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HYPERURICEMIA: A SYSTEMIC REVIEW

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ABSTRACT

Uric acid is a chemical, created in the body by the breaking down of purines. It is excreted out of the body by the kidneys, through urine, after it dissolves in the blood. If it is not excreted out of the body properly, high levels of uric acid gets accumulated which causes gout and kidney stones. Hyperuricemia is usually caused due to the regular intake of food having high content of purine and conditions such as hyperparathyroidism, lead poisoning, renal failure and side effects of chemotherapy. Hyperuricemia occurs when serum urate levels exceed urate solubility, ie, at approximately 6.8 mg/dL. At serum urate levels above this threshold, manifestations of gouty arthritis may occur, although asymptomatic hyperuricemia often persists for many years. Intercritical asymptomatic periods follow the resolution of acute gout flares, but crystals remain in the joint during these intervals and further deposition may continue silently. Ultimately this may lead to persistent attacks, chronic pain, and, in some patients, joint damage.

KEY WORDS: Hyperuricemia • Uric acid • Diagnosis • Cardiovascular disease • Risk.

INTRODUCTION

Hyperuricemia is a common metabolic disorder. It is reported to affect approximately 5% of the general population and more than 25% of hospitalized patients. Plasma uric acid concentration is established by a balance among food intake, endogenous purine degradation, and the elimination of uric acid by the bowel and kidney. Cellular turnover provides a large number of nucleic acids, which are involved in the metabolism of uric acid. The human body partially recycles nitrogen bases and the excess is removed as urate.[1] Uric acid largely exists as urate (the ionized form, pKa is 5.8) at neutral pH. It is the end product of purine

metabolism in humans. High serum levels of urate (hyperuricemia) are causative in gout and urolithiasis, due to the formation and deposition of monosodium urate crystals. Urate is singly charged at neutral pH and at a concentration of 6.8 mg/dL (0.40 mmol/L) in human serum, crystals can form spontaneously. The solubility of urate decreases with increasing local sodium concentration, and decreasing temperature and pH. The latter is an important factor in urate stone-formation in patients with acidic urine. The serum level of urate in man considered to be 'normal' varies among laboratories and in publications, but a range of 3.5 mg/dL (0.2 mmol/L) to 7.0 mg/dL (0.4 mmol/L) is often quoted. Serum urate is usually 0.5-1 mg/dL (0.03-0.06 mmol/L) lower in women compared with men. Serum urate levels in men have increased gradually from 3.5 mg/dl (0.2 mmol/L) in the 1920s to 6.0 mg/dL (0.35 mmol/L) in the 1970s.[2]

Uric acid is the final enzymatic product of an exogenous and endogenous pool of purines. The dominant source of uric acid (two thirds) is endogenous purines (mainly from the liver, intestine and other tissues), while one third derives from the exogenous purines (mainly animal proteins). It can be found in cells and tissues, and under steady-state conditions its production is in balance with uric acid disposal.[3] In recent years there has been a renewed interest in hyperuricemia and its association with a number of clinical disorders other than gout, including hypertension, atherosclerosis, cardiovascular disease, and chronic kidney disease. Indeed, hyperuricemia is commonly part of the cluster of metabolic and hemodynamic abnormalities including abdominal obesity, glucose intolerance, insulin resistance, dyslipidemia, and hypertension all often subsumed under the term "metabolic syndrome". Not only collectively, but also individually, hypertension, obesity, dyslipidemia, hyperglycemia, and insulin resistance are positively correlated with serum levels of uric acid.[4]

Genetic and Biochemical basis of hyperuricemia

There are three different inherited defects that lead to early development of severe hyperuricemia and gout: glucose-6- phosphatase (gene symbol = G6PT) deficiency; severe and partial hypoxanthine-guanine phosphoribosyltransferase (HGPRT, gene symbol = HPRT) deficiency; and elevated 5'- phosphoribosyl-1'-pyrophosphate synthetase (PRPP synthetase, gene symbol = PRPS) activity. The familial association of gout was recognized hundreds of years ago but defining the exact genetic mechanisms was not possible until the advancement of modern genetic tools. Gout and Garrod have been linked in medical literature for more

than a century. He identified uric acid as a normal constituent of the serum of healthy persons and devised a method for detecting its increased concentration in gouty subjects. Over activity of PRS is also an X-linked dominant disorder that can produce hyperuricemia. It is characterized by an overproduction of phosphoribosyl pyrophosphate (PRPP) and uric acid, which can cause hyperuricemia, nephrolithiasis, and gout at an early age. Overactivity of PRS is related to an accelerated transcription of the PRS-I gene, acting as a major determinant of synthesis of PRPP, purine nucleotides, and uric acid. At least three different isoforms of PRPP synthetase have been identified and are encoded by three distinct, yet highly homologous PRPS genes, identified as PRPS1, PRPS2, and PRPS3. The PRPS1 and PRPS2 genes are found on the X chromosome (Xq22–q24 and Xp22.2–p22.3, respectively) and the PRPS3 gene is found on chromosome 7. The PRPS3 gene appears to be expressed exclusively in the testes. All three PRPP synthetase isoforms differ in kinetic and physical characteristics such as isoelectric points (pI), pH optima, activators and inhibitors. Phosphoribosylpyrophosphate synthetase (PRS) superactivity is characterized by hyperuricemia and hyperuricosuria and is divided into a severe phenotype with infantile or early-childhood onset and a milder phenotype with late-juvenile or early-adult onset. Variable combinations of sensorineural hearing loss, hypotonia, and ataxia observed in the severe type are not usually present in the mild type. In the mild type, uric acid crystalluria or a urinary stone is commonly the first clinical finding, followed later by gouty arthritis if serum urate concentration is not controlled. Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) is an enzyme involved in the salvage of purine nucleotides.

HGPRT catalyzes the following two interconversions

hypoxanthine + PRPP <——> IMP + PPi

guanine + PRPP <——> GMP + PPi

A complete or virtually complete loss of HGPRT activity results in the severe disorder, Lesch-Nyhan syndrome. Lesch-Nyhan syndrome is inherited as an x linked trait. Persons with this syndrome are missing or are severely lacking an enzyme called hypoxanthine guanine phosphoribosyltransferase 1 (HGP). The body needs this enzyme to recycle purines. Without it, abnormally high levels of uric acid build up in the body. Hyperuricemia results from a combination of increased generation and decreased excretion of uric acid which is generated when increased amounts of G6P are metabolized via the pentose phosphate pathway. It is also a byproduct of purine degradation. Uric acid competes with lactic acid and

other organic acids for renal excretion in the urine. In GSD I increased availability of G6P for the pentose phosphate pathway, increased rates of catabolism, and diminished urinary excretion due to high levels of lactic acid all combine to produce uric acid levels several times normal. Although hyperuricemia is asymptomatic for years, kidney and joint damage gradually accrue.[5]

Pathophysiology of hyperuricemia

The initial trigger of the 'inflammasome' is from the effect of monosodium urate crystals on cells of the monocyte/macrophage lineage. This leads (via the NALP3 inflammasome) to secretion of IL-1β, which then acts to recruit more inflammatory cells. The detailed mechanism underlying the secretion of IL-1β is not known, but cell damage leading to ATP release and activation of the P2X7 receptor may be involved. Potassium efflux may also be important, as well as generation of reactive oxygen species (ROS). Released IL-1β recruits other inflammatory cells and so amplifies the inflammatory reaction. The result is a burst of inflammatory mediator release. The inflammation spontaneously resolves, perhaps mediated by release of the anti-inflammatory cytokine TGF-β. The inflammasome is considered to be essential in gout and other crystalopathies, but its role in any associated pathology is less clear. It is also unclear if hyperuricemia alone can initiate other pathological processes.

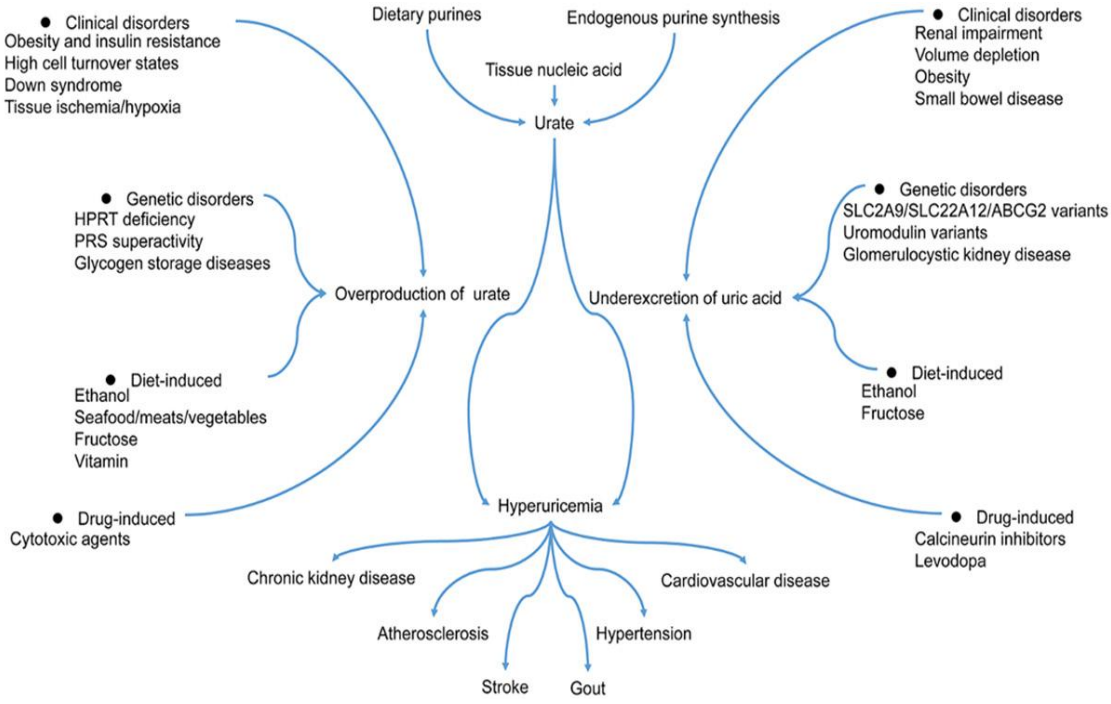
Multivariate analysis has been used to assess if serum urate is an independent risk factor for disease. A positive association has been found between urate levels and a number of important disorders, including hypertension, CKD, CHF, the metabolic syndrome, T2DM, endothelial cell dysfunction, cardiovascular events, and fatty liver disease. The strength of these associations will be discussed below. There are also a few intervention studies, mostly with allopurinol, but these are small and may not be representative of the effects of lowering urate by different mechanisms.

It is important to mention that urate also plays an essential function in humans. The loss of uricase in higher primates parallels the similar loss of our ability to synthesize ascorbic acid, an important anti-oxidant, leading to the suggestion that urate may partially substitute for ascorbate in humans. Both uric acid and ascorbic acid are strong reducing agents (electron donors) and potent antioxidants. In humans, the major extracellular antioxidant capacity of blood comes from urate, but urate can also be pro-oxidant depending on the conditions. Epidemiological data suggest that urate may be important in neuroprotection. The brain is vulnerable to oxidative stress due to its high metabolic rate and high levels of unsaturated

fatty acids. Thus, increased lipid peroxidation could be one explanation for the association found between reduced serum urate levels and CNS disorders such as multiple sclerosis (MS), AML, Parkinson's, Alzheimer's and Huntington's diseases. Patients with MS have significantly lower serum urate levels and there seem to be no reported cases of patients suffering from both MS and gout.

Epidemiology

In recent years, the disease burden of hyperuricemia is increasing, especially in high-income countries and economically developing world with a western lifestyle. The prevalence and incidence of hyperuricemia sub-stantially differ across geographical areas. According to the data from the National Health and Nutrition Examination Survey (NHANES) 2007-2016, a nationally representative survey showed that the prevalence rates of hyperuricemia were 20.2% among men and 20.0% among women between 2015 to 2016 in the United States and the incidence of hyperuricemia remained stable in 2007-2016. The prevalence of hyperuricemia increases in both men (19.7% to 25.0%) and women (20.5% to 24.1%) from 2006 to 2014 in Ireland. In the United States, an epidemiological survey has shown that the prevalence of hyperuricemia substantially increased from 19.1% (1988-1994 years) to 21.5% (2007-2008 years). The National Health and Nutrition Examination Survey (NHANES) 2007-2008 found a similar prevalence of hyperuricemia between women (21.6%) and men (21.2%). Most epidemiological studies show that the prevalence of hyperuricemia is generally higher in high-in-come countries than economically developing world. The reduction of hormone estrogen production in postmenopausal wo-men can decrease the removal of urate from the body result in an increase in urate levels and an elevated risk of developing hyperuricemia. The levels of urate hinge on the dynamic balance between purine-rich foods intake, synthesis of urate within the body, the excretion of urate via urine or the gastrointestinal tract (Figure). Prospective epidemiologic studies have pointed to obesity, hypertension, metabolic syndrome, diuretic use, dietary factors, and chronic kidney disease as risk factors for gout and hyperuricemia. Recently, it turns out that iron overload can enhance serum uric acid levels, indicating a causal connection between hyperferritinaemia and hyperuricemia. It is well known that chronic noncommunicable diseases, such as cardiovascular and rheumatic diseases, are associated with the development of hyperuricemia. An on-set sequence study revealed that hyperuricemia is an earlier-onset metabolic disorder than hypertriglyceridemia, diabetes mellitus, and hypertension.[6]



Mechanisms of hyperuricemia. HPRT, Hypoxanthine-guanine phosphoribosyltransferase; PRS, Phosphoribosylpyrophosphate synthetase.

Role of monosodium urate crystals and inflammation in Gout and Cardiovascular diseases

A clinical consequence of hyperuricemia is the development of gouty arthritis, an excruciatingly painful condition characterized by severe inflammation of the joints and surrounding tissues. Patients with UA concentrations 8.0 mg/dL can deposit as monosodium urate (MSU) crystals in articular joints and bursal tissues. Many studies have demonstrated that the nascent inflammatory response arises as the macrophages that reside within the joint space phagocytes MSU crystals. Once these crystals have been engulfed by the macrophages, they engage with pathogen recognition and toll-like receptors that trigger a pathway leading to the development and activation of the nod-like receptor pyrin domain 3 (NLRP3) inflammasome protein complex. This complex then activates caspase-1 and causes the release of interleukin (IL)-1β, a proinflammatory cytokine. IL-1β, other proinflammatory cytokines, tumor necrosis factor-α, IL-6, and IL-8 stimulate the inflow of neutrophils, which is known to be the primary step in the pathogenesis of gout. Recruited neutrophils are responsible for the eventual deterioration of the affected joints and cartilage through their extracellular release of detrimental reactive mediators such as proteolytic enzymes, chemokines, cytokines, ROS, and prostaglandin E2. As previously discussed, the activation of inflammasomes results in caspase-1 release by immune cells and activation of IL-1β, a proinflammatory cytokine. Van

der Heijden and colleagues studied the effect of selectively inhibiting the NLRP3 inflammasome protein complex using MCC950 to limit the atherosclerotic lesion development in apolipoprotein E knockout mice. The targeted inhibition of the NLRP3 inflammasome using the MCC950 treatment resulted in a significant decrease in the development of atherosclerotic lesions in these murine models, as indicated by measurements of the plaque volume, average plaque size, and maximal stenosis. Previous investigations have demonstrated that cholesterol crystals, like MSU crystals, also activate the NLRP3 inflammasome protein complex, which results in the release of IL-1β. An inflammation pathway is thus triggered. IL-1β induces IL-6, causing the liver to engage in an acute-phase response. As many clinical investigations have elucidated, the C-reactive protein that is formed during an acute-phase response is a biomarker for a risk of developing acute cardiovascular events. The induced inflammation causes a remodeling of the arterial wall and destabilizes atherosclerotic plaque.[7-11]

Role of hyperuricemia in metabolic syndrome

Metabolic syndrome is characterized by the presence of abdominal obesity associated with at least two of the following conditions: hypertriglyceridemia, low high-density lipoprotein cholesterol level, hypertension, increased levels of fasting glucose, or insulin resistance. Patients with metabolic syndrome are at a high risk for developing cardiovascular diseases. Increased UA levels are often associated with metabolic syndrome, but it is unknown whether this condition is merely a consequence of metabolic dysfunction or a causal factor in the development of cardiovascular diseases. Hyperuricemia and hyperinsulinemia are often concomitant. An increase in UA levels precedes insulin resistance in diabetic subjects. Otherwise, insulin reduces renal UA secretion by distal tubular reabsorption. Renal clearance of urate is inversely related to insulin resistance. A possible explanation for this is that hyperuricemia prevents pulmonary arterial endothelial cells from relaxing by reducing the propagation of nitric oxide (NO) in these cells. The consequent vasoconstriction leads to reduced glucose uptake in peripheral tissue, particularly in skeletal muscles. A second hypothesis considers the effects of UA on adipocytes, in which prothrombotic and proinflammatory factors are overexpressed and negatively modulate the expression of peroxisome proliferator-activated γ receptors. Thus, the physiologic activity of peroxisome proliferatoractivated γ receptors regarding the capture of polyunsaturated fat from circulation and subsequent uptake by adipocytes is altered. Insulin sensibility mediates this process. Hyperuricemia is also associated with obesity. UA can affect adipocytes by inducing the up-

regulation of proinflammatory factors such as the adipokine monocyte chemoattractant protein-1 and the down-regulation of the production of an insulin sensitizer and anti-inflammatory factor adiponectin, mimicking the effects seen in obesity. Lowering UA levels using allopurinol in mice with metabolic syndrome and hyperuricemia improved the proinflammatory endocrine imbalance in the adipose tissue, decreased macrophage infiltration of the adipose tissue, and decreased insulin resistance. Hyperuricemia may also play a role in the pathogenesis of hypertension. A recent meta-analysis reported an association between hyperuricemia and hypertension, independent of other risk factors for hypertension. A 13% increase in the risk of an incidence of hypertension was reported per 1 mg/dL increase in serum UA level. There was a linear relationship between UA levels and hypertension with no cutpoint or threshold. This correlation was more prominent in young individuals and women. Potential mechanisms linking hyperuricemia and the development of hypertension include NO and renin-angiotensin pathways. The lack of NO available in pulmonary arterial endothelial cells due to a cellular state of hyperuricemia induces the vasoconstriction, a causal factor associated with hypertension. UA is also reported as an independent risk factor for a decrease in renal functioning and end-stage renal disease.[12-15]

Diagnosis of hyperuricemia

It is possible to measure the amount of uric acid in the blood and urine. Diagnosis typically involves a blood sample, and the measurement is often expressed in milligrams of uric acid per deciliter of blood (mg/dL). A diagnosis of hyperuricemia is considered in:

- Men who have more than 7.0 mg/dL
- Women who have more than 6.0 mg/dL

It is important to note that uric acid levels in the blood naturally fluctuate, and what is considered "normal" may vary depending on the lab doing the analysis.

Not a routine test Unlike lab tests for blood cell counts and cholesterol, a lab test to measure uric acid concentrations is not considered routine in North America and Europe. A doctor will typically only order this test if they have a reason—for example, they suspect a patient has or is at risk of gout.

Asymptomatic hyperuricemia

Signs and symptoms of hyperuricemia are typically associated with urate crystals found in the joints, tendons, or kidneys. People who have abnormally high uric acid levels and no symptoms or signs of urate deposition are said to have asymptomatic hyperuricemia.[16]

Summary

Hyperuricemia does not always lead to the typical clinical manifestations of gout. These symptoms usually only appear in a person suffering with hyperuricemia for 20 to 30 years. The normal course of untreated hyperuricemia, leading to progressive urate crystal deposition, begins with uric acid urolithiasis (urate kidney stones) and progresses to acute gouty arthritis and chronic tophaceous gout. Patients with gout tend to seek medical attention during gout attacks, at which point the standard diagnostic procedure is to search for monosodium urate crystals in synovial fluid. But patients are often seen during the intercritical periods, when, in the absence of tophi, the diagnosis is made on clinical grounds by applying the preliminary American College of heumatology classification criteria. However, classification criteria work best in the study of groups of patients, and they often fail in the evaluation of the individual patient. A clinical approach for the diagnosis of gout may be problematic and may explain why other conditions are often incorrectly diagnosed and treated as gout. Monosodium urate crystals can be found in synovial fluid obtained from asymptomatic gouty joints. Other factors that can precipitate gouty attacks such as trauma, surgery, excessive alcohol consumption, administration of certain drugs and the ingestion of purine-rich foods. Acute gouty arthritis consists of painful episodes of inflammatory arthritis and represents the most common manifestation of gout. Typical manifestations include a patient who goes to bed and awakens by severe pain in the big toe but may also be experienced in the heel, instep or ankle. The pain is described as that of a dislocated joint and is often accompanied or preceded by chills and a slight fever. The pain can become so severe even the simple act of cloth touching the area in unbearable. Gouty arthritis attacks usually dissipate within several hours but can also last for several weeks. Long-standing persistence of MSU crystals may also cause chronic neutrophilic inflammation, osteoclast activation and chronic granulomatous infiltration of the synovium. Microaggregates of MSU crystals occur in all patients with gout, but in some, macroscopic aggregates occur, manifested as tophus formation. Tophi are usually considered to be a late manifestation of gout. The continued development of tophi results in destructive arthropathy (disease of a joint). Aside from gouty arthritis and tophus formation, renal disease is the most frequent complication of

hyperuricemia. Kidney disease in patients with gout is of numerous types. Uric acid stones, which represent 5-10% of all renal calculi in the United States, also result from uric acid precipitation in the collecting system. Uric acid stones are related to uric acid exceeding its solubility in the urine; thus, patients with hyperuricosuria have an increased risk of uric acid nephrolithiasis. Urine oversaturation with uric acid and subsequent crystal formation is determined largely by urinary pH. Individuals who form uric acid stones tend to excrete less ammonium, which contributes directly to low urinary pH. In addition, persons with gout and those who form stones, in particular, have a reduced postprandial alkaline tide (alkaline urinary pH).

CONCLUSION

Hyperuricemia seems to be rising steadily in prevalence over the last decades. High uric acid concentrations are involved in the elevated risk of developing hyperuricemia. Hyperuricemia is a metabolic disease connected with Lesch-Nyhan syndrome and glycogen storage disease-ia. Substantial evidence suggests that hyperuricemia is an underlying risk factor for gout, and it can forecast the evolution of chronic kidney disease, obesity, diabetes, and hypertension. Although numerous studies have demonstrated close correlations between hyperuricemia and multiple comorbidities such as acute and chronic kidney disease, diabetes, metabolic syndrome, cardiovascular disease, hypertension, and dyslipidemia, it is currently unclear that there is a causal relationship between hyperuricemia and multiple comorbidities. Genetic characteristics provide novel perspectives on the physiology and pathophysiology of hyperuricemia. More importantly, genetic studies may provide more precision medicine for individuals. These are various approaches that help manage hyperuricemia. Nevertheless, patient and health-care provider education is the foundation of the successful treatment of hyperuricemia. As a general rule, it is not indispensable to treat most patients with asymptomatic hyperuricemia in the absence of kidney stones or gout. To effectively treat hyperuricemia, reducing the levels of uric acid is crucial, achieved by inhibiting uric acid synthesis and reabsorption, as well as facilitating the excretion of uric acid.

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