A Review on Gout

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Abstract*— The inflammation caused by urate crystals in the joint leads to gout, a common form of inflammatory arthritis. With arthritis as a side effect of this pathological accumulation, gout is now understood to be a disease predominantly caused by urate overload. Numerous significant co-morbidities, such as diabetes, obesity, chronic renal disease, and cardiovascular disease, are linked to it. Everywhere in the world, gout is becoming more common. The understanding of the genetic causes of both hyperuricemia and gout has advanced considerably. It has been determined that specific foods, alcohol, and several drugs are environmental risk factors for gout. But there isn't much proof that reducing these environmental dangers helps people with gout. First, nonsteroidal anti-inflammatories, corticosteroids, colchicine, or interleukin-1 inhibitors are used to treat inflammatory arthritis. The second method of treating gout involves these same drugs. Urate reduction is the second and most crucial method, with a target of 0.36 mmol/L (6 mg/dL) or maybe lower in those with tophi (collections of crystalline urate subcutaneously). In addition to reducing urate, adequate and extended gout flare prevention is necessary to stop the onset of acute flares. The number of available treatments may be greatly increased by the discovery of newer urate-reducing drugs. As medication adherence is low in chronic diseases in general, but especially in gout, patient education about the significance of lifelong urate-lowering therapy and prophylaxis of acute attacks is essential to the effectiveness of treatment.

I. INTRODUCTION

Gout is a prevalent form of inflammatory arthritis that is linked to serious co-morbidities such as type 2 diabetes, cardiovascular disease, and chronic renal disease. Inflammation brought on by urate crystals in the joints is what causes gout. After menopause, it is a prevalent cause of inflammatory arthritis in women and the most frequent inflammatory arthritis in males [1]. However, whereas historically gout has only been seen as a disease that first presents as arthritis, it is now more and more understood to be a urate overload illness, frequently accompanied by severe co-morbidities, and with inflammatory arthritis as a symptom of the later-stage disease [2]. Table 1 displays a recent suggestion to include illness phases. The working-age population is significantly impacted by gout, which also has an effect on physical function, presenteeism at work, and productivity [3-5]. In addition to being poorly understood and managed, gout is becoming more common in wealthy nations [6–9]. The goal of this publication is to discuss the epidemiology of gout, describe its therapies, and draw attention to some of its significant co-morbidities.

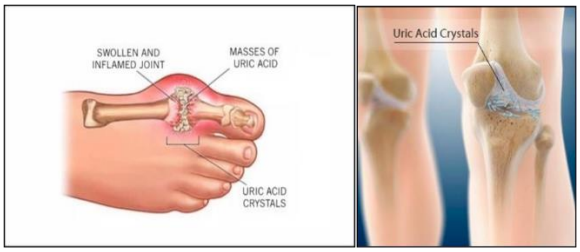

Figure 1.: Accumulation of uric acid crystals in implemented joints

II. GOUT'S SYMPTOMS AND EFFECTS

First metatarsophalangeal joint pain, often known as podagra, is a common but not always universal symptom of a gout episode (or "flare"). Some people may only experience one to two gout attacks in their lifetime or have attacks that happen so seldom that they happen months apart, but the majority will experience increasingly frequent attacks. As the disease continues gout can produce polyarticular attacks and the development of tophi, although tophi can also be the first sign of the condition. Subsequent attacks frequently involve additional joints, such as the knee. An ongoing joint inflammation caused by gout might eventually escalate to a chronic stage**.** Attacks are characterized by a sudden onset of intense pain (over 12–24 hours), which may be accompanied by edema and erythema of the joints directly above. Because severe or polyarticular episodes might mimic septic arthritis, cellulitis, or systemic illness

Table 1 system for gout staging proposed

Gout stage	Symptomatology	Description
A	Asymptomatic	Increased gout risk but no MSU crystal deposition
B	Asymptomatic	MSU crystal accumulation, but no gout symptoms or indications
C	Symptomatic	Crystal deposition at MSU and gout flares in the past or present
D	Symptomatic	Advanced gout that needs specialized treatment

Source. Adapted from Reference. [2].

Note. Patients can move from stage B directly to stage D. MSU – monosodium urate

induce a fever Joint aspiration is required, if at all possible, for diagnostic purposes since septic arthritis is on the differential diagnosis list. The formation of urate renal stones and gouty nephropathy are further consequences of chronic gout and persistent hyperuricemia.

If gout flare-ups are not managed, gout can have a significant negative impact on patients and their families quality of life. Gout sufferers may withdraw themselves from others to avoid potential physical contact during a flare-up since the pain is so severe, which also lowers their self-efficacy in terms of personal care [5,10]. As patients try to avoid the risk of triggering a flare or being caught out of their homes when one happens, the pain associated with recurring flares can also lead to decreased involvement in social and recreational activities [10]. Workplace performance might be significantly impacted by gout. The average number of days missed from work per year for people with gout is 4.6 more than for people without the condition [4], while some people have found that this number is closer to 25 days [5]. In order to account for flare-ups and mobility problems, work activities may need to be adjusted. The fact that chronic gout patients perform badly on health-related quality-of-life tests is therefore not surprising [10]. Together, these show that gout affects more than simply the joints; in fact, gout can significantly affect patients' and their families lives if it is not well managed through treatment, contrary to what is commonly believed.

III. EPIDEMIOLOGY OF GOUT

Fundamentally, gout is an overproduction or underexcretion of urates illness, which historically has been classified as an overload [2]. The transporter ABCG2 has recently been recognised as being crucial in the intestinal excretion of urate [11]. As a result, a brand-new hyperuricemia classification scheme has been proposed (see Table 2).

Clinical gouty arthritis has a high correlation with serum urate levels, and gout risk increases over time with hyperuricemia [12,13]. It should be noted, nevertheless, that gout only occurs in a small percentage of people with hyperuricemia. For instance, hyperuricemia was more common than gout in the US in 2007–2008, where it was 21% [14]. It is unclear why only a small percentage of people with hyperuricemia go on to develop clinical gouty arthritis.

Table 2 A new pathophysiological classification for hyperuricemia.

Type	Subtype
A.Renal overload type	A1.Overproduction type A2.Extrarenal under excretion type
B.Renal under excretion type	

Source. Adapted from Ref. [11].

ABCG2 impairment is hereditary. Note that a patient's hyperuricemia could result from

a number of different factors.

Age-related increases in the prevalence of gout are more pronounced in males than in women. In part, because estrogen encourages urate waste in the urine, women experience gout at a far lower rate than males do before menopause. Studies from the United States, including those from the National Health and Nutrition Survey Examination (NHANES) surveys, as well as

those from New Zealand, China, and the United Kingdom, have revealed that gout is becoming more common [15,16]. Population prevalences have been reported to be between 1% and 6%. This broad range is the result of several genetic and environmental variables in addition to variations in research methodology. In New Zealand, for instance, older Maori and Pacific Islander men are more likely to have the condition than other men [1,17]. Intriguing new research has shown interactions between dietary influences and genetic risk factors for gout, a disease with significant environmental and genetic risk factors.

3.1 GENETICS OF GOUT

Even if a precise estimate of the heritability of gout is difficult to come by, it is certain that significant genetic effects have a significant impact on the chance of developing gout [17]. A very high 60–90% heritability has been shown for the crucial precursor hyperuricemia [18,19]. Recently, several sources have explored the genetics of gout in-depth [20–22]. In a nutshell, early research linked certain transporters, such as SLC2A9 (GLUT9), ABCG2, and SLC22A12, to the likelihood of developing gout. Subsequently, larger investigations found genes critical for carbohydrate metabolism and the control of insulin and glucose levels [23]. The bulk of repeated urate relationships in the most recent analysis was likewise connected to the subset of people who had gout. Having a higher genetic urate score indicates an increased risk of developing gout [23]. This suggests that, in addition to renal urate processing, carbohydrate metabolism is crucial for serum urate levels and, consequently, gout risk.

3.2 THE EFFECTS OF ALCOHOL AND FOOD

Numerous outcomes from extensive epidemiological research have been Foods that can cause gout include sugar-sweetened beverages [24], alcohol [25], red meat [26], shellfish [26], and fruit juice [24]. High fructose content is a contributing factor in several of these correlations [24,27]. High fructose corn syrup (HFCS), a key component of many processed meals, baked goods, and snacks, has the effect of raising serum urate. This is assumed to be because the hepatic metabolism of fructose causes ATP depletion, which leads to an increase in purine oxidation and urate synthesis [28]. Numerous meals have also been demonstrated to offer protection. Several milk products [26], coffee [29], and cherries [30] were included in epidemiological investigations. Consuming skim milk powder enhanced with two dairy fractions (glycomacropeptide and G600 milk fat extract) over the course of three months lowers gout flare-ups, according to intervention trials conducted on gout patients [31]. The therapeutic relevance of these relationships between foods and gout, however, may not be as significant as the focus placed on them in clinical settings [32]. Low-purine diets are challenging to maintain, and there is little proof that they lessen gout flare-ups or long-term joint damage. We contend that encouraging increased adherence to urate-lowering therapy is more likely to be effective than promoting a rigorous low-purine diet. A lot of diet therapy trials for weight loss show that long-term adherence is quite low, even though there is a dearth of data especially in gout [33,34].

3.3 DRUGS AND DIETARY SUPPLEMENTS

An increased risk of gout is linked to both thiazide and loop diuretics [35]. Genetic variations that raise serum urate levels and the use of diuretics, which causes gout to flare up, can interact as well[36]. Diuretics doubled the incidence of gout in those with higher genetic susceptibility to hyperuricemia, while they had no effect on gout risk in people with reduced genetic susceptibility. Epidemiological studies have shown an increased incidence of gout with the use of other anti-hypertensives such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and non-losartan angiotensin II receptor blockers [37]. Losartan and calcium channel blockers, on the other hand, are linked to a lower risk of gout [37]. According to a recent study, taking allopurinol reduced the incidence of gout episodes from aspirin (OR = 1.9 for 100 mg) [38]. Observational studies have shown a negative correlation between serum urate levels and vitamin C intake [39]. Higher vitamin C levels have been linked to decreased gout incidence in prospective studies, and vitamin C supplementation has been linked to lower serum urate levels [40,41]. However, an 8-week, 500 mg/day vitamin C treatment trial that was randomized showed no clinically significant impact on urate reduction [42]. It seems that vitamin C supplementation's impact magnitude is insufficient to support its usage in the treatment of gout.

3.4 CONNECTIONS BETWEEN ENVIRONMENTAL AND GENETIC FACTORS

It is obvious that the interaction between genetics and the environment affects the chance of developing gout [43]. When men from the Pacific island nation of Tokelau immigrated to New Zealand, Prior and colleagues found a startling increase of gout [44]. The prevalence ratio was nine times greater for people residing in New Zealand than for people still in Tokelau throughout a 14-year period of age-standardized prevalence observation. Environmental factors have a significant impact, as shown by the study, which was done between 1968 and 1982. This happened more than 20 years before many modern dietary ingredients that are thought to be detrimental to metabolism, like high fructose corn syrup, were introduced [45,46]. In a reverse version of this study, Australian Aborigines with type 2 diabetes were returned to their pre-hunter-gatherer habitat, which led to considerable weight loss and the normalization of their metabolic dysfunction [47]. Although gout was not particularly addressed, there is a clear correlation between metabolic dysfunction and gout, and recent genetic research suggests that obesity fuels hyperuricemia [48]. Recent studies showing that genetic variations in the renal transporters SLC2A9, ABCG2, and SLC17A1 all alter the response to oral fructose doses provide more direct experimental evidence [49–51].

IV. SUMMARY OF THE TREATMENT

There are two basic types of gout treatment: symptomatic urate-lowering treatment (ULT) is used to treat acute gout episodes and prevent future flare-ups over the long run. Adequate acute gout flare prevention during ULT therapy is essential to the course of treatment. ULT has historically been managed suboptimally, along with the concurrent prevention of flares during ULT.

4.1ACUTE ATTACK TREATMENT

Colchicine, NSAIDs, and corticosteroids are the three main medicinal substances used to treat acute episodes. First-line treatment for acute gout attacks is advised to include colchicine, NSAIDs, and colchicine [52]. When one or two big joints are implicated, intraarticular corticosteroids are a possibility. All of these medications have risks and advantages, with NSAIDs being generally contraindicated in renal and some gastrointestinal illnesses, colchicine being constrained by renal function, and corticosteroids worsening diabetes, a common co-morbidity with gout [53]. Interleukin-1 (IL-1) inhibitors are a more recent treatment option for acute gout flares [54]. A crucial part of the inflammatory response to the monosodium urate crystals during a gout flare is played by the cytokine IL-1. A human antiIL-1 drug called canakinumab can be used to treat sudden gout flare-ups [55]. However, it is more expensive and has a higher risk of infection than standard gout flare therapy. According to the most recent American College of Rheumatology (ACR) guidelines, treatment should begin within 24 hours of the commencement of a flare, and, most significantly, urate-lowering medication (ULT) should not be discontinued during an acute gout flare [52]. A specific medicine should be chosen depending on the level of pain, the number of joints involved, and any co-morbidities that might be present. When episodes are severe or polyarticular, combination therapy may be performed.

4.2 THERAPY TO DECREASE URATE

Allopurinol has been a mainstay of ULT for gout. Xanthine oxidase is blocked by allopurinol, which reduces uric acid generation. Allopurinol is useful for lowering SUA when administered regularly and in appropriate amounts. Although only 2% of patients will experience allopurinol hypersensitivity syndrome (AHS), which has a modest but significant risk of becoming deadly in some of these individuals, the medication is generally well tolerated [56]. The HLA-B*5801 allele, which is more common in people of South East Asian and Central Asian descent, significantly raises the risk. As a result, populations at high risk should undergo testing for this allele.

The Hande renal dose recommendations were put forth in response to the finding that people with impaired renal function have a higher incidence of AHS [57]. These recommendations recommend a maintenance dose schedule depending on renal function and have been widely disseminated and supported. According to studies [58], this diet results in ineffective gout treatment. AHS risk is thought to be influenced by the beginning dose of allopurinol rather than the maintenance dose, according to more recent research

[59]. It has been noted that individuals with impaired renal function require potentially slower dose escalation, which raises the possibility that inducing immunological tolerance may take some time.

This circumstance might be comparable to the abacavir-HLA-B*5701 interaction, which discovered that abacavir bonded to the HLA-B*5701 molecule and changed antigen presentation [60,61]. Because of this, the ACR advises starting allopurinol at no more than 100 mg per day in any patient and 50 mg/day in stage 4 or worse chronic renal disease, and gradually titrating the dose higher every 2–5 weeks to attain target serum urate[62]. As long as there is sufficient patient education and drug toxicity monitoring, the daily dose of allopurinol can be increased from 300 mg.

Reviews of dosing procedures have shown that most doctors typically prescribe ULTs (mostly allopurinol) at doses that are unlikely to lower SUA levels to the desired level of 36 mmol/L (6 mg/dL) [54,63,64]. Many doctors also provide allopurinol at a set dose without checking SUA levels, even though the optimal course of treatment calls for the dose to be increased until the desired SUA levels are reached [63,65]. The FDA has now advocated for this "treat-to-target" approach [64]. Effective gout treatment is still hampered by the use of fixed-dose prescriptions and a lack of physician SUA-level monitoring. A more recent uricostatic ULT called febuxostat has been proven to be successful in lowering SUA levels [65–67]. When compared to allopurinol, febuxostat provides a number of advantages for elderly patients, such as a lower risk of medication interactions and perhaps a safer safety profile for individuals with renal impairment [67]. However, there are some worries regarding potential cardiovascular problems linked to febuxostat, and the cost is a major consideration [54,66,67].

The uricosuric agents are somewhat less often used ULTs (benzbromarone, probenecid, and sulfinpyrazone). These medications increase the excretion of uric acid in urine [67]. Although they are efficient at lowering SUA levels, it was believed that their effectiveness would decline in people with impaired renal function, even at levels that are typical for gout sufferers [67]. Probenecid, however, may be useful in patients with an eGFR of less than 50 mL/min, according to recent research [68]. In particular, in patients with cardiovascular disease who have tight fluid intake limitations, there are worries about kidney damage brought on by the deposition of monosodium urate crystals in the kidneys [66].

Urate is transformed into soluble allantoin by the pegylated recombinant uricase known as pegloticase. The most severe, treatment-resistant diseases are the only ones that should utilize this intravenous medication [69].

According to American College of Rheumatology guidelines, either allopurinol or febuxostat should be used as the first line of therapy; however, third-party payers frequently insist on using allopurinol first because of the significant cost differential [62]. No matter what kind of drug is employed, treating to a target serum urate level is necessary for successful treatment. Urate should ideally be less than 6 mg/dL (36 mmol/L), and ideally less than 5 mg/dL (30 mmol/L), according to the ACR. People with severe illnesses or tophaceous diseases may benefit from this lower target.

4.3 POOR COMPLIANCE WITH URATE-LOWERING TREATMENT

ULT must be taken regularly in order to be effective. According to research, gout patients' compliance with ULT is frequently insufficient for the treatment to be effective [7,63,65,70-72]. Gout patients show notably low levels of medication adherence when compared to people with other chronic diseases [7].

Several causes causing this have been identified through qualitative research among gout patients. Even if they have not had a flare in a while, patients report not knowing that ULT drugs are still required. Additionally, they claim that they are uncomfortable seeking clarification from their healthcare providers because they feel under-informed about gout and ULT [73,74] as a supplier. As a result, it is not surprising that the primary informational sources are frequently family and the local community, which contributes to the persistence of beliefs about gout and its treatment [75]. Numerous significant factors have been identified through qualitative research among gout patients. Patients claim that even if they have not had

a flare in a while, they are unaware that ULT drugs must be taken. Additionally, they express feeling uneasy about seeking clarification from their health care providers and feeling under-informed about gout and ULT.vendor [73,74]. The fact that family and community are frequently the primary information sources and that myths about gout and its treatment are so perpetuated is not surprising [75].

Unmanaged gout can, as previously said, significantly affect patients' quality of life. In order to reduce these effects, ULT is essential. Successful ULT has been demonstrated to significantly enhance health-related quality of life parameters in gout patients [10].

4.4 ACUTE GOUT FLARE PREVENTION DURING ULT

Flares of gout during ULT are a key component of gout treatment that are frequently handled ineffectively and can harm the therapeutic relationship. NSAIDs plus proton pump inhibitors (PPIs), such as omeprazole, or oral colchicine were suggested as first-line therapy in the 2012 ACR recommendations [52]. Additionally, they said low-dose prednisone might be utilized, but the dangers and advantages must be weighed equally. If there is ongoing gout activity, such as tophi, recurring attacks, or chronic gouty arthritis, prevention against acute gout flares should continue. The ACR recommendation task force went on to specifically advise a longer flare prophylaxis period of I 6 months of therapy, (ii) 3 months of therapy following the achievement of the SUA target for patients in whom no tophi have been found, or (iii) 6 months of prophylaxis following the achievement of the SUA target for patients in whom resolution of previously detected tophi has been observed.

4.5 UPDATED TREATMENTS

Arhalofenate is an anti-inflammatory and uricosuric drug, and codeine is a purine nucleoside phosphorylase inhibitor that acts upstream of xanthine oxidase, where allopurinol acts. These newer therapeutics are lesinurad, a uricosuric that blocks URAT1 [77], a kidney urate transporter, and halogenated. A benzodiazepine derivative called levotofisopam is being looked into as a potential treatment for gout since it exhibits uricosuric effects [78].

V. CO-MORBID CONDITIONS

Gout frequently develops alongside other illnesses such as hypertension, renal failure, diabetes mellitus, and cardiovascular disease. Actually, hyperuricemia may serve as a separate risk factor for certain of these ailments [66]. Additionally, several of these ailments and the medications used to treat them can affect SUA levels. In this regard, getting really involves more than just joints and may have significant health repercussions.

5.1 HYPERTENSION

Around 40% of people with gout also have hypertension, making it a common co-morbidity of gout and hyperuricemia [66]. Raised SUA levels are a risk factor for developing hypertension, and ULTs like allopurinol have been proven to lower blood pressure [66,79,80]. Hyperuricaemia may therefore be a cause of hypertension in and of itself.

5.2 KIDNEY DYSFUNCTION

The nature of this link has been disputed [80], despite the fact that chronic renal disease is a well-known co-morbidity of gout. The occurrence of urate kidney stones is known to be influenced by hyperuricemia. Recent epidemiologic and animal investigations indicate that hyperuricemia may cause renal failure and kidney disease on its own [66,80]. This opinion is supported by allopurinol's favorable effects on renal disease in hyperuricemic patients [65]. A recent genetic-epidemiologic investigation that used Mendelian randomization, however, found no evidence to support this information and, surprisingly, revealed that urate enhanced kidney function [81]. Delineating this relationship certainly needs a lot more work.

5.3 DIABETES MELLITUS

Although the basis of this link is complex, numerous cohorts have observed that diabetes is frequent in gout patients [82,83]. According to Choi and colleagues, people with moderately elevated HbA1c levels had a higher chance of developing gout, but as fasting blood glucose or HbA1c climbed, the amount of serum urate decreased. This is probably because blood glucose levels higher than 10 mmol/L have uricosuric effects [84]. These findings were reinforced by research conducted on a sizable cohort of more than 18,000

diabetes patients, in which a low HbA1c was associated with an increased risk of gout [85]. Intriguingly, a subsequent study utilizing Mendelian randomization again revealed that obesity is directly related to elevated serum urate levels [48]. Obesity and type 2 diabetes are strongly associated.

5.4 A CARDIOVASCULAR CONDITION

Hyperuricaemia has been linked to higher cardiovascular morbidity and death, just like hypertension [66,86]. Although greater levels of SUA also increase the risk of CVD mortality in gout patients, it appears that gout may raise the risk of CVD mortality independently of hyperuricemia [86]. There is now conflicting evidence, therefore it is unclear if urate has a causative role in cardiovascular disease [87,88].

5.5 ENHANCING THERAPY

Gout and other chronic diseases frequently co-occur. important to take into account on their own. Nevertheless, a sizable proportion of people will experience gout plus one (if not more) of the illnesses mentioned above in middle to later life due to the chronic nature of these disorders. It is crucial to understand that pharmaceutical therapies for one can have an impact on the other. Beta-blockers, loop, and thiazide diuretics have been reported to raise SUA levels, whereas ACE inhibitors and calcium channel blockers diminish SUA levels [65,66]. Certain antihypertensives can also affect SUA levels. SUA levels are decreased in a similar manner by the lipid-lowering medications atorvastatin and fenofibrate [65,66]. Allopurinol, on the other hand, has been found to lower blood pressure in hypertensive individuals as well as lower CVD morbidity and mortality [65,66,79]. Additionally, it has been demonstrated to decrease the progression of renal illness and can enhance renal function in gout patients [65,66]. In order to maximize the potential advantages of pharmaceutical treatment for gout patients with co-morbidities, the right medication selection is unquestionably crucial.

VI. CONCLUSION

In part thanks to the new medicines that are currently being developed, there is an expanding amount of study into the causes, processes, and management of gout. Still, there is a lot more to discover. Even while affordable treatments are widely available, they are not recommended properly and are often not followed. This is unquestionably multifactorial and involves, but is not limited to, issues with disease education, literacy and numeracy barriers, and intercultural communication. The community also holds a lot of false beliefs that could be harmful and stigmatize people with gout and prevent them from getting the proper care.

Future studies should concentrate on both the fundamental causes of gout pathogenesis, like genetics and cellular inflammation cascades, as well as close-to-the-patient issues, like patient education and therapy concordance. An area the field is presently researching that has the potential to have an enormously wider impact than only those with gout is the connection between urate and a number of significant co-morbidities and whether it is causally related.

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