tophi, resulting from intradermal UA deposits, can appear as subcutaneous nodules or indurated plaques. They have also been reported to cause ulcers and may precede potential articular symptoms [61].

6. UA deposition in the ear, nose, and throat

Several studies have documented the deposition of UA crystals in the larynx, middle ear, surface of the Eustachian tube, and nose. The clinical manifestations of these deposits include conductive hearing loss, otorrhea, hoarseness, odynophagia, dysphagia, and stridor [62,63].

7.UA deposition in other organs

Tophi deposition has been observed in the prostate glands, which may cause chronic

prostatitis symptoms or resemble prostate cancer [64]. Additionally, mammary and pulmonary tophi have been reported as non-specific masses in the mammary glands [10]. UA deposition in the lungs can lead to the formation of lung nodules and endobronchial masses, resulting in bronchial obstruction [65].

Diagnosis of gout.

1.Clinical diagnosis:

Gout is often diagnosable based on clinical findings alone in primary care settings [66]. A well-accepted diagnostic guideline is not available for diagnosing acute gouty arthritis in primary care settings without joint fluid analysis. The bedside diagnosis of acute gout involves the sudden onset of joint pain, particularly in gout-prone joints, typically occurring early in the morning. The pain ranges from moderate to severe (excruciating) with tenderness and no history of trauma, associated with restricted movement and a definite history of a precipitating cause. Precipitation factors may vary depending on the geographical area and individuals. These factors may rarely include food items such as green leafy vegetables, green tea, and ghee, among others (based on the author's experience), apart from common items like alcohol, red meat, and high fructose-containing food. In a sample set from New Zealand, tomatoes were identified as the fourth most frequently self-reported trigger for gout attacks [67]. Identifying these precipitating factors is crucial for treating acute attacks and preventing future flare-ups.

2.Laboratory tests

SUA is usually high and may not always be above the cut-off value of 7mg /dL in males and 6mg /dL in females. HU patients should be evaluated for any comorbidities. Therefore, it is recommended to conduct blood sugar, lipid profile, thyroid function, renal function, liver function, and basic screening for connective tissue disorders. Furthermore, it is essential to measure the serum levels of calcium and phosphorus.

3.Imaging

For patients with an intermediate risk where arthrocentesis is not possible, non-invasive radiological evaluation may assist in supporting the diagnosis. Joint destruction in X-rays of the affected joint may not always be informative. Ultrasound scanning may be useful, showing the double contour sign (DCS), though not always. Dual-energy computed tomography (DECT) has emerged as a valuable investigative tool for diagnosing gout and HU. It can detect even subclinical gout and extra-articular UA depositions. This provides a deeper understanding of the diagnosis of gout and hyperuricemia, which was not previously recognized.

DECT: Revolutionary Diagnostic Tool for Gout

Joint aspiration is the gold standard diagnostic procedure, and histopathological examination of the aspirated fluid, demonstrating negatively birefringent MSU crystals under polarized microscopy, confirms the diagnosis [68,69].

The advent of DECT has enabled the non-invasive diagnosis and quantification of gout by accurately confirming the presence and extent of UA crystals in joints and extra-articular tissues, without the need for painful and often unreliable soft tissue biopsy or joint aspiration. Furthermore, 84.62% sensitivity and 97.92% specificity in the same age and gender groups have been observed. Therefore, DECT has proven to be a highly valuable tool for the precise and efficient visualization of UA crystals in patients exhibiting clinical signs and symptoms of gout [70].

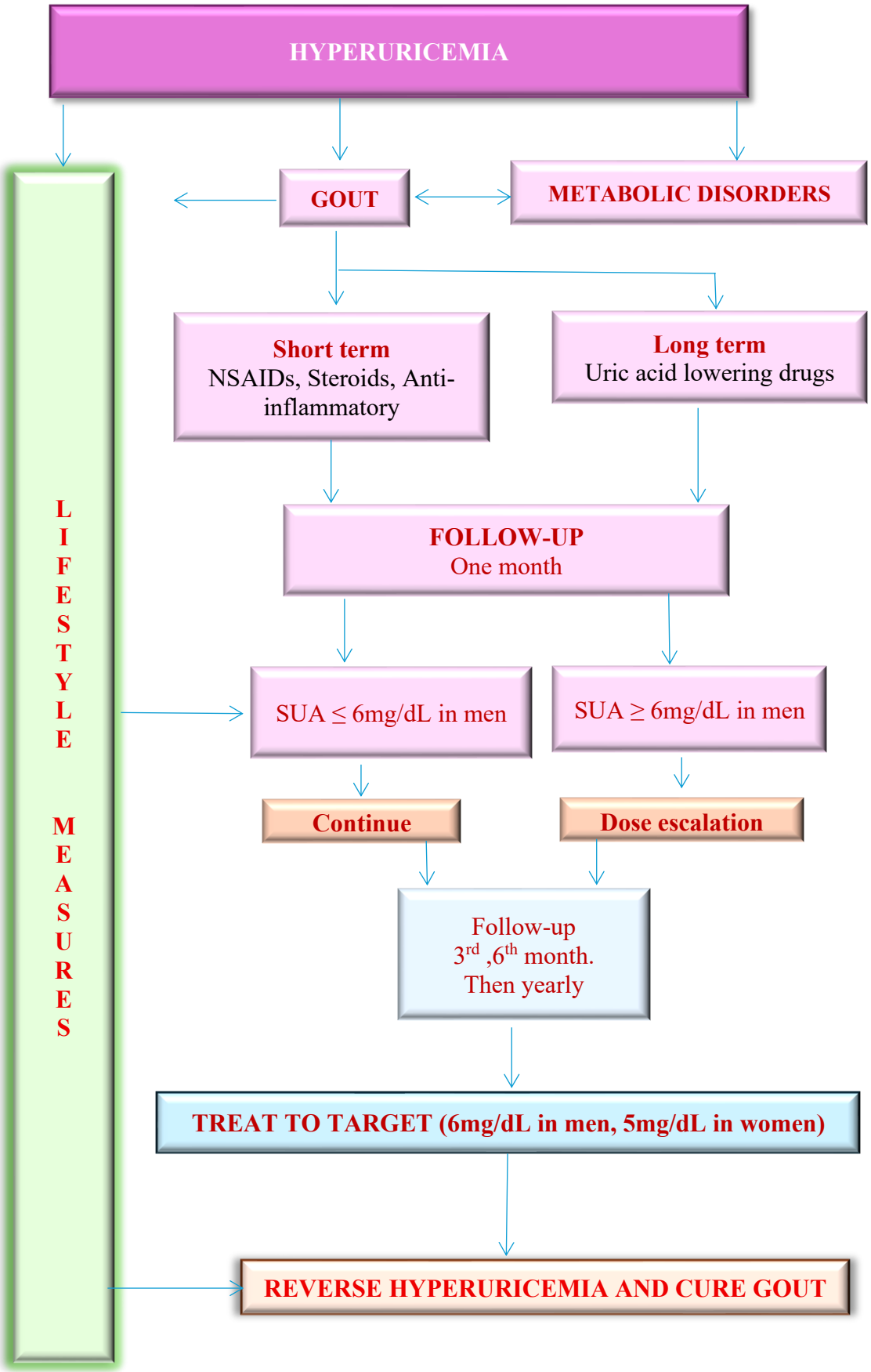

Figure 1: Algorithm for the management of Gout and hyperuricemia

DISCUSSION

HU plays a significant role in the development of gout, a painful condition. HU is currently identified as the second most prevalent metabolic disorder following T2DM. It is characterized not only by arthritis but is also associated with various non-communicable diseases and includes a spectrum of diseases rather than a single entity and impacts multiple bodily systems. The prevalence of HU varies widely across different populations globally, ranging from 2.6% to 47.2%. Gout is linked to various comorbidities and complications that must be addressed in its management. Recent studies have identified several new comorbidities associated with gout [71].

A diverse array of environmental factors, including lifestyle habits such as diet, alcohol consumption, and physical activity, is significantly associated with the development of HU.

Sustained HU leads to an elevated UA pool in the body, resulting in the precipitation of UA crystals in both articular and extra-articular sites. UA deposition in joints does not necessarily result in gout; it may also present as a painless, sub-clinical condition. Recently, several innovative non-purine xanthine oxidoreductase inhibitors have been developed; however, the incidence of gout and urolithiasis continues to increase.

Current guidelines for managing gout

Numerous international guidelines have been established for the management of gout. These include guidelines published by the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the American College of Physicians (ACP) [72,73,74,75]. In the UK, the British Society for Rheumatology (BSR) published its first gout guideline in 2007, updating it in 2017[76,77]. The National Institute for Health and Care Excellence (NICE) released its gout guideline in 2022 [78].

The "treat to prevent symptoms" approach, which was previously recommended, is not currently endorsed by international gout experts. The present goal of gout treatment is to `treat to target`, a standard recognized by medical associations globally. Several key treatment aspects, such as timing, duration, and comorbidities, were not addressed in these guidelines. Some international associations have voiced their concerns about the delays in initiating ULT and the extended use of anti-inflammatory treatment without effectively reducing SUA levels. In treatments where a target is not specified or set at approximately 7mg/dL, UA concentration may frequently exceed this level. This condition could extend the duration required for the resolution of tophi and the normalization of the UA pool. Consequently, gout attacks are likely to persist during this period [79].

It is important to note that 85-90% of individuals with HU do not experience acute flare-ups, similar to how not all individuals with hypercholesterolemia suffer from heart attacks. However, if not treated promptly, metabolic issues may continue to deteriorate, and subclinical gout may persist. Nephrologists do not postpone the treatment of HU in patients with chronic kidney diseases. But what justifies rheumatologists in delaying the treatment of a gout attack with ULT?

Challenges in the Current Guidelines

Many international guidelines do not address key clinical points, such as when to start ULT, how long to continue treatment, and the frequency of follow-ups for SUA. Some associations do not address the screening or management of comorbidities. The treat-to-target approach is also not universally followed. Certain important treatment aspects, such as vitamin C and specific food items that may have beneficial effects, are not mentioned in many guidelines due to the 'absence of evidence'. However, this 'absence of evidence' should not be misinterpreted as 'evidence of absence', especially when considering the long-term use of ULT in managing gout. Also, the significance of non-pharmacological management has not

been adequately emphasized in many guidelines.

Recent organizations, such as the G-CAN panel [80], have raised concerns about the lack of clarity in some recommendations. They also highlighted that these recommendations often overlook the presence of comorbidities and significant hyperuricaemia, which are unlikely to be sufficiently addressed with conservative treatment. These associations advocate for long-term ULT for specific patients, including those in the early stages of gout. Treating without considering an individual patient's response to the specific intent of the drug, such as ULT without monitoring UA levels, may be illogical and without clinical sense. This practice can be compared to prescribing anti-hypertensive medication without measuring blood pressure or diabetes treatment without measuring blood sugar. The G-CAN panel also notes that the ACP clinical practice guideline may lead to overuse of analgesics, colchicine, and steroids for long-term symptom management in gout, due to insufficient focus on the underlying disease pathophysiology [80]. Contrary to the myth that gout disappears between attacks, the reality is that symptom-free intervals do not indicate permanent relief from the condition. ULT is fundamental in the management of gout. Initiating ULT at an earlier stage reduces the likelihood of experiencing acute flare-ups.

Management of Gout within a Metabolic Context

Gout is both a metabolic disorder involving UA accumulation and a self-limiting inflammatory arthritic condition [81]. Therefore, the effective management of gout necessitates addressing both the acute inflammatory episodes (gout attacks) and the underlying metabolic issues through ULT. Maintaining safe SUA levels with ULT is crucial for long-term gout management, aiming to dissolve UA crystals from joints and organs, prevent flares, and resolve tophi. Consistently maintaining safer SUA levels by ULT with lifestyle measures can enhance endothelial functions and potentially reverse chronic metabolic diseases (Fig.1). However, gout frequently remains untreated or inadequately managed. As a metabolic disorder, gout should be managed by targeting HU instead of just alleviating pain. This approach helps to reduce SUA levels, address metabolic issues, decrease systemic and joint inflammation, and alleviate pain effectively. By adhering to this principle, the likelihood of experiencing a gout flare is significantly diminished. Without promptly reducing the SUA levels, achieving complete resolution of gout will remain unattainable.

Key Elements in Gout Management

- Diagnosis of acute gout
- Identification of precipitating factors
- Detection of comorbidities and addressing metabolic issues
- Management of acute gout, including reducing pain, preserving joint function, and preventing flare-ups
- Treatment of hyperuricemia
- Co-administration of non-gout medications with ULT
- Lifestyle modifications aimed at reducing SUA levels
- Patient education about lifestyle measures, recognition of precipitating factors, and management and prevention of gout

Who should treat gout/hyperuricemia?

Rheumatologists consider gout to be a chronic condition that often progresses, with acute flares and a tendency to recur. However, gout is a painful condition, so patients often consult orthopaedic surgeons, non-rheumatologist physicians, or general practitioners for management. Rheumatologists are responsible for providing specialist care to patients with gouty arthritis that is refractory to first-line therapies or those who do not achieve the treatment target despite appropriate use of ULT. Nephrologists handle hyperuricemia with CKD or acute urate nephropathy, cardiologists manage HU with cardiac diseases, and urologists treat uric acid

nephrolithiasis. Hyperuricemia is a condition that affects multiple systems, and therefore, treatment may involve a team of medical professionals from various specialty departments like internists, surgeons, gynaecologists, dermatologists, sexologists, and metabolic physicians. Oncologists use preventive measures to manage SUA levels and treat chemotherapy-induced HU, acute gout, and tumor lysis syndrome. Dietitians are increasingly important today due to the rise of hyperuricemia as a lifestyle-related disease.

Timing of Initiation of ULT

Managing gout requires addressing both acute pain relief and long-term SUA control. Therefore, it is recommended to use a combination of anti-inflammatory medications and ULT. To optimize outcomes, treatment of acute flares should commence at the earliest possible stage, preferably within 12 hours [82]. The timelier the intervention, the swifter the response. Anti-inflammatory treatment must be sustained throughout the duration of the flare, which may last from several days to weeks [83]. This includes analgesics, steroids, colchicine, and IL-1 inhibitors (anakinra, canakinumab). Once the pain begins to subside, it is highly recommended to initiate ULT. Upon complete relief from pain, anti-inflammatory drugs can be discontinued. This `bridging therapy` minimizes the prolonged use of anti-inflammatory medications unnecessarily. ULT can be continued for an extended period with a target of maintaining SUA levels below 6 mg/dL throughout life. It is essential to initiate treatment for tophi even with the presence of pain, promptly by lowering UA levels at an early stage without delay. ULT is also highly recommended for the management of uric acid nephrolithiasis as soon as the diagnosis is confirmed.

Some researchers suggest that the initial gout flare may be preceded by long-term HU and years of asymptomatic UA crystal deposition and therefore recommend starting ULT after the first flare. They suggest that delayed treatment may lead to more UA crystal deposition, increasing inflammation and joint damage. Furthermore, early initiation of ULT in patients with underlying comorbidities has also been recommended. Research indicates that patients with asymptomatic hyperuricemia frequently present with UA crystal deposits, suggesting subclinical gout, which can be identified using DECT. Therefore, ULT should be initiated promptly [84,85].

Patients should be informed about how to self-medicate when they notice initial symptoms. This approach helps in shortening the treatment duration of acute flare-ups. Lifestyle modification is recommended for all patients with HU, regardless of its association with gout or uric acid-related metabolic conditions. These preventive measures can help mitigate the development of future metabolic issues, particularly T2DM.

Advantages of early initiation of ULT

Clinical studies indicate that early initiation of ULT is effective in treating patients more rapidly with recurrent flares, tophi, urate arthropathy, and UA nephrolithiasis. Additionally, this approach prevents flares, treats tophi and urate nephrolithiasis, chronic urate nephropathy, and UA deposition elsewhere in the body, and manages UA-associated metabolic issues. Furthermore, an intensive reduction in SUA levels results in decreased incidence of flares, reduction in tophus size, and improvements in health-related quality of life and activity limitations, within a 6-month treatment period [86].

Is it advisable to initiate ULT during an acute gout attack?

Yes, this is the current answer; combine it with short-term analgesics, with or without steroids. It is believed that starting ULT during an acute gout episode may exacerbate or prolong the flare. This is an established belief. However, it is widely recognized that the acute pain associated with gout attacks is self-limiting and typically resolves within 72 hours without the use of analgesics. Several researchers suggest that initiating ULT

during an acute flare may offer the benefits of improved compliance, reduction in healthcare visits, and decreased overutilization of analgesics and steroids. For relief of gout pain, analgesics with or without steroids are necessary. Initiating ULT concurrently is unlikely to exacerbate the flare, particularly when strict adherence to lifestyle measures is maintained. It is well documented that lifestyle modifications alone can reduce UA levels to normal within three months. Our aim in treating gout is to implement a treat-to-target approach as early as possible. Reducing UA levels can help to decrease systemic inflammation and joint pain. Start ULT with a small dose, gradually increasing it to reach target levels while monitoring SUA. This can help avoid worsening pain. If pain worsens following the early initiation of ULT, it should be continued with an analgesic. This is similar to patients on ULT during a gout flare, who should continue their medication, as stopping temporarily offers no benefit. Lifelong follow-ups are essential for gout treatment and prevention. In an RCT, the initiation of ULT (allopurinol) during an acute gout attack did not result in significant differences in daily pain levels, the frequency of recurrent flares, or inflammatory markers [87]. In a febuxostat clinical study, the number of attacks reported one year after treatment was lower in the group with reduced SUA levels. This indicates that not adequately lowering SUA levels may lead to a higher risk of gout attacks over time [88].

Extensive long-term studies have demonstrated the clear clinical benefits of administering ULT. Achieving target SUA through ULT has been associated with the complete suppression of flares, reduction of tophi, an overall improvement in quality of life, and metabolic issues.

Patient education

Whenever feasible, every gout patient should be informed about the pathophysiology of the disease, treatment options for gouty arthritis, associated comorbidities, and indications for ULT. Inform them about the importance of the precipitating factor in the treatment and prevention of acute flare-ups.

Gout is a chronic and potentially progressive condition that necessitates long-term management. However, many individuals mistakenly perceive gout as an episodic illness, leading to poor medication compliance and inadequate treatment response or paradoxical attacks. Therefore, it is essential to discuss the treatment plan with patients to reduce the risk of gout attacks and address the metabolic complications associated with HU. Educating patients that ULT can cure gout encourages adherence to the treatment regimen [89].

Practical Issues in Short and Long-Term Management

In the management of gout, it is not clear when to start, how to start, which drug is ideal, how long to treat with follow-up, and managing comorbidities. In the majority of patients, flare-ups are due to not adhering to lifestyle recommendations, not taking ULT, and hence high SUA. There is no logic in waiting to disappearance/alleviation of pain. It is similar to hesitating insulin in the treatment of diabetic ketosis. The pain of acute gout is self-limiting with a time range of 72 hours, maximum 4-5 days. With this observation, the concept of managing acute gout should change. Pain relief is not the target; SUA level should be the target and aiming not at the joint but metabolic effects and UA deposition in other tissues should also be considered.

The selection of medication should be guided by the presence of comorbidities, the patient's prior response to treatments, the severity of flares, the number and type of joints involved, and the presence of tophi.

During the initial stages of ULT, some patients with gout may experience an exacerbation of pain, likely due to the release of crystals from dissolving UA deposits. This must be explained to patients and anticipated. This occurrence should not be considered a reason to discontinue or postpone ULT. Patients should be prescribed prophylactic

anti-inflammatory medication concurrently with the initiation of ULT.

Prolonged UA lowering can effectively reduce the frequency of attacks and comorbidities, too. Observational and interventional studies support this concept, and when ULT was discontinued from a group of gout patients who had been attack-free for 5 years, flares recurred if the serum urate level returned to a level above 7.0 mg/dL [90]. The higher the SUA, the more rapidly flares returned. Moreover, if gouty symptoms are prevented with anti-inflammatory agents without concurrently lowering the SUA level, the relentless process of occult UA crystal deposition will eventually set the patient up for worse, more treatment-resistant gout. An article published by Fernando Perez-Ruiz stated that after appropriate long-term treatment of HU in gout, with UA crystal dissolution as the therapeutic target, lifelong treatment can aim to maintain serum urate levels just below the threshold for saturation to prevent new crystal formation. This approach is similar to cleaning a dirty dish: more effort is needed to clean it initially than to maintain its cleanliness. [90]. The higher the SUA level, the more quickly flares returned. Furthermore, managing gout symptoms with anti-inflammatory agents alone, without reducing SUA, may lead to ongoing UA crystal deposition. This continuous deposition can eventually result in treatment-resistant gout, akin to other metabolic disorders [91]. If SUA levels are not treated to target, gout patients may still suffer from recurrent flare and other complications.

A Curable Disease: Why Is It Not Being Cured?

Gout is a curable form of inflammatory arthritis but often goes untreated. Despite new SUA-lowering drugs, gout and urolithiasis cases are rising. Effective treatments exist, yet management remains suboptimal.

Current guidelines aim for the cure of gout, but data show many patients receive inadequate advice and treatment. Gout should be cured, as HU often lacks noticeable symptoms but can lead to metabolic issues and subclinical gout. ULTs are often under prescribed and underdosed. Proper education for both patients and healthcare providers is essential for managing this easily diagnosed and curable form of arthritis, along with understanding the precipitating factors of acute flare.

Many older research articles stated that ULT is unnecessary after a first gout attack. A study by Yu and Gutman found that only 62% of gout patients had another attack within a year [92]. The author has not addressed the developments in subsequent years. Additionally, certain associations recommend excluding asymptomatic hyperuricemia from ULT until SUA levels reach 9 mg/dL. Today, advanced tools like DECT can detect sub-clinical gout and extra-articular UA deposits, making ULT mandatory in these cases. Allopurinol has long been recommended as a first-line ULT, but a 300 mg daily dose fails to reach the target SUA in over half of patients [93]. Although clinical cure is achievable and numerous evidence-based guidelines have been published, the prevalence of the condition continues to rise. Inadequate dose and reluctance in prescribing new UA-lowering drugs, along with non-adherence to lifestyle measures, may contribute to this issue.

The relationship between SUA levels and the probability of flares in gout is inconsistent. The prevalence of gout flares correlated with average SUA levels but not with SUA levels measured at a single point in time [94]. This suggests that SUA levels measured once may not accurately reflect the overall UA load.

Long-term observational studies have demonstrated that maintaining SUA levels below 6 mg/dL leads to a reduction in gout flares over an extended period [95].

Debates on the Prolonged Use of Colchicine in Gout

The primary aim in the management of acute gout is to reduce pain and associated metabolic issues. The older guidelines

emphasise more on colchicine as an anti-inflammatory agent for long duration. Colchicine has 307 known drug interactions, 7 disease interactions, and 1 alcohol/food interaction. Among the total drug interactions, 124 are categorized as major, 177 as moderate, and 6 as minor, according to Drugs.com.

Colchicine is not an analgesic, nor does it reduce UA, nor does it mobilize urate crystals from the tissues where already deposited. Most patients treated with colchicine may require additional anti-inflammatory medications for pain relief [96]. One possible benefit of NSAIDs is their intrinsic analgesic activity, which can reduce pain even before inflammation is completely suppressed [97]. Furthermore, colchicine does not prevent the deposition of UA crystals and UA-associated metabolic issues. Low dose steroid may be a better option in this situation. It reduces the pain and inflammation and has fewer drug interactions. Prescribing a medication like colchicine without sufficiently lowering SUA levels may not effectively manage inflammation. Hence, the importance of prescribing colchicine must be validated on a metabolic background.

What is the target level of uric acid in hyperuricemia management?

Major rheumatology societies advocate a treat-to-target strategy for SUA levels, recommending targets of less than 6 mg/dL for gout. This target is applicable to patients with HU with CKD and heart failure.

Whereas the target is less than 5 mg/dL in more severe cases such as those involving tophi, drug resistance, and nephrolithiasis [98]. During gout management, it may be suitable to consider more than one target for UA levels. In the initial phase of ULT, patients with multiple tophi and gout with a very high value of SUA may require a lower target of less than 5 mg/dl. Once flares and tophi have resolved, a higher target of less than 6 mg/dl may be appropriate [98].

The majority of gout patients successfully reduce SUA levels with the use of a single medication in conjunction with lifestyle modifications [99]. ULT is generally safer and better tolerated than anti-inflammatory drugs like colchicine, analgesics, or steroids, especially for patients with gout-related conditions like CKD, hypertension, T2DM, and CAD [100-102]. After initiating ULT, follow-up should be done after one month. Once the target is achieved, further assessments should take place at three months, six months, and, subsequently, a yearly UA estimation should be performed. If the target is not achieved dose escalation is required.

Clinical benefits of successful ULT

By reducing the frequency and severity of painful gout attacks, long-term ULT can shrink or eliminate tophi, thereby improving joint function and appearance. It prevents chronic arthritis and disability associated with untreated gout. Lowering SUA may reduce the formation of UA stones and slow the progression of CKD. Also, ULT may modestly improve cardiovascular risk markers and metabolic issues. By mitigating chronic inflammation, overall well-being is enhanced.

Limitations: This review relies on prior published studies, so its findings are influenced by the quality, diversity, and possible publication bias of those sources. Because this is a narrative synthesis instead of a systematic review or meta-analysis, its conclusions might be influenced by interpretation and may not include all the available evidence. Additional extensive and carefully conducted prospective studies are necessary to bolster the evidence base and confirm the suggested clinical methodology.

CONCLUSION

Gout is the most common type of curable and metabolically related inflammatory arthritis. It is a crystallo-metabolic disorder characterized by hyperuricemia, which has a spectrum of involvement and affects multiple bodily systems as a metabolic condition, and urate crystals can precipitate in different

parts of the body. Hyperuricemia involves multiple pathogenic mechanisms, including endothelial damage and oxidative stress, apart from crystal deposition. To date, dual-energy CT has redefined the description of gout and hyperuricemia. Healthcare professionals often concentrate on addressing acute episodes rather than considering gout as a metabolic disorder. Gout remains frequently undertreated, mismanaged, and ignoring metabolic issues. Focusing on reducing uric acid levels rather than relying solely on anti-inflammatory prophylaxis is essential to prevent flare-ups and metabolic aspects. Additionally, identifying a biochemical target and promptly initiating treatment are essential to avoid the recurrence of gout and associated comorbidities. Previously, gout management involved various approaches with differing conclusions. Now, it is time to unify these into a single approach. Thus, successful gout treatment involves addressing acute flare, early intervention to reduce serum uric acid, following a treat-to-target strategy, and managing uric acid-related metabolic disorders. Implementing screening programs, patient education regarding lifestyle measures, and regular follow-ups is highly recommended to cure the curable disease.

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