

Gout Through the Ages: Past, Present, and Future

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ABSTRACT

Gout is a disease unique to humans, resulting from the evolutionary loss of functional uricase, the enzyme that converts uric acid to the more soluble allantoin. This loss causes elevation of serum uric acid (SUA). With sustained hyperuricemia, deposition of monosodium urate (MSU) crystals in and around joints and extra-articular tissues occurs. Clinically, gout manifests as recurrent episodes of acute inflammatory arthritis and, when untreated or undertreated, may progress to more frequent flares, tophus formation, and structural joint damage. Persistent hyperuricemia is also linked to nephrolithiasis, chronic kidney disease progression, and increased cardiometabolic burden. This review summarizes gout across the past, the present, and the future. Historical perspectives span early descriptions dating to the Egyptian period and extend through the period just prior to the discovery of light microscopy that led to enabling identification of MSU crystals. The modern era is reviewed through the development of classification criteria; mechanisms of MSU crystal-induced inflammation; genetic determinants of urate homeostasis; and the roles of renal and intestinal urate transport in hyperuricemia. Metabolomic signatures and gut microbiota are discussed alongside current approaches to urate-lowering therapy (ULT) and flare prevention. Future directions include precision, individualized medicine integrating clinical features with molecular and imaging data to improve risk stratification and guide therapy. They also include targeted anti-inflammatory strategies, newer ULT and uricosuric agents, and the application of metabolomics and microbiome science. Finally, the long-term possibility of uricase gene restoration as a transformative approach to reconstitute urate metabolism and potentially modify disease course is discussed.

KEYWORDS gout, hyperuricemia, uric acid, treatment, management

INTRODUCTION

Gout is a chronic inflammatory condition marked by episodes of sudden, painful arthritis caused by long-term high serum uric acid (SUA) levels that exceed solubility and form monosodium urate (MSU) crystals in body tissues, especially in and around joints. If left untreated, the crystal burden increases and can lead to more frequent flares, tophi, and progressive joint damage and deformity. Gout can also affect kidneys,

contributing to renal insufficiency and urinary stones. Hyperuricemia and gout have also been linked to cardiovascular diseases. Gout is essentially unique to humans because of the loss of functional uricase during evolution. Uric acid has both prooxidant and antioxidant properties, with its antioxidant role possibly offering protection against oxidative damage and supporting longevity under certain conditions (1, 2).

Gout is considered an ancient disease, having been described several thousand years ago. With advances in clinical medicine, substantial progress has been made in the diagnosis and management of gout. In addition, several emerging strategies are currently being developed to improve gout control in the future. This review focuses on the diagnosis and management of gout from antiquity to the future.

THE ANCIENT PERIOD

The oldest evidence of gout in humans was identified in the uric acid-containing urinary calculi in an Egyptian mummy from approximately 7000 BC (3) and by the presence of a tophus at the great toe of an Egyptian mummy (4). Unfortunately, nothing was known about the characteristics of the disease at that time.

The documented history of gout dates back to ancient Greece, when Hippocrates (460–370 BC), known as the ‘Father of Medicine,’ described gout as the ‘unwalkable disease’ and used the term “*podagra*” to refer to acute arthritis of the big toe. He believed that gout was the result of an excess of one of the human humors. He wrote 5 aphorisms on gout which remain valid until now. These aphorisms are 1) eunuchs do not get gout or become bald, 2) women do not get gout unless their menstrual periods cease, 3) young men do not get gout before they become sexually active, 4) gout-related inflammation usually subsides within 40 days, and 5) gout attacks are more common in spring and autumn (5). Aelius Galenus (129–216 AD) was another Greek physician, described as “the most accomplished of all medical researchers of antiquity,” who described the characteristics of gout and tophi. Galen believed that human diseases were caused by imbalance of the four human humors: 1) blood (sanguine), associated with the heart and air; 2) yellow bile (choleric), associated with the liver; 3) black bile (melancholic), associated with the spleen; and 4) phlegm (phlegmatic), associated with the brain and water (6).

Interestingly, despite the long duration of the Roman and Byzantine periods, there was not much information regarding gout. However, it was recognized that gout was more prevalent among the rich and was sometimes named the “disease of kings.” This likely reflected the very high consumption of wine among the wealthy. Unfortunately,

Roman wines were sometimes prepared with grape syrup to enhance the color, sweetness, and preservation, which was boiled down in a lead pot, resulting in contamination with lead. This could cause lead poisoning, renal toxicity, and gout (7). Whether this led to the end of the Roman empire is speculative (7, 8).

No specific treatment for gout was identified during the Egyptian period; however, there was evidence that the Egyptians treated several diseases by using plants, animal products, and minerals. In addition, they also used precious metals and stones to prevent disease (9). Hippocrates believed that diet could efficiently control and prevent gout. His treatment included using high-dose white hellebore to induce vomiting and diarrhea; however, this herb could be toxic to the cardiovascular and neurological systems (10). He also suggested scorching the veins contiguously with the affected joint. The first evidence of a pharmacologic approach to the treatment of gout probably started with Alexander of Tralles, a Greek physician during the 6th century (around 600 AD), who used autumn crocus (*Colchicum autumnale* - which contains colchicine) as a powerful purgative during that time. Due to the toxicity of autumn crocus, it was not used to treat gout for several centuries (11).

THE MODERN PERIOD

Diagnosis of gout

The modern period of gout might be considered to have started when Antoni van Leeuwenhoek (1632–1723 AD), a Dutch scientist, invented the microscope in 1677 to examine parasites and bacteria (12). With his microscope, he also observed a solid material resembling chalk in patients with gout but did not know its nature. Approximately 100 years later, in 1787, the British chemist William Hyde Wollaston identified the chemical structure of uric acid (13). During this period, Thomas Sydenham (1624–1689), an English physician who also suffered from gout, gave a very clear clinical description of an acute gout attack (5). During the 19th century, Alfred Baring Garrod, a British physician, emphasized the close link between gout and elevated uric acid. He described these deposits as crystalline and interstitial and proposed that urate deposition is a primary driver of the inflammatory process rather than a consequence of it. Unfortunately, many physicians

at that time did not accept his explanation (14). An association between gout and uric acid was clearly demonstrated by McCarty et al. in 1961 when he identified MSU crystals, using both ordinary and polarized light microscopy, in synovial fluid obtained from patients with acute gouty attacks (15). He performed an experiment in which injection of MSU crystals into himself and canine joints caused an acute gouty arthritis attack shortly after the injection (16).

Classification criteria

Since the discovery of MSU crystals, the knowledge of hyperuricemia and gout has expanded markedly. Several classification criteria have been developed, including Rome 1963 (17), New York 1966 (18), American Rheumatism Association (ARA) 1977 (19), Mexico 2010 (20), the Netherlands 2010 (21), and the most recent 2015 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria (22). All of these criteria have shown variable sensitivity and specificity, with overall acceptable performance (22–24). The advantage of the 2015 ACR/EULAR classification criteria is that the diagnosis can be made without identification of MSU crystals, and the criteria are based on a weighted scoring system. Those who have a score of ≥ 8 can be classified as gout. In addition to obtaining scores based on the location of joint involvement, the characteristics and time course of typical arthritis, and SUA levels, scores can also be obtained from advanced imaging modalities (e.g., ultrasound (US), dual-energy computed tomography (DECT), or magnetic resonance imaging (MRI)) that show specific imaging characteristics of gout. These instruments have shown high sensitivity and specificity for MSU deposits (25, 26). Use of these imaging techniques is not only for diagnosis of gout but also for monitoring dissolution of MSU crystals during follow-up (27). However, these classification criteria have some limitations. The clinical characteristics of gout, such as the characteristic episodic pattern of joint inflammation and the time course of gout flares, might vary among individuals, making it difficult to obtain these scores using the current classification criteria (22). Moreover, a limitation of these criteria is that individuals who meet the minimal score may not actually have gout, whereas

individuals with other diseases may exceed the minimal score required for gout classification (24).

Pathogenesis of gout

The pathogenic mechanism of hyperuricemia in gout was initially demonstrated in 1965 by Wyngarden, who found that patients with gout required SUA levels approximately 2–3 mg/dL higher than normouricemic controls to achieve the same level of uric acid excretion through the kidney, indicating that gout patients had a defect in urinary excretion of uric acid (28). In addition, during that same period, Lesch-Nyhan syndrome, a rare sex-linked recessive disease characterized by severe hyperuricemia and severe neurological deficits (cerebral palsy, mental retardation, movement disorder, and aggressive behavior), was identified and was later found to be due to deficiency of hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) enzymes that convert hypoxanthine to inosine monophosphate in the purine and uric acid synthesis pathway (29, 30).

Pathogenesis of MSU crystal-induced inflammation

MSU crystal-induced inflammation became a central focus of gout research soon after MSU crystals were identified as the cause of acute gouty arthritis. Early work showed that shortly after neutrophils and mononuclear phagocytes ingest MSU crystals, crystal-containing phagosomes fuse with lysosomes; subsequent rupture of the phagolysosomal membrane causes cell injury or death and the release of inflammatory mediators (31). These mediators include prostaglandins, kinins, proteolytic enzymes, and reactive oxygen species, which amplify local inflammation and recruit additional leukocytes (32). Later studies showed that MSU crystals, when combined with lysosomes, can activate NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, leading to activation of caspase-1 and production of interleukin-1 β (IL-1 β), a key cytokine driving the acute gout flare (33–37). MSU crystals can also act as danger signals by priming and augmenting inflammatory signaling through Toll-like receptors and activating the MyD88 intracellular pathway, thereby promoting further IL-1 β production (37). Multiple cell types, including neutrophils, monocytes/macrophages, and lymphocytes, are involved

in this process (37). Activated neutrophils can generate neutrophil extracellular traps (NETs), which may both intensify inflammation and participate in subsequent containment of crystals (38).

The resolution of a gout flare involves coordinated counter-regulatory mechanisms such as crystal coating/opsonization; apoptosis and efferocytosis of recruited cells with increased transforming growth factor β (TGF- β); induction of anti-inflammatory cytokines, such as IL-10 and IL-37 (33, 37, 38); activation of transcriptional regulators such as PPAR γ (36); and engagement of specialized pro-resolving lipid mediators (e.g., lipoxins, resolvins, protectins, and maresins) that limit leukocyte recruitment and promote restoration of tissue homeostasis (38).

Uric acid transporters

Several decades later, researchers found that defect in renal excretion of uric acid was due to abnormalities in several tubular urate transporters that control uric acid excretion, including urate transporter 1 (URAT1), glucose transporter 9 (GLUT9), ATP-binding cassette sub-family G member 2 (ABCG2), and other organic anion transporters (OATs) (39). In addition, with advances in genetic studies, several genetic loci have been found to be associated with these urate transporter abnormalities, for example, SLC22A12 for URAT1, SLC2A9 for GLUT9, SLC22A11 for OAT4, and SLC22A13 for OAT10 transporters. These genetic abnormalities differ among ethnic groups, and several loci are commonly observed among individuals of Asian descent (SLC22A12, ABCG2, SLC2A9, and others minor alleles) (40–42).

Generally, hyperuricemia can be classified into 2 types, according to renal excretion. The under-excretion type (urine uric acid [UUA] < 600 mg/day on a purine-free diet), the major cause of hyperuricemia, is mainly caused by abnormality of URAT1 transporter in the renal tubules. However, a recent study found that abnormality in ABCG2 (both in the renal tubules and intestinal mucosa) also plays an important role in hyperuricemia. Defects in the ABCG2 transporter result in diminished intestinal uric acid excretion, and a shift toward increased renal uric acid excretion (or renal overload type) (43). However, selection of urate lowering therapy (ULT) is still based on whether the patient is classified as a uric acid un-

derexcretor (UUA < 600 mg/day) or an overexcretor (UUA $\geq$ 600 mg/day).

Gut microbiota

Recently, gut microbiota has been linked to many human diseases through its role in modulating immunity. Gut microbiota may contribute to both the development and prevention of hyperuricemia. Several *Lactobacillus* species can break down inosine and guanosine, thereby inhibiting uric acid biosynthesis and reducing intestinal purine absorption, which helps maintain lower uric acid levels. In contrast, other bacteria such as *Escherichia* and *Shigella* species can secrete xanthine deaminase, an enzyme that converts hypoxanthine and xanthine to uric acid, resulting in higher uric acid level. Furthermore, *Phascolarctobacterium* and *Bacteroides* species have been reported to be prominent and proposed as part of a “core microbiota” in gout patients. *Bacteroides* species have been associated with purine metabolism and may influence urate handling, including pathways related to conversion of uric acid to allantoin. Long-term consumption of diets enriched with fructose, purines, and fat can modify the composition of the gut microbiome, which can affect the intestinal role in purine and uric acid metabolism. On the other hand, elevation of SUA can induce chronic inflammation in the intestinal tract, potentially resulting in further changes to the composition of the gut microbiome. This supports a bidirectional relationship between the gut microbiome and uric acid (44–46).

Treatment of gout

Due to the toxicity of autumn crocus, this plant was not used for the treatment of gout until 1833, when Pierre-Joseph Pelletier and Joseph Bienaimé Caventou, two French chemists, isolated colchicine from the root of autumn crocus (47). Unfortunately, colchicine was not used in the treatment of gout until 1967, when Wallace performed a clinical study using high-dose colchicine for the treatment of gout and showed its therapeutic effectiveness, despite many patients developing diarrhea (48). This high-dose regimen of colchicine was used as a therapeutic diagnostic test for gout for several decades. In 2010, Terkeltaub et al. found that a loading regimen of low-dose colchicine was as effective as a high-dose regimen,

but with fewer adverse events (49). A recent study showed that a non-loading colchicine regimen was also as effective as a loading low-dose regimen (50).

Aspirin, the first non-steroidal anti-inflammatory drug (NSAID), was identified in 1897 and was synthesized and marketed two years later. Interestingly, aspirin at high dose has a uricosuric effect, whereas at low dose it causes hyperuricemia. However, aspirin was not recommended for the treatment of gout due to concern that it could interfere with SUA levels and aggravate acute gout attacks. The second NSAID, phenylbutazone, synthesized in 1949, was effective in controlling acute arthritis in gout (51). It also has a uricosuric effect. However, it was withdrawn from the market around 1980 due to its association with blood dyscrasia (52). Subsequently, several NSAIDs (such as indomethacin, ibuprofen, naproxen, diclofenac, etc.) were developed and remain widely used in the treatment of gout. However, gastrointestinal toxicity is recognized as a major adverse effect of these compounds. Around 1990, the COX-2 enzyme was identified as a major mediator of inflammation in the prostaglandin pathway. Subsequently, specific COX-2 inhibitors, such as celecoxib and etoricoxib were developed and have been shown to be as effective as traditional NSAIDs, with fewer gastrointestinal side effects (53, 54).

Urate lowering therapy

The fundamental principle of gout treatment is preventing recurrent flares and promoting MSU crystal dissolution. This goal of treatment is not only to control symptoms but also to bring the disease into remission by using ULT. Currently, three classes of ULT are available: xanthine oxidase inhibitors (XOIs; allopurinol, febuxostat, and topiroxostat), uricosuric agents (probenecid, benzbromarone, sulfinpyrazone, and dotinurad), and uricase-based therapy (pegloticase). The concept of treat-to-target (T2T) in gout began around 2012, when physicians realized that bringing SUA down below its saturation point, typically < 6.0 mg/dL can lead to dissolution of crystals, prevention of flares, and possibly bring gout into remission. In achieving this goal, patients' education and adherence to medications, as well as SUA monitoring, play a very important role in reaching

the target (55, 56). Currently, clinical remission is defined as no gout flares over 12 months, absence of subcutaneous tophi, and SUA < 0.36 mmol/L (< 6 mg/dL) over 12 months (57). However, this definition does not include criteria confirming complete resolution of MSU crystal deposition from the body.

Several international rheumatology organizations, including the ACR (58), the EULAR (59), and the Asia-Pacific League of Associations for Rheumatology (APLAR) (60), have recommended XOIs, particularly allopurinol, as first-line therapy for hyperuricemia in gout, and consider uricosuric agents when patients cannot tolerate allopurinol or XOIs, or have an inadequate response to them. Uricase-based therapy is reserved for those who fail to respond to XOIs or uricosurics. The major concern regarding XOIs, particularly allopurinol, is the development of severe cutaneous adverse reactions (SCAR) or allopurinol hypersensitivity syndrome (AHS). This life-threatening condition is strongly associated with the presence of HLA B*58:01, which is more prevalent in East and Southeast Asian populations (61, 62). Genetic screening is recommended prior to initiating allopurinol in individuals of East and Southeast Asian descent, including Han Chinese, Koreans, and Thais (58), and in countries or areas where the population has a gene frequency of > 5% (60, 62). However, routine HLA B*58:01 screening prior to allopurinol initiation is complicated in developing and least developed countries by population diversity, limited access to the test, and associated costs, thus hindering widespread implementation. The limitation to widespread implementation of HLA-B*58:01 screening is its relatively low positive predictive value, largely because AHS is rare; therefore, a positive result indicates increased risk rather than certainty of hypersensitivity. Cost-effectiveness analysis of HLA B*58:01 testing before initiating allopurinol in East and Southeast Asia, where the prevalence of HLA B*58:01 is high, has shown conflicting results (63–68).

Looking at the primary pathophysiology of hyperuricemia in gout, there is a defect in urate transporters, particularly URAT1 in renal tubules, leading to diminished renal excretion of uric acid; therefore, use of uricosuric agents that act on URAT1 should address the primary mechanism of hyperuricemia and gout. However, the presence

of urinary tract stones, advanced renal insufficiency, and possible drug–drug interactions with cytochrome P450–metabolized medications are major limitations to their use. Interestingly, a 2025 report from a gout registry from the Asia Pacific region found that only 3% of gout patients received uricosuric agents (69). The very low rate of uricosuric agent use in the Asia Pacific region might be related to the limited availability of uricosuric agents, physicians' lack of familiarity with their use, and the prioritization of XOIs as recommended by international guidelines. A negative history of passing stones or flank pain suggestive of urinary calculi, absence of red blood cells on urinalysis, and a spot urine uric acid-to-creatinine ratio < 0.2 , which suggests uric acid underexcretion, may increase clinicians' confidence in prescribing uricosuric agents (70).

THE FUTURE

Newer imaging modalities

In future clinical practice, gout may still be a clinical diagnosis, with synovial fluid examination reserved for situations where diagnostic uncertainty remains. However, among individuals at risk for gout, identifying MSU crystal deposition earlier, ideally before the first episode of acute arthritis, would be of interest, as this could enable timelier counselling and preventive management. In this context, US and DECT may play a greater role in detecting subclinical MSU crystal depositions prior to the onset of acute arthritis (71, 72). As these technologies continue to become smaller and more portable, their use in ambulatory settings may become more feasible. Nevertheless, their diagnostic yield, particularly for US, will remain operator-dependent and will require appropriate training; therefore, US and DECT are best framed as adjunctive modalities that can support decision-making in selected diagnostically challenging or high-risk cases, rather than as universal necessities for early diagnosis.

Genetic study

In the future, identification of genetic variants that predispose individuals to hyperuricemia may enable a more personalized approach to gout prevention and management (40–42). Genetic testing in children with a family history of gout could help identify individuals who are likely to develop

sustained hyperuricemia and gout, supporting earlier lifestyle counselling, closer monitoring of SUA, and probably initiation of ULT earlier in selected high-risk patients. Genetic profiling may also inform treatment selection by clarifying whether hyperuricemia is driven predominantly by reduced renal urate excretion, impaired extra-renal urate excretion, or both. It also could help predict variability in treatment response or prognosis. Ultimately, genetic markers could be integrated with clinical and imaging data to support precision prevention strategies and optimize long-term outcomes.

Metabolomics

Metabolomics is the comprehensive measurement of small molecules, or metabolites, in biological samples such as blood, urine, or synovial fluid. It provides a real-time assessment of biochemical function and activity that reflects genetic background, diet, comorbidities, the microbiome, and environmental exposures. Metabolomic profiling may support precision medicine by enabling molecular phenotyping, discovery of diagnostic and prognostic biomarkers, and identification of actionable metabolic pathways that could be targeted therapeutically (73). A study has shown that metabolomic profiles differ between the acute and intercritical periods of gout, and that specific metabolites may help identify patients at risk of imminent attacks (74). Therefore, this might help inform earlier or more individualized preventive strategies alongside clinical assessment and imaging.

Newer pharmacological therapy

Looking at the pathogenesis of acute gout, multiple inflammatory pathways are involved, such as NLRP3 inflammasome, the mitogen-activated protein (MAP) kinase family, the cysteine-dependent aspartate-directed protease (caspase) system, the mitochondrial pyruvate carrier (MPC) pathway, TGF- β , and the NET system. These pathways are being investigated as potential therapeutic targets for acute arthritis in gout (33, 75). Several ULTs, including uricosuric agents, XOIs, and uricase-based therapies, are currently being investigated in clinical trials (76). Among these three ULT classes, uricosuric agents are among the most extensively investigated. Many

of them target the URAT1 transporter. This trend indicates that treating gout by targeting the primary pathogenic mechanism of renal urate transport, particularly URAT1, is receiving more attention. As the ABCG2 has recently been found to be involved in urate excretion in the intestine and kidney, drugs targeting the ABCG2 transporter for the management of hyperuricemia will be of interest.

With the advances of nanotechnology, this system has come to play an important role in clinical medicine. It offers innovative solutions to limitations in traditional drug delivery systems. These nanoparticles, ranging from 1-100 nanometers in size, have unique properties, including a high surface area-to-volume ratio, enhanced solubility, and the ability to bind to specific tissues or cells, making them highly effective in delivering therapeutic agents (77). Several types of nanomaterials are used to develop nanoparticles, including polymeric nanoparticles, lipid-based nanoparticles, metallic nanoparticles, magnetic nanoparticles, and silica nanoparticles. Colchicine, allopurinol, and uricase formulations using nanotechnology have recently been under development (78). It might be possible that this technology will be applied to existing and novel therapies to treat gout in the future.

Modification of gut microbiota

Because alterations of the gut microbiome have been shown to be associated with hyperuricemia, manipulation of the gut microbiome is another potential means to decrease SUA (44). Plant-based components, such as ginsenosides, curcumin, and flavonoid compounds, have been shown to reduce SUA (45). Certain strains of *Lactobacillus* species can reduce uric acid production by uptaking and degrading inosine, guanosine, and adenosine in the intestine, thereby reducing the intestinal absorption of uric acid from the gastrointestinal tract (79). For example, a study found that patients with hyperuricemia or gout who took yogurt that contained *Lactobacillus gasseri* PA-33 demonstrated a significant reduction in SUA without serious side effects (80). Therefore, modification of gut microbiota may reduce SUA and could be applicable as a treatment, or as adjunctive treatment, for hyperuricemia and gout in the future.

Restoration of the uricase gene

The completion of the human gene sequence in the early 21st century led physicians to be able to identify areas of uricase gene deletion. Missense mutation at codon 119, and non-sense mutation at codon 33 in the human uricase gene, leading to loss of urate oxidase activity, and the sequence-specific oligonucleotides responsible for these mutations have been identified (81, 82). With advances in gene editing technology, the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), scientists are able to edit genes (either insertion or deletion), edit single or multiple base pairs, and regulate gene expression (either activation or suppression), which can treat, prevent, or cure genetically related human diseases (83). A recent study using this technique inserted the deleted uricase gene into human liver cells and found that the liver cells could not only prevent hyperuricemia but also correct other metabolic abnormalities (84, 85). It may be possible to restore this gene in humans in the future.

Uricase restoration: potential benefit and risk

Prooxidant and antioxidant properties of uric acid have been well recognized (86, 87). Urate itself is an electron donor and can trigger several relevant reactive oxygen species (ROS), including superoxide anion, hydroxyl radical, and hydrogen peroxide. These ROS can further stimulate several intracellular signaling pathways related to inflammation. Conversely, uric acid is a major antioxidant in the body, accounting for approximately two-thirds of the body's antioxidant capacity, in part by stimulating superoxide dismutase, a major antioxidant enzyme. These antioxidant properties could prevent cellular destruction and probably help explain the expanding human lifespan.

Whether the higher brain function, particularly cognitive function and intelligence, in humans when compared with other primates, is related to higher SUA as a result of human evolution is not clearly understood. High SUA has been found to be associated with higher intellectual and cognitive function (88). A study in healthy individuals found that higher SUA levels were associated with higher intelligence quotient (IQ) scores (89-91). Another study found that elderly individuals with mild cognitive impairment had lower SUA than those who did not (92).

The effect of SUA on neurological diseases also shows conflicting results. Several meta-analyses, and systematic reviews, have reported that hyperuricemia was associated with an increased risk of stroke, cardiovascular events, and all-cause mortality (93, 94), and hyperuricemia treatment has also been reported to be associated with reduced all-cause mortality and improved cardiovascular outcomes (95). These findings support the prooxidant effects of hyperuricemia and its association with other comorbidities, particularly hypertension.

Regarding neurodegenerative diseases, such as Alzheimer disease (AD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS), studies have shown that patients with these neurodegenerative diseases had lower SUA, and that lower SUA levels were associated with advancement and progression of disease (96, 97). These findings may support the antioxidant effect of uric acid in mitigating oxidative stress-induced neuron degeneration and/or its neuro-protective effect. It remains unclear whether lower SUA in neurodegenerative disease partly reflects reverse causality (e.g., disease-related weight loss, reduced caloric intake, inflammation, or frailty), rather than a direct causal role of SUA. However, there is also evidence that hyperuricemia can have detrimental effects on brain tissue. High SUA has been shown to be correlated with cognitive impairment, and patients with gout also had smaller brain volume and were vulnerable to the development of neurodegenerative disease (98, 99), as well as an increased risk of stroke (100). This appears to contrast with the studies above linking higher SUA with better cognitive performance; however, gout and hyperuricemia frequently coexist with cardiometabolic comorbidities and systemic inflammation, which may mediate vascular brain injury and cognitive decline. Therefore, the long-term balance between the benefits and risks of low SUA resulting from uricase restoration should be considered.

CONCLUSIONS

Gout results from the evolutionary loss of functional uricase in humans, which leads to hyperuricemia and subsequent MSU crystal deposition. This evolutionary change, which led to higher SUA levels in humans than in other primates, may

have been associated with enhanced intellectual and cognitive function. Although the clinical features and course of gout are well recognized and effective treatments are available, unmet needs in gout management remain. Advances in nanotechnology may enable newer and more effective drug-delivery strategies, improve efficiency and allow more targeted therapy. In addition, progress in human genome editing may eventually permit restoration of this ancient gene. However, evidence regarding the association between SUA and neurodegenerative disease and stroke remains conflicting. Therefore, any attempt to restore the uricase gene should be approached cautiously, with close attention to potential long-term neurological and vascular outcomes.

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The author declares no conflict of interest

AUTHOR CONTRIBUTION

W.L. was solely responsible for conceptualization, literature review, and writing (original draft and editing) of this manuscript.

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